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Forecasting Serious Hematological Toxicity in Patients with Gastrointestinal Cancer Undergoing Chemotherapy based on 5-FU: An Application of Bayesian Network Modeling

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Abstract

Approximately 30% of patients with gastrointestinal cancer undergoing 5-Fluorouracil (5-FU)-based chemotherapy experience severe toxicity. Presently, there is a dearth of effective tools for identifying individuals at risk within this context. This study aims to fill this gap by constructing a predictive model using a Bayesian network, a robust probabilistic graphical model known for its interpretable predictions. Employing a dataset encompassing 267 gastrointestinal cancer patients, the data underwent preprocessing and was partitioned into TRAIN and TEST sets in an 80%:20% ratio. Variable importance was assessed using the RandomForest algorithm, employing the MeanDecreaseGini coefficient. The Bayesian network model was designed using the bnlearn R library, utilizing a 10-fold cross-validation on the TRAIN set, and optimizing the network structure with the aic-cg method. Model performance was evaluated through accuracy, sensitivity, and specificity, employing cross-validation on the TRAIN set and independent validation on the TEST set. The model displayed favorable performance, achieving an average accuracy of 0.85 (±0.05) and 0.80 on the TRAIN and TEST datasets, respectively. Sensitivity and specificity were 0.82 (±0.14) and 0.87 (±0.07) for the TRAIN dataset, and 0.71 and 0.83 for the TEST dataset. A user-friendly tool was developed for clinical deployment. Despite some limitations, our Bayesian network model exhibited a strong capacity to predict the likelihood of severe hematological toxicity in gastrointestinal cancer patients undergoing 5-FU-based chemotherapy. Future investigations should concentrate on validating the model using larger patient cohorts and in diverse clinical scenarios.

Keywords: Haematotoxicity prediction • Neutropenia • Thrombocytopenia

Introduction

Majority of gastrointestinal cancer patients undergo systemic therapy involving 5-Fluorouracil (5-FU) as a part of their treatment regimen. Among these patients, as many as 30% experience severe chemotherapy-related toxicity, an adverse outcome that can lead to fatal consequences in up to 1% of cases. This toxicity not only prompts unnecessary hospitalizations but also diminishes their quality of life and adversely impacts overall survival rates. The spectrum of toxic effects includes myelosuppression, mucositis, nausea, vomiting, fatigue, and diarrhea, with instances of neurotoxicity and cardiotoxicity documented as well. When combined with other drugs like irinotecan, oxaliplatin, or docetaxel in conventional combinations, the toxicity profile worsens considerably [1,2].

Despite the prevalence of this issue, there has been a scarcity of studies investigating the relationship between baseline clinical and analytical characteristics and the probability of severe toxicity development. Consequently, the existing predictive tools for identifying high-risk patients remain limited and fail to personalize the prediction. In recent years, the oncology field has witnessed an increased interest in leveraging machine learning and artificial intelligence techniques. Bayesian networks, in particular, have shown potential due to their capability to model intricate relationships among multiple variables, incorporating prior knowledge and accommodating updates as fresh data emerges. This sets them apart by providing a comprehensive understanding of the diverse factors contributing to the emergence of severe toxicities in patients subjected to 5-FU-based chemotherapy. This distinctive approach contrasts with many existing predictive models that rely on opaque AI models [3].

Literature Review

The novelty of our study lies in the transparency and interpretability of our predictive model. In contrast to black-box models like deep learning, often criticized for their lack of interpretability, our Bayesian network model enables a clear comprehension of the interdependencies between variables. This transparency holds critical significance in the medical domain, where comprehending the rationale behind a prediction can hold as much importance as the prediction itself.

In this context, our study endeavors to develop and validate a Bayesian network model tailored for anticipating severe toxicity in patients with gastrointestinal cancers undergoing 5-FU-based chemotherapy. This approach bears the potential to enhance patient outcomes, streamline healthcare procedures, and pave the way for further research and model enhancement [4].

