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MACHINE LEARNING–BASED PREDICTION OF CHEMOTHERAPY TOXICITY IN COLORECTAL CANCER: A PERSONALIZED RISK STRATIFICATION APPROACH

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ABSTRACT

Background: Machine learning models learn feature connections from data to learn general behavior. The goal was to build a prediction model to identify the percentage of patients with colorectal cancer who are at increased risk of chemotherapy-induced toxicity and to determine the factors that affect treatment-related side effects. Methods: Ninety-five features of the health of 74 patients prior to the first round of chemotherapy were chosen for training data, using general toxicity as the predictor. Following data processing, Random Forest models were constructed to balance accuracy and interpretability. Results: We developed a machine learning predictor that ranks numerical and categorical features for toxicity. Conclusions: The use of artificial intelligence to predict and manage toxicities in the treatment of colorectal cancer is a major step forward in the direction of more individualized and precise medical care.

KEYWORDS: Metastatic Colorectal Cancer; Artificial Intelligence; Prediction Model; Chemotherapy Toxicity.

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1. INTRODUCTION

Colorectal cancer (CRC) is a major malignancy around the world. Current recommendations include chemotherapy as adjuvant therapy for select stage II and most stage III tumors and as a backbone systemic treatment for stage IV. In any case, it can have a significant impact on progression-free and overall survival, with adverse events to be taken into consideration. The game changed with the licensing of two monoclonal antibodies against the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) for the first-line therapy of metastatic CRC (mCRC). The toxicity profiles of targeted therapies are different (rash, diarrhea, hypertension, hypothyroidism, proteinuria, depigmentation and hepatotoxicity) but the median overall survival of mCRC patients has exceeded 30 months [1] These toxicities have correlated with therapeutic responses.

Adjuvant chemotherapy is given to >21% of stage II CRC patients, 60% of stage III patients, and nearly all stage IV patients with good performance status. The present experiment, which is based on other tools such as "ColonPrediscores" (adapted for elderly patients) that consider polychemotherapy, hypoalbuminemia, C-reactive protein, ECOG PS, metastatic disease, age, alkaline phosphatase, and sex, justifies the need to predict adverse outcomes in this large cohort (especially during the first cycle of chemotherapy). These features were independent predictors [2] in developing our model.

AI is a major change in the management and treatment of colorectal cancer towards more personalized and accurate medical care. Yang et al. reported that AI could be used for treatment regimen selection and patient prognosis evaluation, which is a significant advancement in the field.

The prediction of patient survival has been improved by AI methods to find microenvironment indicators in histology images. With this method you can get a more precise prediction by observing the behavior and probable consequences of the cancer. AI can identify high-risk individuals for liver metastases in early-stage (T1) colorectal cancer patients at diagnosis using machine learning algorithms. Finding it early helps doctors develop better ways to treat the disease and may even increase the chances of survival. AI is also applied for therapeutics decision-making besides diagnostics and prognostics. AI algorithms can provide patient-specific treatment approaches with massive information combined and patterns that humans could miss. This includes identifying whether patients might benefit from certain chemotherapy regimens, targeted medicines, or surgical procedures, improving therapeutic efficacy [3].

Machine learning (ML) and artificial intelligence (AI) have been employed in the last decade to predict systemic cancer treatment issues. ML and AI can help healthcare professionals to adjust treatment programs and lower severe toxicities by analyzing datasets and integrating many factors. AI-driven models may have the ability to learn continuously from real-world input to improve signature performance. The FDA has proposed a regulatory framework for AI-based medical devices [4].

In our work we used different modeling tools to explore whether genetic backgrounds or other patient factors could predict treatment related toxicity, contributing to the momentum of using AI in the management of colorectal cancer. This research is important for side effect management of cytotoxic therapy. Based on recent advances in AI for prediction of survival and metastasis, we hypothesized that the traits of patients influence their sensitivity to side effects of cancer therapy. We want to translate this knowledge to the effect of AI on colorectal cancer treatment options that take into account genetics and patient specific characteristics.

