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

Rebecca J. Lee, PhD, MBChB¹,²; Oskar Wysocki, PhD²,³; Cong Zhou, PhD²; Rohan Shotton, MBChB¹,²; Ann Tivey, MBBS¹,²; Louise Lever, BSc; Joshua Woodcock, BSc; Laurence Albiges, MD, PhD⁴; Angelos Angelakas, MD⁵; Dirk Arnold, MD, PhD⁶; Theingi Aung, MD⁷; Kathryn Banfill, MBChB¹,²; Mark Baxter, MBChB²; Fabrice Barlesi, MD, PhD⁸,⁹; Arnaud Bayle, MD⁹,¹⁰; Benjamin Besse, MD, PhD¹⁰; Talvinder Bhogal, MBChB¹¹; Hayley Boyce, MBBS⁵; Fiona Britton, PhD, MBChB¹²; Antonio Calles, MD, PhD¹²; Luis Castelo-Branco, MD, PhD¹³,¹⁴,¹⁵; Ellen Copson, MBChB, PhD¹⁶; Adina E. Croitoru, MD, PhD¹⁷; Sourbha S. Dani, MD¹⁸; Emily Dickens, MBChB¹⁹,²⁰; Leonie Eastlake, MBChB²¹; Paul Fitzpatrick, PhD²²; Stephanie Foulon, MSc²²,²³; Henrik Frederiksen, MD, PhD²⁴; Hannah Frost, BSc²; Sarju Ganatra, MD²⁵; Spyridon Gennatas, MD, PhD²⁶; Andreas Genthjø, PhD²⁷; Fabio Gomes, MD, PhD²⁸; Donna M. Graham, PhD, MBChB²⁹; Christina Hague, MBChB³; Kevin Harrington, PhD, MBChB³⁰,³¹; Michelle Harrison, MBChB³²; Laura Horsley, PhD, MBChB³³; Richard Hoskins, BSc²⁷; Prerana Huddar, MBChB³⁴; Zoe Hudson, PhD, MBChB³⁵; Lasse H. Jakobsen, PhD³⁶; Nalnine Joharatnam-Hogan, MBBS³⁷,³⁸; Sam Khan, MD³⁹; Umar T. Khan, MD⁴⁰,⁴¹; Khurum Khan, MD⁴²; Christophe Massard, MD, PhD⁴³; Alec Maynard, MD⁴⁴,⁴⁵; Hayley McKenzie, MBBS⁴⁶; Olivier Michieli, MD, PhD⁴⁷; Anne C. Mosenthal, MD⁴⁸; Berta Obispo, MD⁴⁹; Rushin Patel, MD⁴⁹; George Pentheroudakis, MD, PhD⁵⁰; Solange Peters, MD, PhD⁵¹,⁵²; Kimberly Rieger-Christ, MD⁵³; Timothy Robinson, PhD, MBChB⁵⁴,⁵⁵; Jacobo Rogado, MD, PhD⁵⁶; Emanuela Romano, MD, PhD⁵⁷; Michael Rowe, BMBS⁵⁸; Marina Sekacheva, MD, PhD⁵⁹; Roseleen Sheehan, MBChB⁶⁰; Julie Stevenson, BSc³; Alexander Stockdale, MD⁶¹; Anne Thomas, PhD, MBChB⁶²,⁶³; Lance Turtle, PhD, MBBS⁶⁴; David Viñal, MD, PhD⁶⁵; Jamie Weaver, PhD, MBChB⁶⁶; Sophie Williams, MD⁶⁷; Caroline Wilson, MBChB⁶⁸; Carlo Palmieri, MD, PhD⁶⁹,⁷⁰; Donal Landers, PhD, MBChB³; Timothy Cooksley, MBChB⁷¹; ESMO Co-Care; Caroline Dive, PhD²; André Freitas, PhD⁷²,⁷³,⁷⁴; and Anne C. Armstrong, PhD, MBChB¹²

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 (O₂) 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 vs 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.
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.

