

Machine Learning Approaches to Predict Symptoms in People with Cancer: Systematic Review

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Abstract

Background: People with cancer frequently experience severe and distressing symptoms associated with their cancer and its treatments. Clinicians and researchers continue to struggle with accurately predicting which symptoms will develop and in which individuals with cancer. Machine learning algorithms can improve the ability to predict symptoms prospectively.

Objective: The aim of this systematic review is to synthesize the literature that has used machine learning algorithms to predict the development of cancer symptoms, as well as to identify the predictors of these symptoms.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. We conducted a systematic search of CINAHL, Embase, and PubMed for English records published from 1984 to August 11, 2023, using the following search terms: 'cancer', 'neoplasm', specific symptoms, 'neural networks', 'machine learning', specific algorithm names, and 'deep learning'. All records that met the eligibility criteria were individually reviewed by two co-authors, and key findings were extracted and synthesized.

Results: A total of 42 studies were included, the majority were published after 2017. Most were conducted in North America (43%) and Asia (40%). The most prevalent category of algorithms was supervised machine learning, accounting for 93% of the studies. Each of the methods — deep learning, ensemble classifiers, and unsupervised machine learning — constituted less than 3% of all studies. The machine learning algorithms with the best performance were Logistic Regression (17%), Random Forest (13%), Artificial Neural Networks (9%), and Decision Tree (9%). The most commonly included primary cancer sites were head and neck (22%) and breast (19%). However, in 41% of the studies, the specific cancer site was not explicitly mentioned. The most frequently studied symptoms were xerostomia (14%), depression (13%), pain (13%), and fatigue (10%). Significant predictors across the studies included age, gender, type/number of prior treatments, cancer site, cancer stage, chemotherapy agents, radiotherapy dose and volume, chronic disease, comorbidity, and previous symptoms such as depression, anxiety, fatigue, pain, and sleep disturbance.

Conclusions: This review outlines the algorithms employed for predicting symptoms in individuals with cancer. Given the diversity of symptoms people with cancer experience, analytic approaches that can handle complex and non-linear relationships is critical. This knowledge can pave the way for crafting algorithms tailored to specific symptom. Additionally, to improve prediction precision, future research should compare cutting-edge machine learning strategies such as deep learning and ensemble methods with traditional statistical models.

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Original Manuscript

Machine Learning Approaches to Predict Symptoms in People with Cancer: Systematic Review

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Abstract

Background: People with cancer frequently experience severe and distressing symptoms associated with their cancer and its treatments. Predicting symptom in patients with cancer continues to be a significant challenge for both clinicians and researchers. The rapid evolution of machine learning highlights the need for a current systematic review to improve cancer symptom prediction.

Objective: The aim of this systematic review is to synthesize the literature that has used machine learning algorithms to predict the development of cancer symptoms, as well as to identify the predictors of these symptoms. This is essential for integrating new developments and identifying gaps in existing literature.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses checklist. We conducted a systematic search of CINAHL, Embase, and PubMed for English records published from 1984 to August 11, 2023, using the following search terms: 'cancer', 'neoplasm', specific symptoms, 'neural networks', 'machine learning', specific algorithm names, and 'deep learning'. All records that met the eligibility criteria were individually reviewed by two co-authors, and key findings were extracted and synthesized. We focused on studies using ML algorithms to predict cancer symptoms, excluding non-human research, technical reports, reviews, book chapters, conference proceedings, and inaccessible full-texts.

Results: A total of 42 studies were included, the majority were published after 2017. Most were conducted in North America (18/42, 43%) and Asia (16/42, 38%). Sample sizes in most studies (27/42, 64%) typically ranged between 100 to 1,000 participants. The most prevalent category of algorithms was supervised machine learning, accounting for 39 out of 42 (93%) studies. Each of the methods — deep learning, ensemble classifiers, and unsupervised machine learning — constituted less than 3 out of 42 (3%) of all studies. The machine learning algorithms with the best performance were Logistic Regression (9/42, 17%), Random Forest (7/42, 13%), Artificial Neural Networks (5/42, 9%) and Decision Tree (5/42, 9%). The most commonly included primary cancer sites were head and neck (9/42, 22%) and breast (8/42, 19%), with 17 out of 42 (41%) not specifying the site. The most frequently studied symptoms were xerostomia (9/42, 14%), depression (8/42, 13%), pain (8/42, 13%), and fatigue (6/42, 10%). Significant predictors were age, gender, treatment type/number, cancer site/stage, chemotherapy, radiotherapy, chronic diseases, comorbidities, and various physical/psychological factors.