2. MATERIALS AND METHODS

A. Study Endpoint

The main aim of the study was to develop a machine-learning model to predict toxicity after the first chemotherapy treatment of patients with colorectal cancer. This effort was directed to go beyond the adjuvant or metastatic treatment scenario to ensure the broad applicability and help control and reduce the chemotherapy side effects [5].

B. Patient Data Preprocessing

The dataset contains 74 patients with 95 initial attributes. The categorical features were one-hot encoded and separated by type into categorical and numeric features. This produced 140 characteristics. Toxicity in 57 patients (77.0 %). At least 1 adverse event occurred in toxic patients. Toxicity was considered present (yes) if any grade 1 event was reported. The predictor was overall toxicity and we trained on 95 parameters that show how the patient is doing prior to the first chemotherapy cycle (Figure 1) [6].

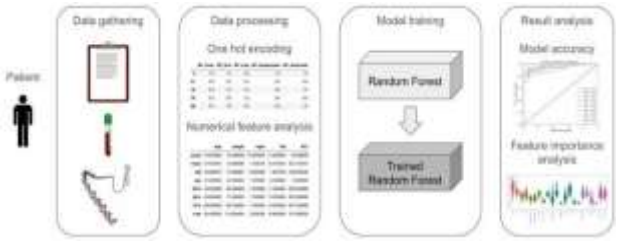


Figure 1. Data processing framework structure chart.

C. Study Population

Our study included 74 colorectal cancer patients treated consecutively in the Regional Institute of Oncology Iasi, Romania, between January 2018 and December 2019, who met the inclusion and exclusion criteria [7].

Main Inclusion Criteria

- Age over 18 years;
- ECOG = 0, 1 or 2;
- Pathology confirmed colon or rectal cancer;
- TNM Stage II, III or IV;
- The tissue sample is primed for genetic testing.
- At least one course of first line chemotherapy;
- Evaluation of toxicity and late adverse events after the first cycle of treatment.
- Investigator must demonstrate adequate bone marrow function to allow for local chemotherapy protocols.

Main Exclusion Criteria

- Prior chemotherapy for colorectal or other malignancies;
- Active infections, including TB, hepatitis B, C and HIV;
- No follow-up, makes it difficult to monitor adverse effects after chemotherapy.

D. Treatment Regimens and Associated Toxicity

We only included patients who had received at least one round of chemotherapy and who had been assessed for toxicity. Patients may have received biologic therapy for metastatic disease according to all-RAS and BRAF mutations. Some patients received capecitabine or 5-fluorouracil monotherapy or doublet treatment (oxaliplatin or irinotecan + fluoropyrimidine backbone) according to international recommendations. At the time the study started, immunotherapy was not a standard first-line treatment for metastatic disease. We included MSI or MMR status in our analysis where available, although testing was optional [8].

Serum chemistry, hematological and coagulation tests were performed and evaluated for the study after the first chemotherapy cycle. The regimen protocol dictated whether exams were done 14 or 21 days after treatment. The primary endpoint of this trial was safety and assessment of treatment efficacy was optional. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria 5.0 [9].

E. Machine Learning Models

Problem was modeled as a categorical predictor. The research included several patient characteristics, therefore we used random forest (RF) models . A Random Forest model is created using sub-datasets. A forest of decision trees (DTs) is built for each sub dataset. RF builds a lot of DTs that are more robust and can generalize better on the dataset.

It is also good that RF can look at a small number of features per tree trained every iteration (we used a maximum of the square root of a total number of features). This method is used to overcome the “curse of dimensionality” when the number of characteristics is larger than the number of patients. When classifying a new sample, each DT in the RF votes and contributes to the final decision of the forest. The classification is based on the maximum score [10].

For model training, a dataset was built with 95 features and one prediction column that showed true if there was any toxicity and false if there was no toxicity. The class weight is set to “balanced” because of the variation in toxicity cases. We trained 100 trees per model with a max depth of 2.

