https://doi.org/10.31925/farmacia.2026.1.23 **ORIGINAL ARTICLE**

RISK STRATIFICATION OF COVID-19 SEVERITY IN CANCER PATIENTS USING MACHINE LEARNING ALGORITHMS

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Abstract

This study aimed to explore the use of machine learning models for classifying COVID-19 severity in patients with cancer, based on clinical, radiological, and demographic data collected at hospital admission. A cohort of 235 oncological patients with confirmed SARS-CoV-2 infection was analysed using a four-category severity framework (mild, moderate, severe, critical). Several machine learning approaches were evaluated, including linear, non-linear, and ensemble-based models within an error-correcting output codes (ECOC) framework. Performance was assessed using accuracy and one-*vs*-rest ROC analysis with area under the curve (AUC). Internal validation was performed through cross-validation. Model performance varied across approaches and severity classes. Linear methods showed limited separation between neighbouring categories, while non-linear and ensemble models provided more consistent identification of advanced disease. Ensemble bagging achieved the most stable performance across classes, whereas RUSBoost showed less consistent results for intermediate stages. Machine learning models may assist in severity stratification in oncological COVID-19 patients; however, results require cautious interpretation and external validation before clinical implementation.

Rezumat

Acest studiu a evaluat utilizarea modelelor de machine learning pentru clasificarea severității COVID-19 la pacienții oncologici, pe baza datelor clinice, radiologice și demografice disponibile la internare. Au fost analizați 235 de pacienți cu neoplazii și infecție confirmată cu SARS-CoV-2, utilizând un sistem de clasificare în patru categorii de severitate (ușoară, moderată, severă, critică). Au fost testate mai multe tipuri de modele, incluzând metode liniare, non-liniare și ansambluri, integrate într-un cadru ECOC (error-correcting output codes). Performanța a fost evaluată prin acuratețe și analiză ROC one-*vs*-rest, exprimată prin aria de sub curbă (AUC). Validarea a fost realizată prin cross-validare internă. Performanța a variat în funcție de model și categorie de severitate. Metodele liniare au prezentat dificultăți în separarea claselor adiacente, în timp ce modelele non-liniare și cele de tip ansamblu au identificat mai constant formele severe și critice. Modelul bazat pe bagging a arătat cea mai stabilă performanță globală. Modelele de machine learning pot contribui la stratificarea riscului, însă rezultatele necesită validare externă înainte de aplicarea clinică.

Keywords: machine learning, oncological, covid-19, predictive models

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 and quickly progressed into a global health crisis. The rapid rise in cases overwhelmed healthcare systems and emphasised the importance of recognising patients at risk of severe disease at an early stage. Clinical presentation varies widely, from mild symptoms to severe respiratory failure requiring intensive care or mechanical ventilation, and in some cases leading to death. Differences in symptom

profile and laboratory findings have been widely documented (1, 2).

High-risk groups, such as elderly individuals and patients with pre-existing conditions, including cancer, are especially vulnerable. In these populations, the risk of complications and mortality is substantially higher, underscoring the importance of tailored clinical management strategies (3). Identifying oncology patients who are more likely to deteriorate may help clinicians prioritise monitoring and allocate resources more appropriately in routine care (2).

In recent years, artificial intelligence (AI) and machine learning (ML) have gained increasing attention in healthcare as tools for analysing complex clinical data and supporting medical decision-making. ML techniques can capture non-linear patterns that are difficult to detect using traditional approaches, and have been applied in areas such as oncology, infectious diseases, and other medical domains (4-6) Advances in computing power and the expansion of digital health records have facilitated the development of predictive models, although their integration into clinical practice still requires thorough validation and transparent reporting (7-9).

In oncology, ML techniques are increasingly used for risk stratification, outcome prediction, diagnostic assistance, and imaging and pathological data (10-12). These applications illustrate the growing interest in data-driven methods for managing clinically complex situations, including the care of cancer patients during the COVID-19 pandemic.

Against this background, the present study aimed to develop a predictive model based on ML using clinical, radiological, and demographic data from cancer patients hospitalised with COVID-19. The aim is to explore whether machine learning could help better understand severity patterns at admission, without replacing clinical judgement.