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. A diverse spectrum of clinicopathologic syndromes have been reported, ranging from asymptomatic cases to multiorgan failure and death. 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. 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. In three large case series and a meta-analysis of 18,650 patients, fatality rates of 10%-30% were observed in patients with cancer. 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.

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. A living review of risk prediction models has reported that current models are highly susceptible to bias and are poorly reported. 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. 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 (O2) 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

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.
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), O2 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 O2 (as generally it is only given in hospital) and the severity of COVID-19 disease indicated by prediction for O2 requirement and death. If patients were already on supplementary O2 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 al18 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 R2 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 Explanations19; 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 work20 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 (NEWS220; 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 O2 (group 1) was 25%, required O2 but did not die (group 2) was 29%, and admitted plus required O2 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.

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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 | 5 | 1 | 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 |

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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 |
|----------|---------|------------------------|---------------------|--------------------------------------|-----------------------------------------------|-----------------|------------------------|
| No. (%)  | 920     | 152 (16.5)             | 232 (25.2)          | 265 (28.8)                           | 271 (29.5)                                    | 0.292 < .001    | s                      |
| 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] | 0.209 < .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 | ns |
| 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, 41.0] | 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 | ns |
| 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 | ns |
| 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 died | 356 (38.7) | 70 (46.1) | 116 (50.0) | 78 (29.4) | 92 (33.9) | -0.129 < .001 | ns |

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

| Variable                                      | Overall    | Discharged (score = 0) | Admitted (score = 1) | Admitted + Required O₂ (score = 2) | Admitted + Required O₂ + Died (score = 3) | Correlation<sup>a</sup> | Multivariable RFE SHAP |
|-----------------------------------------------|------------|------------------------|----------------------|-------------------------------------|------------------------------------------|-------------------------|------------------------|
| Immunotherapy, No. (%) of patients discharged, admitted, required O₂, and death | 54 (5.9)   | 14 (9.2)               | 11 (4.7)             | 15 (5.7)                            | 14 (5.2)                                | -0.041                  | NS                     |
| Targeted therapy, No. (%) of patients discharged, admitted, required O₂, and death | 106 (11.5) | 22 (14.5)              | 25 (10.8)            | 29 (10.9)                           | 30 (11.1)                               | -0.027                  | NS                     |
| Radiotherapy, No. (%, no missing) of patients discharged, admitted, required O₂, 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                     |
| 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                 |

**NOTE.** *P* ≥ .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.

<sup>a</sup>Spearman correlation for numeric and point biserial correlation for categorical features.

<sup>b</sup>Excluded from RFE because of > 20% missing data.

<sup>c</sup>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)
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 R² 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 O₂ 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 O₂ 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 O₂ 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, O₂ 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, O₂ requirement, and death), whereas France had the lowest prediction (AUROC 0.69, 0.77, and 0.71 for admission, O₂ requirement, and death, Data Supplement).
Supplement). On average, the AUROC in the entire validation cohort was 0.69, 0.69, and 0.70 for admission, O₂ 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 cancerspecific 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 O₂ 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, O₂ 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 \( (P < .001, \text{Kruskal-Wallis H-test, Data Supplement}). \)

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 \( \text{O}_2 \) 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 \( \text{O}_2 \) 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 \( \text{O}_2 \).

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).\(^2\)\(^2\) 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, \( \text{O}_2 \) 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.\(^2\)\(^0\) Although NEWS2 has its own limitations and has been criticized, especially in applicability to primary care,\(^2\)\(^3\) 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.\(^1\)\(^5\) 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
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.