F. Statistical Analysis

Statistical analysis was performed using SPSS v25.0 (SPSS, Inc., Chicago, IL, USA) The comparison of quantitative and ordinal variables was performed with Mann-Whitney U test. The comparison of groups was performed with Chi-square test. One-way ANOVA was used for comparisons between the three groups. Statistical significance was set at a p-value of < 0.05. Statistical analysis was performed using Python (version 3.10.9). We install Python packages such as pandas, sklearn, seaborn and matplotlib. Demographic profiles of the two subgroups were compared by Student's t-test or Pearson chi-square.

3. RESULTS

A. Patients’ Characteristics

Our research was based on characteristics from 74 patients. The study group was composed of 68%

female and 39% male patients. The median age in the study group was 63; 53.8% of patients were 65 or older.Liver metastases were the most common (59.6%) followed by peritoneal (34.6%). In our analysis, the most common first line treatment was Capecitabine+Oxaliplatin (CAPOX), followed by folinicacid, FOLFOX and Capecitabine monotherapy (Table 1) [11].

Table 1. Patient Demographics.

Category	Variable	Sub-category	No. of Patients (%)
Demographics	Total Patients	—	74 (100%)
	Sex	Male	35 (47.3%)
		Female	39 (52.7%)
	Age	Median	63 years
		< 65 years	48 (46.2%)
		≥ 65 years	56 (53.8%)
	Smoking Status	Non-smokers	94 (94.1%)
		Smokers	6 (5.8%)
	ECOG PS	0	4.8%
Tumor Characteristics	Primary Location	Left colon	82 (78.8%)
		Right colon	22 (21.1%)
	Metastasis	Liver	62 (59.6%)
		Peritoneal	34.6%
		Lung	18 (17.4%)
		Other sites	9 (8.7%)
	Tumor Type	Ulcerated	84 (80.8%)
		Mucinous	15.4%
		Signet ring	3.8%
	Tumor Grade	G1	8 (7.7%)
		G2	86 (82.7%)
		G3	10 (9.6%)
Treatment	Primary Tumor Surgery	Yes	71 (68.3%)
		No	33 (31.7%)
	Metastases Surgery	Yes	12 (11.5%)
		No	92 (88.5%)
	Chemotherapy	FOLFOX	32 (30.8%)
		CAPOX	45 (43.3%)
		FOLFIRI	10 (9.6%)
		PEIRI	2 (1.9%)
		FUFOL	2 (1.9%)
		Capecitabine	13 (12.5%)
	Biological Therapy	Bevacizumab	55 (52.8%)
		Cetuximab	16 (15.4%)
		Panitumumab	6 (5.8%)
		None	26 (25%)
Genetic Mutations	KRAS	Exon 2	42 (40.4%)
		Exon 3	3 (2.9%)
		Exon 4	2 (1.9%)
	NRAS	Exon 2	1 (1%)
		Exon 3	4 (3.8%)
		Exon 4	0 (0%)
	BRAF	Exon 15	3 (2.9%)
	PIK3CA	Exon 20	4 (3.8%)
	TP53	Exon 4	5 (4.8%)
		Exon 5	23 (22.1%)
		Exon 6	4 (3.8%)
		Exon 7	19 (18.2%)
		Exon 8	18 (17.3%)
		Exon 9	3 (2.8%)
		Exon 10	—
		Wild Type	52 (50%)
Molecular Status	RAS/BRAF	Wild Type	49 (47.1%)
		Mutated	55 (52.9%)
	Other Marker	Yes	20 (19.2%)
		No	84 (80.8%)

B. Patients' Toxicity Profile

Treatment led to a decrease in white blood cells, neutrophils, neutrophil to lymphocyte ratio and platelets.GGT, creatinine and LDH levels were significantly increased as shown in Figure 2 and Table 2.