Materials and Methods

Data collection

This study utilised a dataset comprising 237 cancer patients with different histopathological types of malignant neoplasms (*e.g.*, gynaecologic, lung, gastrointestinal, hepatobiliary, prostate, breast, and blood cancers) diagnosed with COVID-19, to predict the severity of their disease. They were admitted between March 2020 and July 2023 to the coronavirus care unit of the "Victor Babeş" Infectious Disease Hospital in Craiova, Romania. Admissions were based on the World Health Organization (WHO) criteria for COVID-19 diagnosis and management (13).

The selected patients were undergoing treatment for an active oncological condition at the time of hospitalisation. The study excluded individuals with benign or borderline tumours, as well as patients whose cancer was considered cured and who had no significant cancer-related health complications, as their prognosis closely resembles that of non-cancer patients. Patients with malignant tumours were not excluded on the basis of tumour type, location, stage, or treatment approach, to capture the heterogeneity of this population.

Of the initial cohort, 235 patients were included in the final machine learning analysis due to the complete availability of severity classification data.

Severity classification

Disease severity was defined a priori based on clinical, physiological, and radiological criteria recorded during hospitalisation and independently of the machine learning modelling process. Patients were stratified into four severity categories reflecting clinically meaningful differences in COVID-19 progression: Class 0 (Mild): patients with non-critical symptoms and signs, no requirement for supplemental oxygen, and no radiographic evidence of pneumonia; Class 1 (Moderate): patients presenting with non-critical symptoms, but with radiological evidence of pneumonia, and not requiring advanced oxygen support; Class 2 (Severe): patients with severe clinical presentation, including respiratory distress, oxygen saturation below 93% (SpO_2 < 93%), and/or abnormal blood gas values (PaO_2 < 60 mmHg and/or $PaCO_2$ > 50 mmHg). Patients in this group usually required advanced oxygen support but were not classified as critical; Class 3 (Critical): patients who required admission to intensive care, invasive mechanical ventilation, or who developed life-threatening COVID-19 complications.

The distribution of patients across severity categories was as follows: Class 0, n = 14; Class 1, n = 51; Class 2, n = 94; and Class 3, n = 76, resulting in an imbalanced class distribution.

Predictive variables and outcome definition

Machine learning models were trained using demographic, clinical, and laboratory variables available at or near the time of hospital admission. Variables that directly defined disease severity categories-such as ICU admission and invasive mechanical ventilation-were used exclusively for outcome classification and were not included as predictive features in the machine learning models, in order to avoid outcome leakage.

Additional clinical factors, including obesity and the presence of systemic inflammatory response syndrome (SIRS), were considered as baseline descriptors of patient status. Radiological findings were used to support clinical characterisation, where available, but were not used to redefine severity classes during model training.

Model development and validation

Several supervised ML models were used to classify COVID-19 severity in patients with cancer. The following algorithms were tested within an Error-

Correcting Output Codes (ECOC) multi-class framework: Support Vector Machines (SVM), Decision Trees, K-Nearest Neighbours (KNN), Naive Bayes, and Discriminant Analysis. In addition, ensemble-based methods were assessed, including standard ensemble bagging and RUSBoost ensemble learning, incorporating random undersampling.

The ECOC framework was employed to address the four-class classification problem by breaking it down into a series of binary comparisons. The final class assignment was obtained by combining the outputs of these classifiers through the standard ECOC decoding procedure. All models were implemented using the MATLAB Statistics and Machine Learning Toolbox.

Model performance was evaluated using 10-fold cross-validation, with the dataset repeatedly split into training and testing sets to minimise overfitting. Performance was evaluated using overall accuracy and one-*vs*-rest receiver operating characteristic (ROC) curves, with results reported as area under the curve (AUC) values. Class-level performance patterns were further examined using confusion matrices and ROC curve analysis.

The variables were used in their original form, without scaling or reduction procedures. While this reflects real-world clinical data, it may have influenced the performance of distance-based classifiers.

Ethical considerations

Written informed consent was obtained from all participants before inclusion in the study. The research was carried out in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of "Victor Babeș" Infectious Disease Hospital in Craiova on 24.05.2021, (applicable between 24.05.2021 - 24.05.2026). In 2024, due to changes in the composition of the team, another ethics committee approval was requested and issued on 31.12.2024 (applicable between 01.06.2024 - 31.12.2028) by the same committee.

This study explored the feasibility of using machine learning models to classify COVID-19 severity in patients with cancer within a four-category clinical framework. The focus was on comparing model behaviour under internal validation condition.