Conclusions: This review outlines the algorithms employed for predicting symptoms in individuals with cancer. Given the diversity of symptoms people with cancer experience, analytic approaches that can handle complex and non-linear relationships is critical. This knowledge can pave the way for crafting algorithms tailored to specific symptom. Additionally, to improve prediction precision, future research should compare cutting-edge machine learning strategies such as deep learning and ensemble methods with traditional statistical models.

Keywords: Machine learning; Deep learning, Cancer symptoms; Prediction model

Introduction

Cancer poses considerable physical and psychological challenges for those diagnosed with the disease. The Global Cancer Observatory (GLOBOCAN) estimated that there were 19.3 million new cancer cases and 43.8 million individuals living with cancer within five years of diagnosis globally in 2020 [1]. Symptoms such as fatigue, pain, nausea, vomiting, depression, and anxiety often persist

beyond treatment [2-5], detrimentally affecting individuals' quality of life [6]. Moreover, people with cancer frequently grapple with multiple intertwined symptoms [7], intensifying their distress [8]. Unmanaged cancer symptoms can lead to an increased healthcare utilization, including emergency department visits and unscheduled hospitalizations to address these symptoms, a decline in the quality of life (QOL) [9], and even a reduced life expectancy. Providing precision symptom management tailored to the individual at the right moment has the potential to significantly improve outcomes crucial for both people with cancer and their healthcare providers. Accurately predicting and addressing these symptoms is fundamental to providing such precision in symptom management.

Artificial Intelligence (AI), which encompasses machine learning (ML) and deep learning (DL) models, that excel at handling complex, high-dimensional, and "noisy" data and have proven effective in diagnosing diseases, predicting disease recurrence, improving quality of life, and managing symptoms [10-16]. There's growing interest in ML within the emerging field of predictive analytics for cancer symptoms. ML contributes to the development of robust clinical decision systems, enhancing overall healthcare delivery [17]. ML algorithms can be broadly categorized into supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning. Deep learning, a subset of ML, addresses complex tasks such as speech recognition, image identification, and natural language processing [18].

This paper seeks to offer a comprehensive and systematic review of the literature on the application of ML algorithms in predicting symptoms for people with cancer. Conducting this review of a rapidly expanding body of literature is imperative to understand the current state of the science for ML models in symptom prediction for cancer and to guide future research based. This exploration aims to provide a comprehensive understanding of the current state of research, identify areas for improvement, understanding the limitations and gaps in current literature, such as a lack of specific focus on ML models for cancer patients. By comparing model performances across diverse symptom prediction tasks, we can identify best practices, highlight areas for improvement, and offer informed recommendations that will propel the field of predictive analytics in cancer symptoms research forward.

Methods

Search strategy and Data Sources

This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) protocol [19] and involved a comprehensive database search spanning

from 1984 to August 11, 2023, including PubMed, Embase, CINAHL, and Google scholar. Search terms encompassed "cancer," "neoplasm," "signs and symptoms," "neural networks," "machine learning," and specific algorithm names. In our study, we employed Boolean expressions, utilizing specific combinations of keywords and phrases, acknowledging the variability in terminology across studies. Search results were compiled using the EndNote 20 software. The detailed search strategy, which employs Boolean expressions, can be found in Multimedia Appendix 1.

Inclusion and exclusion criteria

To identify relevant research focusing on the application of ML methods in predicting cancer symptoms, we applied the following inclusion criteria: (1) papers published in English; (2) studies that utilized ML algorithms; and (3) research specifically aimed at predicting cancer symptoms. Exclusion criteria were as follows: (1) non-human studies; (2) technical reports; (3) review papers; (4) book chapters or series; (5) conference proceedings; and (6) studies for which full texts were unavailable. Two authors, N.Z. and N.Y., independently screened and cross-checked the candidate records. During the screening process, conducted using EndNote 20, any disagreements were resolved by consulting a third reviewer (SGW). The screening process involved an initial review of titles and abstracts, followed by a full-text examination to determine the study's eligibility for inclusion in the review.

Data Extraction and Analysis

In our study, we implemented a systematic, multi-step process for data synthesis. Initially, relevant studies were identified and selected based on predefined inclusion and exclusion criteria. Two independent researchers, N.Z. and N.Y., extracted data from 42 selected studies. They worked independently to mitigate bias and enhance the accuracy of the data extraction process. In cases of discrepancies, these were resolved through discussion or consultation with a third reviewer, S.G.W. The extracted data were aggregated, involving the collation of study characteristics such as research location, sample size, study design, types of ML algorithms, validation metrics, identified significant predictors, cancer types, and the specific symptoms focused on. This comprehensive approach enabled us to reduce bias and increase the reliability of our findings. For the analysis, we employed both quantitative and qualitative methods. Quantitative data, like frequencies and percentages, were compiled and analyzed using Python. This included the creation of insightful plots and heatmaps to identify patterns and trends, illustrating relationships between variables, and highlighting key findings in an easily digestible format. Qualitative aspects, such as algorithm implementation or

study design, were explored through narrative synthesis. This allowed for a deeper understanding of the context and nuances in the application of ML algorithms for cancer symptom prediction.