AFFILIATIONS
1The Christie NHS Foundation Trust, Manchester, United Kingdom
2The University of Manchester, Manchester, United Kingdom
3Cancer Research UK Manchester Institute Cancer Biomarker Center, The University of Manchester, Alderley Park, United Kingdom
4Department of Medical Oncology, Gustave Roussy, Villejuif, France
5Department of Oncology, Haematology and Palliative Care, Asklepios Klinik Altona, Hamburg, Germany
6Weston Park Cancer Center, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom
7Division of Molecular and Clinical Medicine, Ninewells School of Medicine, University of Dundee, Dundee, United Kingdom
8Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France
9Drug Development Department (DITEP) Gustave Roussy—Cancer Campus, Villejuif, France
10Oncostat U1018, Inserm, Paris-Saclay University, Labeled Ligue Contre le Cancer, Villejuif, France
11The Clatterbridge Cancer Center NHS Foundation Trust, Liverpool, United Kingdom
12Hospital General Universitario Gregorio Marañón, Madrid, Spain
13ESMO-CoCARE Steering Committee, European Society for Medical Oncology, Lugano, Switzerland
14NOVA National School of Public Health, Lisboa, Portugal
15Department of Medical Oncology, University Hospital Center of Algarve, Faro, Portugal
16Cancer Sciences Academic Unit, Southampton University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom
17Medical Oncology Department, Fundeni Clinical Institute, Bucureşti, Romania
18Lahey Hospital and Medical Center, Burlington, MA
19Oncology Department, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom
20University Hospitals Plymouth NHS Trust, Crownhill, Plymouth, Devon, United Kingdom
21Biostatistics and Epidemiology Office, Gustave Roussy, University Paris-Saclay, Villejuif, France
22Department of Haematology, Odense University Hospital, Odense, Denmark
23The Royal Marsden NHS Foundation Trust, London, United Kingdom
24Department of Haematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
25The Institute of Cancer Research NIHR Biomedical Research Center, London, United Kingdom
26Ninewells Hospital and Medical School, Dundee, United Kingdom
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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.

AUTHOR CONTRIBUTIONS

Conception and design: Rebecca J. Lee, Oskar Wysocki, Cong Zhou, Theangi Aung, Hannah Frost, Sarju Ganatra, Kevin Harrington, Richard Hoskins, Anne C. Mosenthal, George Pentheroudakis, Solange Peters, Lance Turtle, Carlo Palmieri, Donal Landers, Andre Freitas, Anne C. Armstrong

Financial support: Caroline Dive

Administrative support: Rebecca J. Lee, Louise Lever, Anne C. Mosenthal

Provision of study materials or patients: Rebecca J. Lee, Laurence Albidges, Dirk Arnold, Kathryn Banfield, Adina E. Croitoru, Stephenie Foulon, Henrik Frederiken, Andreas Glenthaj, Kevin Harrington, Laura Horsley, Nalini Johartram-Hogan, Christophe Massard, George Pentheroudakis, Timothy Robinson, Emanuela Romano, Roseleen Sheehan, Alexander Stockdale, David Vifail, Caroline Wilson, Carlo Palmieri, Caroline Dive

Collection and assembly of data: Rebecca J. Lee, Oskar Wysocki, Rohan Shotton, Ann Tieve, Louise Lever, Joshua Woodcock, Laurence Albidges, Angelos Angelakas, Dirk Arnold, Theangi Aung, Kathryn Banfield, Mark Baxter, Fabrice Barlesi, Arnaud Bayle, Benjamin Besse, Talvinder Bhogal, Hayley Boyce, Fiona Britton, Antonio Calies, Ellen Copson, Adina E. Croitoru, Soubhra S. Dani, Elena Dickens, Paul Fitzpatrick, Stephanie Foulon, Henrik Frederiken, Sarju Ganatra, Spyridon Gennatas, Andreas Glenthaj, Fabio Gomes, Donna M. Graham, Christina Hugane, Kevin Harrington, Michelle Harrison, Laura Horsley, Richard Hoskins, Prerana Huddar, Zoe Hudson, Lasse H. Jakobsen, Nalini Johartram-Hogan, Sam Khan, Umar T. Khan, Khurum Khan, Christophe Massard, Alec Maynard, Haynel McKenzie, Olivier Michielin, Berta Obispo, Rushin Patel, George Pentheroudakis, Solange Peters, Kimberly Rieger-Chist, Timothy Robinson, Jacobo Rogado, Emanuela Romano, Michael Rowe, Marina Sekacheva, Roseleen Sheehan, Alexander Stockdale, Anne Thomas, David Vifail, Jamie Weaver, Sophie Williams, Caroline Wilson, Carlo Palmieri, Timothy Cooksley, Caroline Dive, Anne C. Armstrong