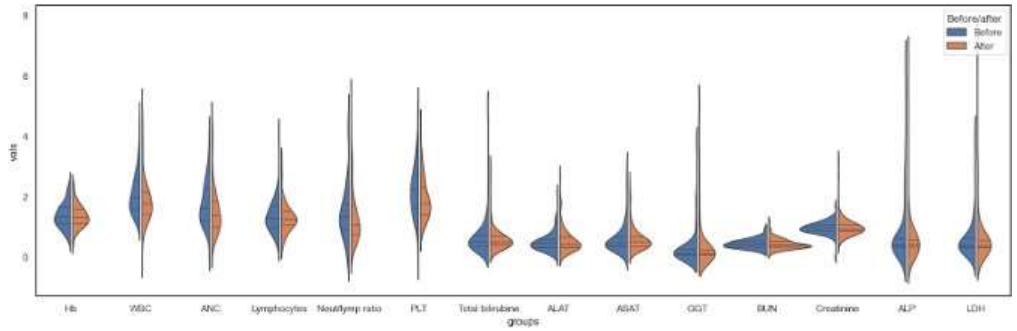


Figure 2. Distribution of hematology and chemistry parameters before and after chemotherapy.

Table 2. The report from toxicology.

Profile	Toxicity Type	No. of Cases (%)
Hematologic	Anemia	2 (2.70%)
	Neutropenia	3 (4.05%)
	Platelet-related toxicity	0 (0.00%)
Non-Hematologic	Liver	32 (43.20%)
	Cardiac	0 (0.00%)
	Neurologic	18 (24.30%)
	Digestive	10 (13.50%)
	Fatigue	25 (33.7%)
	Insomnia	3 (4.05%)
	Allergic	2 (2.70%)
	Other	5 (6.80%)

C. Model Validation

Using a k-fold cross-validation method, we conducted ten independent experiments by randomly shifting the dataset and dividing the train and test sets. The confusion matrix demonstrates the classes' imbalance, but the model accurately predicts the False (No Toxicity) class (Figure 3). The presented ROC curve (AUC on the training set ranging from 0.91 to 0.97) demonstrates that the model learned the relationships between features, making it possible to use the model for real-world data prediction (Figure 4).

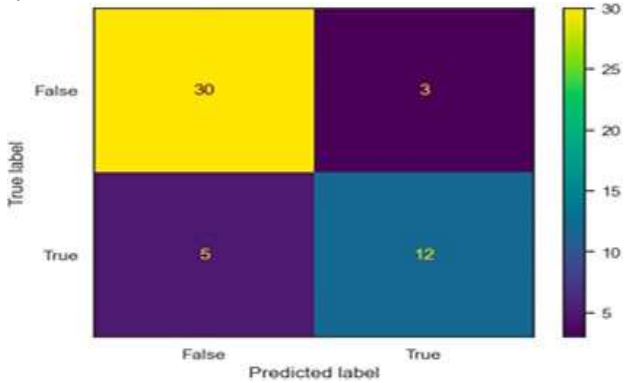


Figure 3. Confusion matrix to validate the model.

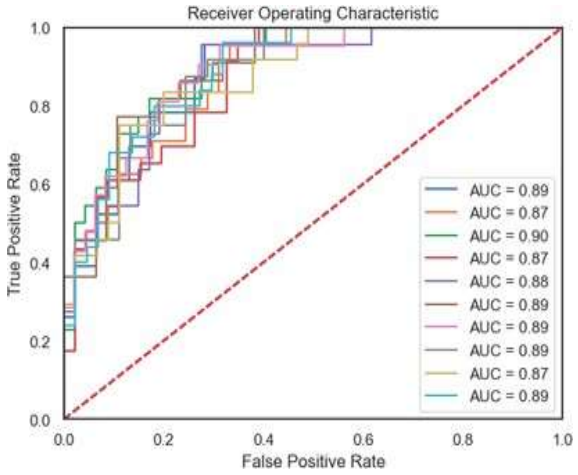


Figure 4. Model validation ROC.

D. Important Categorical Variables

Mucinous adenocarcinoma, T4b stage (tumor that has grown into or attached to other organs or structures), oligometastatic disease, no biologic treatment, M1c (peritoneal cancer spread), smoking history, and KRAS mutations are the primary categorical variables of interest. The model's predictions are significantly influenced by the presence or absence of the specified attributes, which will always have a linear increase or decrease in the likelihood of a particular outcome—positive or negative correlation—as shown in Table 3[13].