We conducted a cross-analysis to compare findings from different studies, assessing the effectiveness of various ML algorithms across different cancer types and symptoms, and identifying common predictors of success and challenges faced. Finally, we interpreted the findings in the context of the existing literature. We discussed how our results align with or differ from previous studies and what new insights our synthesis brings to the field of ML in cancer symptom prediction.

Results

Overall results

A search across the three databases produced 1,788 papers. After removing 289 duplicates, we screened the records for titles and abstracts, excluding another 1,352 irrelevant records. However, one study was not retrieved. We reviewed the full text of the remaining 146 records, omitting 105 due to absence of ML application in predicting cancer symptoms ($n=69$), being non-research articles ($n=34$), and being non-English ($n=1$). In the second phase, we intend to include Google Scholar in our research methodology to capture an additional 113 articles not found in our main databases, although one study was not retrieved. We reviewed the full text of the remaining 99 records, ultimately excluding all of them for reasons like lacking ML applications in cancer symptom prediction ($n=89$) and being non-research articles ($n=10$). Eventually, 42 studies met the inclusion criteria, as depicted in Figure 1.

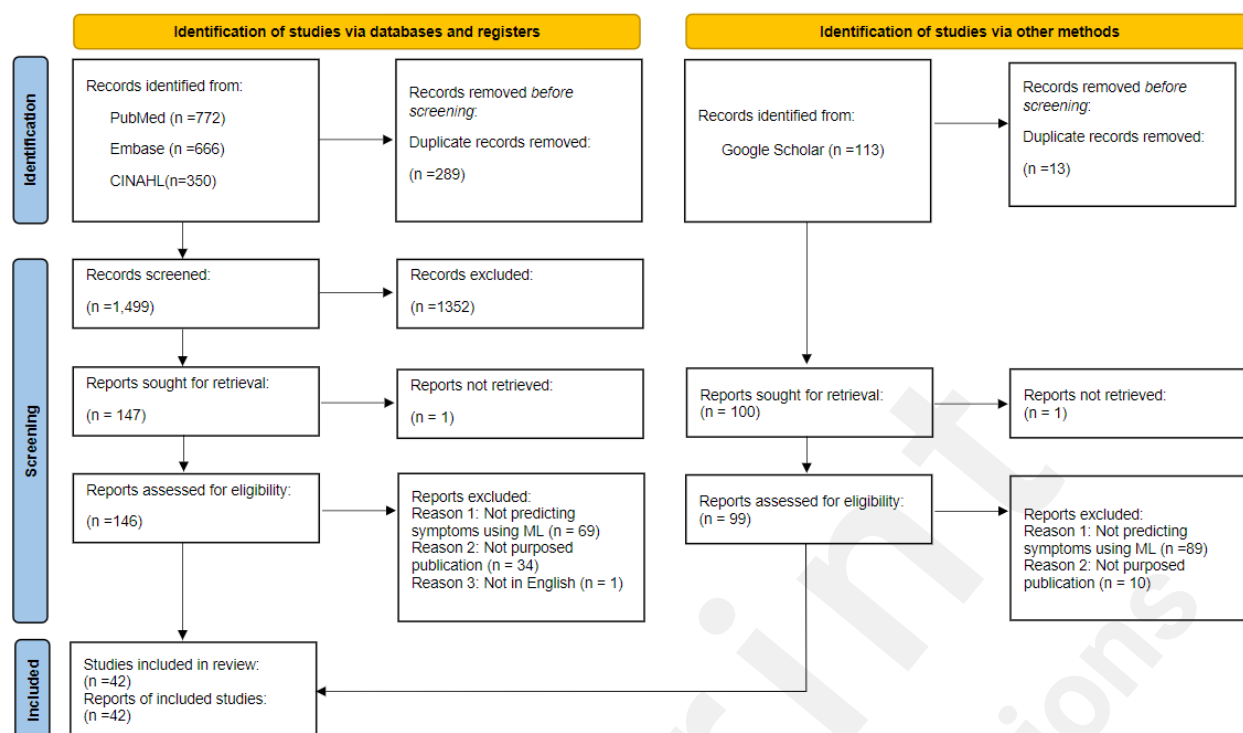


Figure 1. PRISMA flowchart

Of the 42 studies, 100% are listed in PubMed, while Embase covers approximately 88% (37 studies), and CINIAL includes about 43% (18 studies). Figure 2 visually represents the distribution and overlap of these research articles across the databases.