Data analysis and interpretation: Rebecca J. Lee, Oskar Wysocki, Cong Zhou, Dirk Arnold, Theangi Aung, Fabrice Barlesi, Arnaud Bayle, Luis Castelo-Branco, Sarju Ganatra, Andreas Glenthaj, Donna M. Graham, Christine Hugane, Khurum Khan, Solange Peters, Timothy Robinson, Roseleen Sheehan, Julie Stevenson, Anne Thomas, Carlo Palmieri, Andre Freitas, Anne C. Armstrong

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

CORRESPONDING AUTHOR

Rebecca J. Lee, BSc, MBChB, Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Rd, Manchester M20 4BX, United Kingdom; Twitter: @beckilee;
e-mail: Rebecca.lee-3@manchester.ac.uk.

EQUALLY CONTRIBUTION

R.J.L., O.W., and C.Z. equally contributed to this work. C.D., A.F., and A.C.A. equally contributed to this work.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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**Rebecca J. Lee**  
**Speakers’ Bureau:** AstraZeneca  
**Research Funding:** Bristol Myers Squibb (Inst), AstraZeneca/MedImmune (Inst)

**Rohan Shotton**  
**Honoria:** Servier  
**Travel, Accommodations, Expenses:** Servier

**Laurence Albigès**  
**Consulting or Advisory Role:** Bristol Myers Squibb (Inst), Ipsen (Inst), Roche (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Merck (Inst), MSD (Inst), AstraZeneca (Inst), Janssen (Inst), Eisai (Inst), Corvus Pharmaceuticals (Inst), Bellerophon Therapeutics (Inst)  
**Research Funding:** Bristol Myers Squibb (Inst)  
**Travel, Accommodations, Expenses:** BMS, MSD

**Dirk Arnold**  
**Employment:** Asklepios Kliniken  
**Honoria:** Bayer, Merck Serono, Roche/Gentech, Servier, Bristol Myers Squibb, Merck Sharp and Dome, AstraZeneca, Amgen, Boston Scientific, Pierre Fabre, Ipsen  
**Consulting or Advisory Role:** Bayer, Merck Serono, Biocompatibles, Terumo, Bristol Myers Squibb, MSD Oncology, AstraZeneca  
**Research Funding:** Roche/Gentech (Inst), Sanofi (Inst), Oncolytics (Inst)  
**Travel, Accommodations, Expenses:** Boston Scientific  
**Uncompensated Relationships:** ESMO Council, ESMO Journals (Ann Oncol, ESMO Open), German Society for Hematology and Medical Oncology, German Cancer Society, European Organisation for Research and Treatment of Cancer (EORTC)

**Kathryn Banfill**  
**Stock and Other Ownership Interests:** Roche (I)  
**Honoria:** AstraZeneca

**Mark Baxter**  
**Honoria:** Ipsen  
**Travel, Accommodations, Expenses:** Ipsen

**Fabrice Barlesi**  
**Honoria:** Genentech/Roche, Pfizer, Pierre Fabre, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, Novartis, Merck Serono, MSD Oncology, Takeda, Bayer, Seattle Genetics, Mirati Therapeutics  
**Consulting or Advisory Role:** Roche/Gentech, Pfizer, Novartis, Pierre Fabre, Bristol Myers Squibb, AstraZeneca/MedImmune, Boehringer Ingelheim, Lilly, Merck Serono, MSD Oncology, Takeda, Bayer, Mirati Therapeutics  
**Research Funding:** Roche/Gentech (Inst), AstraZeneca/MedImmune (Inst), Bristol Myers Squibb (Inst), Pierre Fabre (Inst), AbbVie (Inst), Amgen (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Eisai (Inst), Lilly (Inst), Ipsen (Inst), Innate Pharma (Inst), Novartis (Inst), Merck Serono (Inst), MSD Oncology (Inst), Pfizer (Inst), Sanofi/Aventis (Inst), Takeda (Inst)  
**Travel, Accommodations, Expenses:** Roche/Gentech, Bristol Myers Squibb, AstraZeneca/MedImmune, MSD Oncology