Table 3. The principal categorical variables.

Variable	Result Value
Treatable disease	0.080979
Treatment setting	0.060790
Mucinous adenocarcinoma	0.044297
T4a	0.039078
Oligometastatic disease	0.031902
No biological therapy	0.031272
M1c	0.030110
Smoking	0.030024
KRAS	0.028041

E. Important Numerical Variables

Blood urea nitrogen, creatinine, dosage reduction, gamma-glutamyl transferase, platelets, absolute neutrophil count, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, and white blood cells were the most significant numerical variables in our model (Figure 5, Table 4).

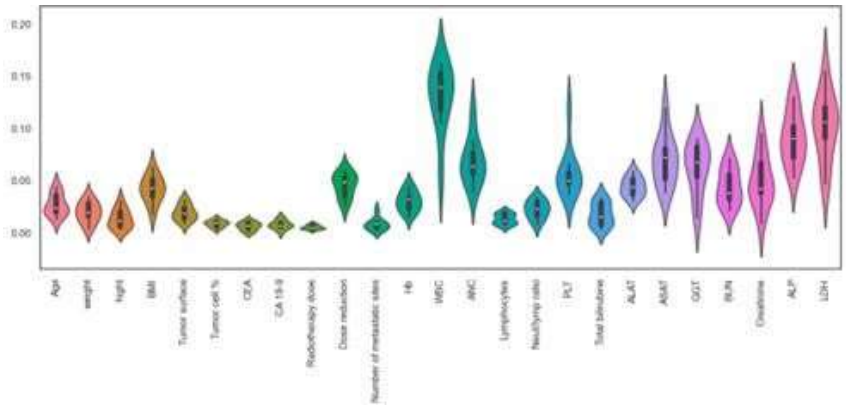


Figure 5. features that have values in numbers.

Table 4. Numbers matter.

S. No.	Variable	Value
1	WBC	0.128490
2	LDH	0.101582
3	ALP	0.090471
4	ASAT	0.069813
5	ANC	0.068928
6	GGT	0.061723
7	PLT	0.058054
8	Creatinine	0.049182
9	Dose Reduction	0.045479
10	BUN	0.044141

4. DISCUSSION

The toxicity of treatments has been predicted by researchers. In a prospective cohort study conducted in 115 US practice locations, a risk model for neutropenic events was developed and validated for 3760 patients with common solid tumors or malignant lymphoma who were beginning a new chemotherapy treatment. A regression model was developed and tested after samples were divided at random. The derivation and validation populations did not differ significantly in the results. During the first cycle, there were more neutropenic issues. Key risk factors included previous chemotherapy, low white blood cell count, impaired hepatic and renal function, and a dose delivery rate of less than 85 percent. With 96% positive and negative predictive values, 34% sensitivity, and 59% specificity at a projected risk cut point of 10%, the model performed well. Additional research demonstrated that the model was able to predict the risk of febrile neutropenia across multiple cycles of chemotherapy, and thus to help guide the appropriate and cost-effective use of supportive therapy in these patients [14].

Numerous studies suggested that colorectal cancer chemotherapy-induced toxicity could be predicted using a number of indicators. A risk prediction nomogram for fluoropyrimidine-induced cardiotoxicity in colorectal cancer was created by Wang et al. with the intention of counseling patients and stratifying their risk prior to chemotherapy. MJ Deenen, et al. The potential of genetic biomarkers: the association of DPD gene single nucleotide polymorphisms and haplotypes with capecitabine's toxicity and efficacy in advanced colorectal cancer. Chemotherapy-induced damage in colorectal cancer has been linked to additional clinical indicators. The non-alcoholic fatty liver disease fibrosis score was found to be a good predictor of the hematological toxicity of colorectal cancer chemotherapy, according to Yahagi et al., and Park et al. looked at the assessment, neuroprotection, and treatment of chemotherapy-induced neurotoxicity. Clinicians usually expect side effects after chemotherapy, but machine learning (ML) models are being used to optimize cancer treatment. These patient-specific models improve efficacy of therapy and reduce toxicity. An ML-based model for predicting neutropenia that estimates the risk at the beginning of a chemotherapy cycle was developed by Wiberg et al. Cho et al. have used ML to predict febrile neutropenia in breast cancer patients receiving chemotherapy. The use of ML to predict chemotherapy-induced hematological toxicities in rhabdomyosarcoma patients has been presented by Cuplov and Andre. These papers show that machine learning can predict the harm from chemotherapy.