Results and Discussion

The final analysis included 235 patients with cancer and confirmed SARS-CoV-2 infection for whom complete severity classification data were available. Model performance was evaluated using this cohort to examine differences in predicted COVID-19 severity across clinical categories.

ECOC with Discriminant Analysis

Model performance for the ECOC framework with Discriminant Analysis was examined through the confusion matrix and one-*vs*-rest ROC curves (Figures 1 and 2). The results indicated moderate separation between severity categories.

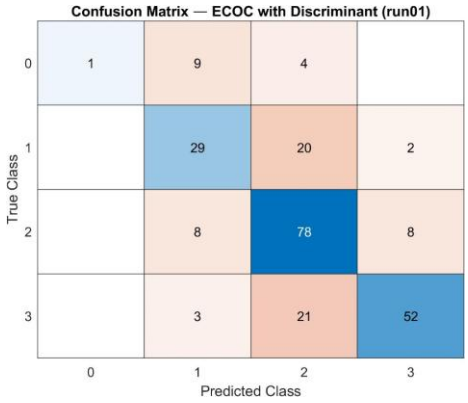

Figure 1.
Confusion matrix illustrating the performance of the ECOC–Discriminant Analysis classification model

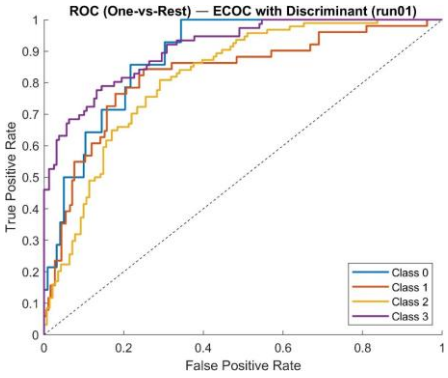

Figure 2.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–Discriminant Analysis model

Classification accuracy was highest for Class 2, with 78 correctly identified cases, though some cases were still reassigned to neighbouring categories. In contrast, Class 0 showed limited discrimination, with only one correct classification and most cases assigned to higher severity groups. Moderate and severe cases frequently overlapped, making clear separation difficult. For Class 3, 52 cases were correctly identified, but confusion with severe disease persisted.

ROC analysis was consistent with these findings. Discrimination was strongest for advanced disease stages and more modest for mild and moderate categories. The ECOC–Discriminant Analysis approach showed moderate discrimination and limited separation between adjacent severity categories.

ECOC with KNN

When combined with KNN, the ECOC framework produced uneven results across severity classes (Figures 3 and 4).

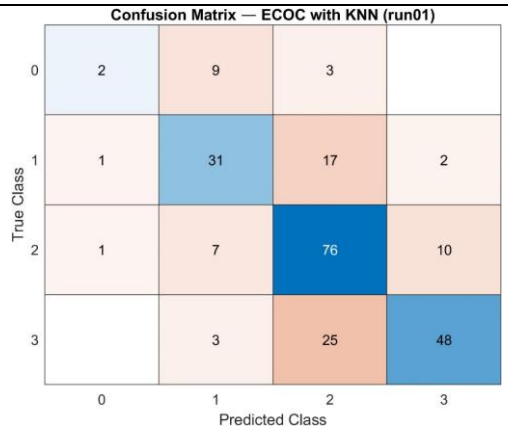

Figure 3.
Confusion matrix illustrating the performance of the ECOC–KNN classification model

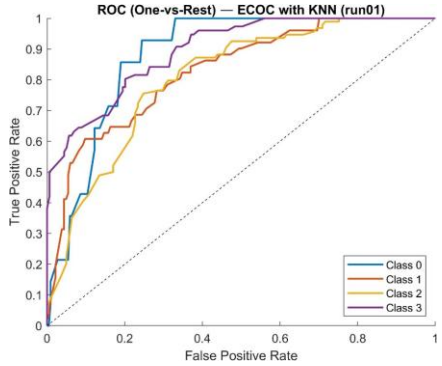

Figure 4.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–KNN model

Performance was strongest for Class 2, with 76 correctly classified cases, although confusion with Class 3 remained evident. A total of 48 critical cases were correctly classified; some were labelled as severe. The separation between severe and critical disease was therefore incomplete.

Results were less consistent for intermediate and mild disease. In moderate disease, 31 cases were classified correctly, although many were reassigned to the severe category. Only two mild cases were classified correctly; most were assigned to higher severity categories.