**Benjamin Besse**  
**Research Funding:** AstraZeneca (Inst), Pfizer (Inst), Lilly (Inst), Onxeo (Inst), Inivata (Inst), AbbVie (Inst), Amgen (Inst), Blueprint Medicines (Inst), Celgene (Inst), GlaxoSmithKline (Inst), Sanofi (Inst), Takeda (Inst), Cristal Therapeutics (Inst), Daiichi Sankyo (Inst), Janssen Oncology (Inst), OSE Immunotherapeutics (Inst), BeiGene (Inst), Boehringer Ingelheim (Inst), Roche/Genentech (Inst), Tolerxo Pharmaceuticals (Inst), 4D Pharma (Inst), Aptitude Health (Inst), Ceregentis (Inst), Chugai Pharma (Inst), Genzyme (Inst), Ipsen (Inst), Turning Point Therapeutics (Inst), Eisai (Inst)

**Antonio Calles**  
**Honoria:** AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Gentech, Lilly, Novartis, Merck Sharp & Dohme, Bristol Myers Squibb, Amgen, Bayer, Takeda, Sanofi/Regeneron  
**Consulting or Advisory Role:** Boehringer Ingelheim, Roche/Gentech, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Bristol Myers Squibb, Takeda, Igen Biotech, Sanofi/Regeneron  
**Research Funding:** MSD Oncology

**Ellen Copson**  
**Honoria:** Roche, Pfizer, AstraZeneca, Lilly, Novartis  
**Consulting or Advisory Role:** Lilly, NanoString Technologies, Pfizer, Sanofi/Aventis, Roche  
**Speakers’ Bureau:** Roche, Pfizer, AstraZeneca, Sanofi/Aventis  
**Research Funding:** SECA, AstraZeneca (Inst)  
**Travel, Accommodations, Expenses:** Roche, AstraZeneca

**Adina E. Croitoru**  
**Consulting or Advisory Role:** Ipsen, Pfizer, MSD Oncology  
**Research Funding:** Bristol Myers Squibb (Inst), Amgen (Inst), Astellas Pharma (Inst), Exelixis (Inst), Merck (Inst), Merck KGaA (Inst)  
**Travel, Accommodations, Expenses:** Merck, Servier

**Leonie Eastlake**  
**Travel, Accommodations, Expenses:** Servier

**Paul Fitzpatrick**  
**Stock and Other Ownership Interests:** AstraZeneca/MedImmune  
**Research Funding:** AstraZeneca/MedImmune (Inst)  
**Other Relationship:** Pistoia Alliance, EHDEN IMI project

**Henrik Frederiksen**  
**Research Funding:** AbbVie (Inst), Gilead Sciences (Inst), Sanofi (Inst)

**Hannah Frost**  
**Research Funding:** AstraZeneca (Inst)

**Sajju Ganatra**  
**Expert Testimony:** Haymarket Medical Education  
**Travel, Accommodations, Expenses:** Haymarket Medical Education

**Andreas Glenthøj**  
**Honoria:** Novo Nordisk  
**Consulting or Advisory Role:** Novartis, Celgene/Bristol Myers Squibb, Bluebird Bio, Sanofi, Novo Nordisk, Agios  
**Research Funding:** Sanofi, Saniona A/S  
**Travel, Accommodations, Expenses:** Agios

**Fabio Gomes**  
**Honoria:** AstraZeneca, Merck Serono, Roche

**Donna M. Graham**  
**Consulting or Advisory Role:** Clinigent Group  
**Speakers’ Bureau:** Cancer Drug Development Forum  
**Research Funding:** Pfizer (Inst)