Using only the Random Forest algorithm, our study was successful in predicting drug-related

toxicity in colorectal patients following the first dose of chemotherapy. On the other hand, Li Chao et al. used ML models for predicting fluoropyrimidine-induced cardiotoxicity in patients with colorectal cancer. With an accuracy of 0.607, their study found that the XGBoost algorithm performed best. Despite their distinct focus and methods, both studies demonstrate that ML models are capable of predicting toxicities associated with chemotherapy. The Random Forest method is used in our work to predict global effects of chemotherapy other than cardiotoxicity. A further study predicted adverse events from eight chemotherapy regimens (FOLFOX, FOLFIRI, paclitaxel, and GP) using EHR data and three machine learning (ML) algorithms (logistic regression, decision trees, and artificial neural networks). Anorexia, diarrhea, peripheral neuropathy, hypersensitivity, stomatitis, hand foot syndrome, and constipation were among the symptoms they anticipated. Eight adverse drug reactions were predicted by the models using logistic regression, which was the most accurate. As Random Forest was useful for that, this difference might suggest that the effectiveness of an ML algorithm depends on the context, such as the toxicities being predicted, the dataset, and the treatment regimens.

More recently, further studies have shown that ML models are able to predict Irinotecan toxicity in each treatment cycle, with a particular focus on leukopenia, neutropenia, and diarrhea. Our decision to use RF models for the large number of characteristics in relation to the number of patients was supported by this study's finding that Random Forest (RF) was the most effective method for predicting leukopenia. This indicates that situations, toxicity predictions, and chemotherapy regimens like Irinotecan can be worked with by RF. The reliability and efficacy of Random Forest in handling complex medical data and predicting adverse outcomes with significant therapeutic implications demonstrate its use in models for predicting chemotherapy toxicity.

A. Important Categorical Variables and Clinical Relevance

- **Curable Disease, Treatment Setting, Oligometastatic Disease:** We found high scores for curable illness, treatment setting (adjuvant or metastatic) and oligometastatic disease (0.080979, 0.060790 and 0.031902). In metastatic disease, the chemotherapy was administered with a palliative intent, and dose reductions were possible frequently. Adjuvant 5-fluorouracil (5FU) and leucovorin were evaluated for adverse events and survival outcomes in colorectal cancer (CRC) patients. In early-stage CRC patients, they investigated the connection between clinically measurable toxicity and outcomes. In adjuvant CRC patients treated with 5FU, adverse events such as neutropenia, mucositis, and nausea/vomiting were found to be predictive of survival outcomes such as DFS and OS. In addition, more research is needed to determine whether categorical factors are associated with treatment-related toxicity in a positive or negative way and how this might be interpreted in clinical practice.
- **Mucinous Adenocarcinoma:** A type of colorectal cancer with at least 50% mucinous component is called mucinous adenocarcinoma. Patients with mucinous colorectal adenocarcinoma and CRC receive the same treatment. We recommend that the FOLFIRI regimen be evaluated first because Liu et al. found that the FOLFIRI regimen could extend PFS for 5 months in patients with mucinous colorectal cancer ($p=0.038$). dMMR/MSI-H, mucinous, inflammatory, hypermutated, and containing KRAS and BRAF mutations were more prevalent in proximal tumors. When there is a poor prognosis, the entire pharmaceutical dose is frequently given. This may result in even more unpleasant events.
- **T4a and M1c:** In T4 lesions, micrometastasis occurs more frequently. Therefore, they may require more aggressive treatment, such as chemotherapy at higher doses. Patients with T4 colorectal cancer may benefit from chemotherapy with a dose intensity (DI) greater than 80%, according to IDEA research. based on the observed trend of higher DI-associated survival in this subgroup. This increased intensity of treatment increases the risk of side effects and toxicity. T4a scored 0.039078 in our study, which indicated that T4a was a robust clinical indicator for toxicity prediction. A total of 636 LACRC patients were enrolled in the study by Nie et al. from 2017 to 2019 to develop a predictive nomogram for overall survival. In the trial, TNM staging was a predictor of survival. This nomogram was better at predicting patients' outcomes, which may be useful for customizing treatment plans. Because the various stages have an impact on survival and increase the likelihood of treatment-related complications, the TNM classification method is more complicated. The significance of a precise TNM stage in directing treatment choices, improving patient outcomes, and controlling the toxicities associated with chemotherapy for LACRC is emphasized by our and other studies.