The ECOC–KNN model was more consistent in identifying advanced disease than in separating earlier stages**.**

ECOC with Linear classifier

The ECOC framework combined with a linear classifier showed limited discrimination across severity classes (Figures 5 and 6).

In Class 2, 71 patients were correctly classified, although errors were common in both directions, with cases shifting towards moderate and critical categories. For critical disease, 53 cases were predicted correctly, but overlap with severe presentations remained evident.

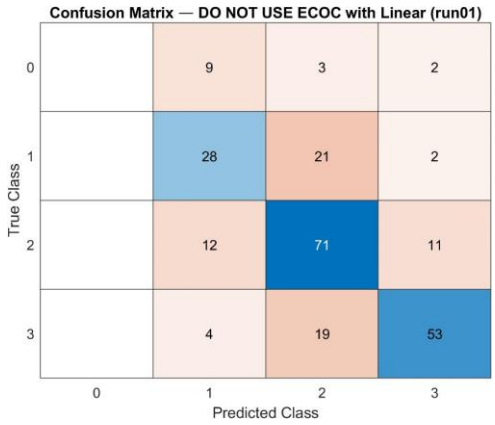

Figure 5.
Confusion matrix illustrating the performance of the ECOC model combined with a linear classifier

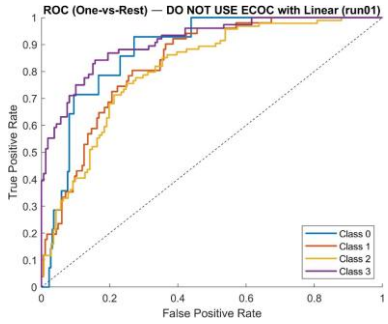

Figure 6.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC model using a linear classifier

Twenty-eight moderate cases were correctly classified; many were recorded as severe. Mild cases were frequently assigned to higher severity levels.

ROC analysis indicated discrimination above chance level for all classes, although separation remained modest, particularly for mild and moderate disease. Generally, the ECOC–linear model provided only moderate performance and was less effective in separating adjacent severity categories within this cohort.

ECOC with SVM

The ECOC framework combined with a SVM classifier showed improved and more balanced performance across severity classes compared with linear models (Figures 7 and 8).

The highest number of correct predictions was observed in Class 2, where 87 cases were classified appropriately, with only limited reassignment to neighbouring categories. In Class 3, 56 cases were correctly predicted, although some overlap with severe disease remained. In moderate disease, 36 cases were classified correctly, although several were recorded as severe. Only six mild cases were correctly identified.

ROC curves showed clearer separation for severe and critical disease, whereas mild and moderate stages were less distinctly separated. The ECOC–SVM model provided more consistent separation of advanced disease stages, although differentiation between neighbouring categories was still incomplete.

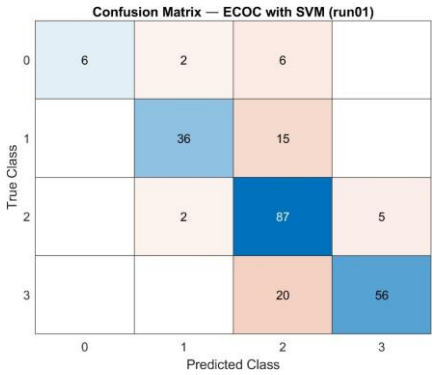

Figure 7.
Confusion matrix illustrating the performance of the ECOC–SVM classification model

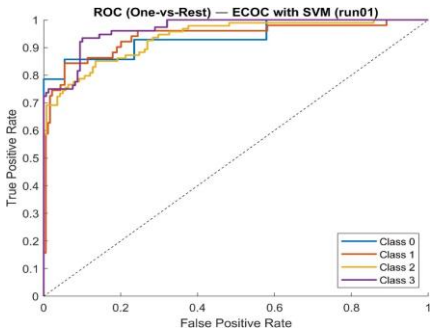

Figure 8.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–SVM model

ECOC with Decision Tree

The ECOC framework combined with a Decision Tree classifier showed moderate and relatively balanced performance across severity classes (Figures 9 and 10).