We delve into the methodology employed to construct the network, encompassing the selection of pertinent variables and parameters, along with the assessment of the model's efficacy in both training and validation sets. Ultimately, we delineate the possible clinical implications of this strategy and identify prospects for subsequent research and model refinement. Our study involved a retrospective analysis of 267 medically fit patients with locally advanced or metastatic gastrointestinal tumors. These patients exhibited satisfactory hematological, renal, and hepatic functions and received systemic 5-FU-based chemotherapy either in the neoadjuvant setting or as a first-line intervention, following evaluation by a multidisciplinary tumor board at our institution from 2010 to 2020.

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Discussion

Eligible participants were aged 18 years or older, possessed an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 1, and had a confirmed diagnosis of locally advanced cancer (gastric, colon, rectal, or pancreatic) or liver metastasis arising from colorectal or pancreatic adenocarcinoma, all qualifying for active systemic therapy. Notably, individuals undergoing concurrent chemoradiation were excluded from the analysis. Additionally, patients undergoing second or subsequent lines of treatment for metastatic disease were not considered to prevent potential bias. Variability in toxicity is partly attributed to differences in drug pharmacokinetics, variations in co-existing conditions (cardiac, hepatic, or renal diseases), predisposing factors (age and gender), fluctuation in dihydropyrimidine dehydrogenase (DPD) activity, peripheral blood mononuclear cell functionality, Telomere Length (TL), or platelet lymphocyte ratio (PLR) [5].

Presently available methods for identifying patients at risk of 5-FU-related toxicity encompass pharmacogenetic assays for predicting DPD activity, polymorphisms in Thymidylate synthase and Methylenetetrahydrofolate reductase, plasma uracil and dihydrouracil ratio measurement, quantification of FUDR as an indicator of 5-FU degradation, analysis of fecal microbiota, or genetic variations in ABCC1/MRP1 genes [6]. However, none of these approaches encompass the entire spectrum of functional polymorphisms or include clinically relevant parameters, contributing to a significant portion of unexplained toxicity cases.

More recently, machine learning techniques have emerged to predict neutropenic events through electronic medical records. Their model, focused on interpretability and clinical applicability, achieved commendable out-of-sample area under the receiver operating characteristic curve of 0.865 based on 20 clinical features. While their approach centered on leveraging EMRs and validating known risk factors, our study adopts a Bayesian network model offering a probabilistic viewpoint, thereby allowing for a nuanced comprehension of the interplay among various factors. Furthermore, our model's emphasis on gastrointestinal cancer and specific chemotherapy regimens imparts a specialized lens, potentially yielding more precise predictions for this subgroup of patients.

Conclusion

Our investigation underscores the potential of the developed Bayesian network model to improve the predictability of severe toxicity, specifically neutropenia, leukopenia, and thrombocytopenia, in patients with gastrointestinal cancer who are undergoing chemotherapy regimens involving 5-FU. Nevertheless, it is essential to acknowledge the inherent limitations of our study, with the primary concern being the restricted sample size, which might have impacted the model's performance.

The constrained sample size not only potentially diminishes the statistical strength of our conclusions but may also restrict the model's ability to comprehensively grasp the intricate and multifaceted interplays among variables, particularly within a more expansive and varied patient population. The dynamics of these interplays could differ significantly in a broader context, potentially influencing the model's predictive efficacy. As we look ahead, further research should prioritize the validation of this model using larger, independent patient cohorts while addressing issues like missing data and sample size constraints. Additionally, efforts should be directed towards integrating a wider array of variables into the model to refine its precision and robustness, thereby augmenting its predictive capacity for severe toxicity in this specific patient group. Future research endeavors could explore collaborative initiatives aimed at accumulating and analyzing more extensive datasets. Such endeavors would yield a more holistic comprehension of variable interactions within a broader patient cohort, contributing to the enhancement and calibration of the model. This, in turn, would bolster its reliability and practicality in predicting severe toxicity. Through collective endeavors, we can strive to develop a more accurate and resilient model for prognosticating severe toxicity in patients undergoing 5-FU-based chemotherapy.

Acknowledgment

None.

Conflict of Interest

None.

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