- **Smoking:** Clinically significant toxicity and efficacy have been linked to individual variation in anticancer drug pharmacokinetics. A comprehensive investigation into the impact of smoking on the efficacy and tolerability of systemic cancer treatment was carried out by Jassem et al. By activating growth and survival pathways and conferring resistance to apoptosis, nicotine may alter the efficacy of chemotherapy, according to preclinical data. Because smoking alters the medication's clearance and toxicity, dosage adjustments may be necessary to achieve the best therapeutic response in smokers. A meta-analysis by Bergman et al. looked at how smoking affected cancer treatment outcomes and toxicity. There was no statistically significant difference in the risk of chemotherapy-induced toxicity between smokers and nonsmokers in one analysis of nine studies with 3307 patients and 13 toxicities of chemotherapy (pooled OR 0.92; 95% CI 0.53 to 1.60). To see if smoking affected the toxicity of taxanes and platinum-based chemotherapy, subgroup analyses were carried out. There was no link between smoking and any toxicity from chemotherapy, according to these studies. Peppone et al. also looked at the impact of smoking on the burden of symptoms in 947 cancer patients undergoing treatment at a 6-month follow-up. During treatment and at six months, smokers had a greater total burden of symptoms than nonsmokers. Before starting treatment, smokers who had quit had the same symptoms as nonsmokers. The findings point to a connection between smoking and a greater burden of symptoms during and after cancer treatment, highlighting the significance of targeted efforts to quit smoking in order to reduce treatment interruptions and enhance quality of life after treatment.

B. Strengths and Limitations

The current study was constrained by the large number of to be evaluated factors and the small number of patients. Although the group was homogeneous, we collected our parameters using actual data rather than randomized controlled trials in order to accurately represent the clinical characteristics of the eastern Romanian mCRC community. This study would be able to comprehend each patient by analyzing each type of toxicity. Lastly, although the models can provide us with solid indicators of prediction quality, a new validation cohort would be helpful in evaluating our model's ability to predict chemotoxicity. This experiment is powerful because it trains a model of chemotherapy toxicity that is easy to understand. In a clinical setting, blood tests, clinical measurements, and factors that the patient has discussed are readily available.

5. CONCLUSIONS

We did not investigate the possibility of synergy between chemotherapy and biologic therapies for side effects, despite the fact that our analysis predicts any drug-related toxicity in patients with colorectal cancer following the first dose of chemotherapy. We took into account patient characteristics that, regardless of the drug class, might be used to predict various kinds of toxicity. Without the use of drug class interactions, we were able to construct a more general toxicity model using this method. It is important to note that cutaneous toxicity has been studied as a predictor of therapeutic response, particularly in anti-EGFR treatment. Because of its significance, we appreciate conducting research on this relationship. We will then investigate the relationship between treatment success and skin toxicity caused by biologic therapy. By demonstrating the effects of biologic medicines on toxicity and efficacy, this would also be beneficial to our prediction models and patient care. Other cancer treatments and treatment regimens could benefit from this study. In short, doctors can use our machine learning method to find patients who are more likely to have side effects from treatment and might need to be watched more closely. Our proof of concept demonstrates the possibility of using artificial intelligence to analyze patients' biological and tumoral features and to predict future adverse events that could delay chemotherapy administration and therefore influence the treatment results.

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