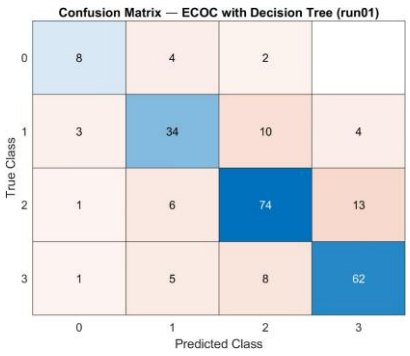

Figure 9.
Confusion matrix illustrating the performance of the ECOC–Decision Tree classification model

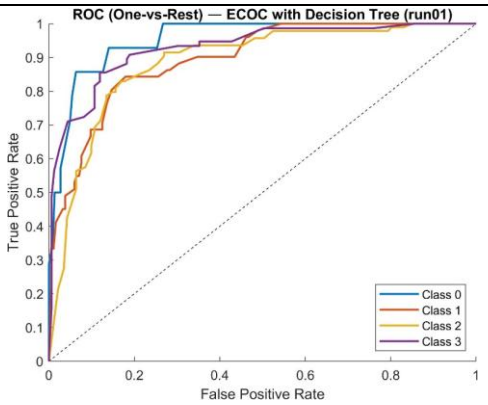

Figure 10.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–Decision Tree model

Critical disease was recognised most consistently, with 62 correct predictions and limited confusion with severe cases. In comparison, 74 cases of severe disease were correctly classified, although some overlap with neighbouring categories persisted.

For moderate presentations, 34 predictions were accurate, while several cases shifted either towards milder or more advanced stages. Eight mild cases were classified correctly, while several were assigned to higher severity categories.

The ROC curves supported these findings, showing clearer separation for severe and critical disease, whereas mild and moderate classes were less distinctly separated. The ECOC–Decision Tree model, therefore, provided reasonable class separation, although differentiation between neighbouring severity stages remained incomplete.

ECOC with Ensemble Bagging

The ECOC framework combined with ensemble bagging showed the strongest overall performance among the evaluated models (Figures 11 and 12).

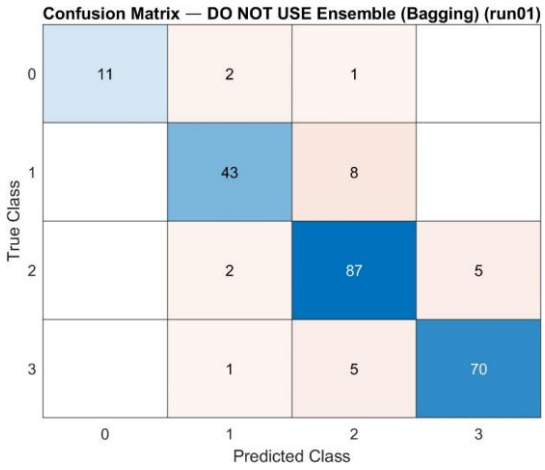

Figure 11.
Confusion matrix illustrating the performance of the ECOC–ensemble bagging classification model

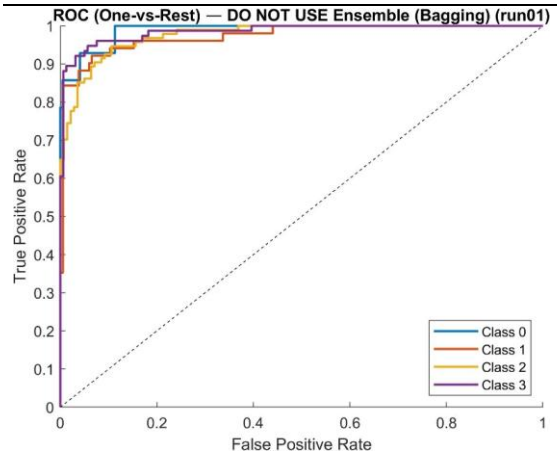

Figure 12.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–ensemble bagging model

High classification accuracy was observed across all severity classes. Correct classification was achieved in 87 severe and 70 critical cases. Moderate presentations were correctly classified in 43 instances, while 11 mild cases were accurately identified, the highest count for this category among the tested models.

However, these findings should be interpreted cautiously, given the single-centre dataset and reliance on internal cross-validation. External validation would be required to confirm the robustness of this approach.

ECOC with RUSBoost ensemble

The ECOC framework combined with RUSBoost showed variable performance across severity classes (Figures 13 and 14).