**Kevin Harrington**  
**Honoria:** Arch Oncology (Inst), AstraZeneca (Inst), BMS (Inst), Boehringer Ingelheim (Inst), Merck Serono (Inst), MSD (Inst), Oncoly...
Berta Obispo

**Expert Testimony:** Bristol Myers Squibb

**Research Funding:** Amgen, Pierre Fabre

**Consulting or Advisory Role:** Olivier Michielin

Faron Pharmaceuticals, Pharmaceutical, Blueprint Medicines, Innate Pharma, PharmaMar, Faron Pharmaceuticals

**Honoraria:** Springer Nature

**Travel, Accommodations, Expenses:** Iovance Biotherapeutics (Inst), Phosplatin Therapeutics (Inst)

Lasse H. Jakobsen

**Honoraria:** Takeda, Roche

Khurum Khan

**Honoraria:** Servier

**Consulting or Advisory Role:** Bayer Health

Christophe Massard

**Consulting or Advisory Role:** Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, BMS, Celgene, Debiopharm Group, Genentech/Roche, Ipsen, Janssen, Lilly, MSD, Novartis, Pfizer, Sanofi, ORION, Taiho Pharmaceutical, Blueprint Medicines, Innate Pharma, PharmaMar, Faron Pharmaceuticals

Olivier Michieli

**Consulting or Advisory Role:** Bristol Myers Squibb, MSD, Novartis, Roche, Amgen, Pierre Fabre

**Research Funding:** Bristol Myers Squibb

**Expert Testimony:** Bristol Myers Squibb

**Travel, Accommodations, Expenses:** Bristol Myers Squibb, MSD

Anne C. Mosenthal

**Honoraria:** Springer Nature

Berta Obispo

**Honoraria:** Sanofi, Lilly, Angelini, LEO Pharma, Rovi

**Consulting or Advisory Role:** Rovi

George Penteroudakis

**Honoraria:** Roche, Amgen, Bristol Myers Squibb, MSD, Merck

**Consulting or Advisory Role:** Roche, Amgen

**Research Funding:** Roche (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Merck (Inst), AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst)

**Travel, Accommodations, Expenses:** Sanofi, MSD, Roche, Amgen, BMS

Solangie Peters

**Honoraria:** Roche (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Pfizer (Inst), MSD (Inst), AstraZeneca (Inst), Takeda (Inst), Illumina (Inst), Medscape (Inst), Takeda (Inst), AstraZeneca (Inst), Takeda (Inst), Roche (Inst), Amgen (Inst), Janssen (Inst), Regeneron (Inst), Merck Serono (Inst), Boehringer Ingelheim (Inst), Takeda (Inst), Lilly (Inst), AbbVie (Inst), Bayer (Inst), Biocartis (Inst), Debiopharm Group (Inst), Illumina (Inst), PharmaMar (Inst), Sanofi (Inst), Seattle Genetics (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), Incyte (Inst), Biovent (Inst), Clovis Oncology (Inst), Vaccibody (Inst), Phosplatin Therapeutics (Inst), Foundation Medicine (Inst)

**Research Funding:** Roche (Inst), BMS (Inst), MSD (Inst), Amgen (Inst), Lilly (Inst), AstraZeneca (Inst), Pfizer (Inst), Illumina (Inst), Merck Serono (Inst), Novartis (Inst), Biodexis (Inst), Boehringer Ingelheim (Inst), Iovance Biotherapeutics (Inst), Phosplatin Therapeutics (Inst)

**Travel, Accommodations, Expenses:** Roche, Bristol Myers Squibb, MSD, Sanofi, Incyte

Uncompensated Relationships: Journal of Thoracic Oncology, ESMO, European Thoracic Oncology Platform (ETOP), Annals of Oncology (I)