Critical disease showed relatively strong results, with 71 correct predictions and limited misassignment. Fifty severe cases were classified correctly, although some were recorded as critical. Only 23 moderate cases were correctly identified, with many labelled as mild. All mild cases were classified correctly, but this result should be viewed with caution, given the small sample size.

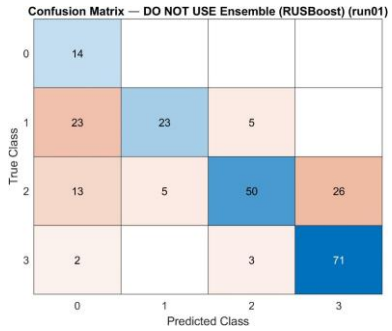

Figure 13.
Confusion matrix illustrating the performance of the ECOC–RUSBoost ensemble classification model

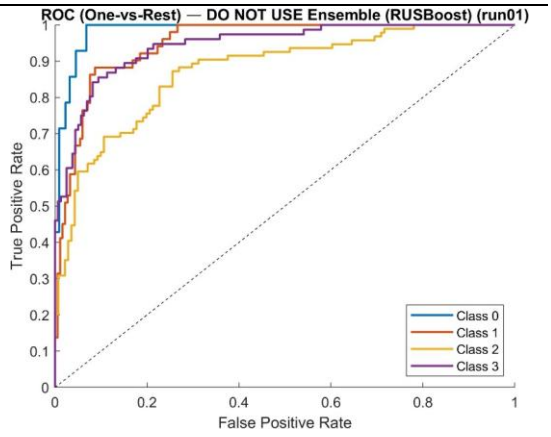

Figure 14.
One-*vs*-rest ROC curves illustrating class-level discrimination for the ECOC–RUSBoost ensemble model

The ROC curves followed a similar pattern, with clearer separation for critical and mild disease and less distinct discrimination for intermediate stages. Overall, the ECOC–RUSBoost approach produced uneven results across severity categories and did not consistently improve classification compared with other models.

Comparative performance across models

When the models were viewed side by side, differences in behaviour became apparent. Linear approaches struggled most with separating neighbouring severity categories, particularly between moderate and severe disease. This suggests that simple decision boundaries may not reflect the way severity presents clinically in this cohort.

Non-linear models appeared to manage advanced disease more consistently, although separation between all severity stages was not complete. KNN and SVM performed more steadily for severe and critical cases, while moderate presentations remained harder to distinguish. Decision Trees showed relatively even results, but without clear separation between neighbouring categories.

Within the ensemble approaches, bagging provided the most stable results across severity groups. RUSBoost showed greater variation, particularly for moderate and severe disease.

These findings should be interpreted taking the study design into account. The limited sample size and the use of internal cross-validation may have influenced the reported performance. For this reason, the models should be viewed as exploratory and require confirmation in independent cohorts before clinical application.

COVID-19 presents with a wide range of clinical manifestations, from mild respiratory symptoms to severe acute respiratory syndrome and multi-organ failure. In patients with cancer, progression can be rapid and less predictable, particularly when

treatment is delayed or complications arise (14, 15). For this reason, early identification of patients at higher risk remains an important part of clinical management.

Patients with cancer are at increased risk of severe COVID-19 and higher mortality. This increased risk is linked to immune suppression resulting either from the malignancy itself or from treatments such as chemotherapy and radiotherapy, both of which can reduce the body's response to SARS-CoV-2.

While certain anticancer therapies have been investigated for possible antiviral effects, balancing cancer treatment during active infection presents practical challenges in routine clinical care. Cytotoxic therapies, such as those that cause leukopenia, increase the susceptibility to infections. This shows how important are the continuous observation and adaptable strategies are to address both conditions effectively (16, 17). Disease severity in oncology patients can be difficult to predict, given the influence of multiple clinical, biological, and treatment-related factors. Prior work in oncology suggests that combining clinical and biochemical information may improve the evaluation of disease progression and treatment-related risks (18).

It is very hard to predict outcomes in cancer patients because of the uncertain risk factors that are specific to cancer. Physicians must carefully manage the two risks posed by untreated malignancies: the cancer itself and the potential for severe infections, triggered by certain anti-cancer therapies (19).

Thanks to the rise of digital technologies and big data, AI algorithms have become an important part of healthcare systems, outperforming traditional statistical methods. These improvements make it possible to do a more sophisticated analysis by using large datasets to provide information that classical methods cannot achieve (20, 21). ML, a key element of AI, uses algorithms that improve with data. Model performance generally improves with larger and higher-quality datasets. In oncology research, such approaches have been used to analyse large clinical datasets to support the assessment of disease outcomes and therapeutic decision-making (22).

These algorithms update their parameters as they learn from previous errors, rather than following fixed rules. It changes and improves its predictions based on this feedback. This approach is different from traditional programming, which only follows predefined rules and logical structures, such as "if-else" statements. ML models do not depend solely on predefined rules, but adjust their behaviour based on patterns observed in the data. This flexibility makes them suited to problems characterised by complexity and variability, where traditional algorithmic logic may be insufficient (23, 24).

ML algorithms have shown significant potential in various aspects of COVID-19 management. They have been used to estimate disease severity, ICU admission, and mortality risk, while also helping determine how treatments work and supporting the discovery of new drugs. Deep learning models have further supported these efforts, contributing to outbreak prediction, tracking virus spread, and supporting vaccine and drug research (25-27).

Previous studies have applied machine learning models to estimate COVID-19 outcomes, drawing on clinical and demographic information such as vital signs, laboratory findings, medication history, and comorbidities (28-30).

Operating these kinds of parameters, another study concluded that the developed and validated suite of risk assessment tools predicts poor outcomes in COVID-19 patients based on routinely collected hospital admission data. These tools performed well in identifying low-risk patients and showed promise for identifying high-risk individuals, though careful consideration of false positives and negatives is necessary. These methods provide a rapid, data-driven way to guide prognosis, make the best use of resources, determine treatment decisions, and support enrollment in clinical trials. However, more testing in clinical situations is needed for further validation. The approaches could also be adapted for future viral outbreaks, which would improve readiness and care strategies (31).

Research in tumour biology and treatment response suggests that disease behaviour depends on several interacting factors. Similarly, in our analysis, models that were able to capture such interactions tended to perform better than those based on simpler statistical assumptions (32). Systemic diseases are known to produce objective functional changes that may not be evident clinically, reflecting the complex interactions underlying disease severity (33).

ML algorithms differ in their ability to predict outcomes across classes. Their suitability may vary depending on the task. In addition, performance is influenced by the volume and quality of training data. Model performance often improves with larger datasets, which can enhance the stability of predictions and highlight the value of high-quality data in ML applications (34, 35).

In this study, we compared several machine learning approaches to assess how well they classified COVID-19 severity in patients with cancer. Rather than focusing on a single algorithm, different modelling strategies were evaluated to better understand how they respond to a heterogeneous and imbalanced clinical dataset.

The models differed in their performance. Linear approaches had difficulty separating adjacent severity stages, whereas non-linear methods identified severe and critical cases more reliably. SVM and ensemble techniques appeared less

influenced by changes in data partitioning during cross-validation.

Despite this, the separation between severity categories was not uniform across all classes. Severe and critical cases were identified more consistently than mild or moderate presentations, possibly because of overlapping clinical features and the imbalanced class distribution.

Among the ensemble models, bagging showed more stable results across severity groups. RUSBoost varied more, particularly for intermediate stages.

Although non-linear and ensemble approaches tended to yield stronger results in this cohort, these findings require careful interpretation. The single-centre design and reliance on internal validation limit how widely these findings can be applied. Validation in larger and independent cohorts is therefore needed.

Conclusions

This study provides an exploratory assessment of machine learning methods for classifying COVID-19 severity in patients with cancer within a four-category clinical framework. This analysis shows that model behaviour differed according to methodological choices and the characteristics of the dataset, particularly within a clinically heterogeneous cohort.

In practical terms, these results should be interpreted with caution. The models do not provide a definitive prediction tool, and external validation in independent cohorts is required before considering wider clinical use.

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Not applicable.

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Not applicable.

Availability of data and materials

The data generated in the present study are included in the figures of this article.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of "Victor Babeș" Infectious Disease Hospital in Craiova (no. 6290/24.05.2021 for the 24.05.2021-24.05.2026 time frame and later revised on 18828/31.12.2024 for the 01.06.2024-31.12.2028 time frame). The secondary approval was issued upon request because of changes in the composition of the team working on the project. Both approvals are valid and applicable until their expiration date. Informed consent was obtained from all subjects involved in the study.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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