Kimberly Rieger-Christ

**Research Funding:** Veracyte, Ravel, Grail, Exact Sciences, Nucleix

Timothy Robinson

**Travel, Accommodations, Expenses:** Daiichi Sankyo/Lilly

Emanuela Romano

**Consulting or Advisory Role:** AstraZeneca/MedImmune (Inst), Bristol Myers Squibb (Inst), Roche/Genentech (Inst)

**Research Funding:** Bristol Myers Squibb, Amgen

**Travel, Accommodations, Expenses:** AstraZeneca/MedImmune, Bristol Myers Squibb, Roche

Michael Rowe

**Honoraria:** MSD

**Speakers’ Bureau:** Servier

**Travel, Accommodations, Expenses:** Astellas Pharma

Anne Thomas

**Consulting or Advisory Role:** BMS

**Speakers’ Bureau:** Bristol Myers Squibb

**Expert Testimony:** BMS

Lance Turtle

**Speakers’ Bureau:** Eisai (Inst)

David Viñal

**Speakers’ Bureau:** Servier

**Travel, Accommodations, Expenses:** Merck

Caroline Wilson

**Consulting or Advisory Role:** Roche, Pfizer

Carlo Palmieri

**Honoraria:** Pfizer

**Consulting or Advisory Role:** Pfizer, Daiichi-Sankyo, Lilly, Novartis, Seattle Genetics

**Research Funding:** Pfizer, Daiichi-Sankyo

**Travel, Accommodations, Expenses:** Roche

Donal Landers

**Employment:** AstraZeneca, Athenex

**Leadership:** DeLondra Oncology

**Stock and Other Ownership Interests:** DeLondra Oncology

**Research Funding:** AstraZeneca (Inst)

Timothy Cooksley

**Honoraria:** Bristol Myers Squibb Foundation

Caroline Dive

**Consulting or Advisory Role:** Biocartis, Merck, AstraZeneca, GRAIL, Boehringer Ingelheim

**Research Funding:** AstraZeneca, Astex Pharmaceuticals, Bioven, Amgen, Carrick Therapeutics, Merck, Taiho Oncology, GlaxoSmithKline, Bayer, Boehringer Ingelheim, Roche, BMS, Novartis, Celgene, Epigenex Therapeutics, Amgen, Menarini, Clearbridge Biomedics, Thermo Fisher Scientific, NeomEd

André Freitas

**Research Funding:** AstraZeneca (Inst)

Anne C. Armstrong

**Stock and Other Ownership Interests:** AstraZeneca (I)

**Consulting or Advisory Role:** Gilead Sciences, MSD
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### ESMO COCARE LIST OF AUTHORS

| Author            | Affiliation                                                                                     |
|-------------------|-----------------------------------------------------------------------------------------------|
| Abigail Temple    | The Royal Marsden NHS Foundation Trust, London, United Kingdom                                 |
| Natasha Duperray  | The Royal Marsden NHS Foundation Trust, London, United Kingdom                                 |
| Aasfa Nadeem      | The Royal Marsden NHS Foundation Trust, London, United Kingdom                                 |
| Olivia Chudy      | The Royal Marsden NHS Foundation Trust, London, United Kingdom                                 |
| Vlad Croitoru     | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Diana Bogdan      | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Irina Sandra      | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Madalina Soanca   | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Ana Maria Tirdea  | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Irina Cazacu      | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Miron Monica      | Medical Oncology Department, Fundeni Clinical Institute, Bucharest, Romania                     |
| Marina Vitorino   | Hospital Professor Doutor Fernando Fonseca, Lisbon, Portugal                                   |
| Salah Khalil      | South Egypt Cancer Institute, Assiut, Egypt                                                    |
| Snežana Šušnjar    | Department of medical oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia |
| Widyanti Soewoto  | Oncology Division, Department of Surgery, Sebelas Maret University, Surakarta, Indonesia        |
| Ana Cardeña       | Hospital Universitario Fundación Alcorcín, Alcorcín, Spain                                    |
| Mohamed Djerouni  | Department of Oncology, Dr Saadane Hospital, Algeria                                           |
| Vittorio Fusco     | Oncology Unit, Azienda Ospedaliera SS Antonio e Biagio e C.Arigno                               |
| Teresa Alonso Gordo| Hospital Universitario Ramón y Cajal, Madrid, Spain                                              |

(Continued in next column)