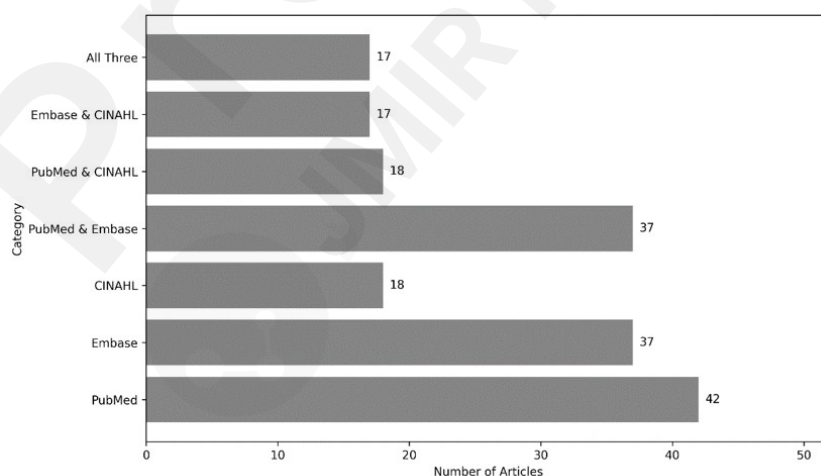


Figure 2. Distribution of research articles among databases and overlaps

The data extracted from these studies, which includes reference number, research location/year, data type, cancer site, symptoms, significant predictors, ML algorithms, and validation methods, are detailed in Table 1, and Table 2 in Multimedia Appendix 2. Two individual's researchers (N.Z and N.Y) separately extract data from each study, working independently of each other. This approach is

used to reduce bias and increase the accuracy of the data extraction process. If discrepancies arise between the two independent authors, they are usually resolved through discussion or by consulting a third reviewer (S.G.W).

Table 1. Details of Included Studies (N=42)

Refere	Country / Year	Data type/ the number of data	Population	Cancer Symptoms	Significant Predictors	Algorithms	Validation Methods
[1]	China/2023	Clinical data/1152	People with breast cancer	Pain	Post-menopausal status, urban medical insurance, history of at least one operation, underwent general anesthesia with fentanyl and sevoflurane, and received axillary lymph node dissection.	LR^e, RF^f, GBDT^g, XGB^h	Random
[2]	China/2023	Clinical data/494	People with Advanced Cancer	Cognitive Impairment	Cancer course, anxiety, age.	LR, ANN ⁱ	Random
[3]	USA/2023	Clinical Data/1152	Cancer survivors with osteoarthritis	Depression	Age, Education, Care Fragmentation, Polypharmacy, and Zip Code Level Poverty.	XGB	10-Fold CV ^{an}
[4]	USA/2023	Clinical data/1217	People with cancer receiving CTX ^b	Morning Fatigue	13 Individual Li-Fraumeni Syndrome items.	EN^j, RF, LASSO^k, LR (Filtered/Unfiltered) RPAR^l, SVM^m	Random
[5]	China/2023	Clinical data/565	People with cancer	Fatigue	Pain score, Eastern Cooperative Oncology Group score, Platelet Distribution Width, and Continuous Erythropoiesis Receptor Activator.	LR, RF , NB ⁿ , XGB	5-Fold CV
[6]	Italy/2022	Clinical data/21	People with cancer	Pain	N/A	SVM, RF, MP^o , LR, AdaBoost ^p	10-Fold CV
[7]	Japan/2022	Clinical data/808	People with cancer	Social distress, spiritual pain, pain, dyspnea, nausea, insomnia.	N/A	LR, RF, Light GBM^q, SVM, Ensemble	5-Fold CV
[8]	Italy/2022	CT ^a image data/ 61	People with Oropharyngeal cancer receiving RT ^c	Xerostomia	Weight pre-RT, Induction CHX, Sex, Platinum Based CHX, Current CHX, Alcohol history, Age at diagnosis, Smoking history, Surgery, Clinical tumor, Clinical node.	SVM, CNN ^r	10-Fold CV
[9]	Japan/2022	Clinical data/ 284	People with breast cancer	Insomnia	General fatigue, Physical fatigue, and cognitive fatigue.	L2 penalized LR, XGB	8-Fold CV
[10]	Korea/2022	Clinical data /935	People with cancer receiving CTX	Nausea-vomiting, Fatigue-anorexia, Diarrhea, Hypersensitivity, Stomatitis, Hand-foot syndrome, Peripheral Neuropathy, Constipation	Earlier history of Adverse Drug Reaction, comorbidity, cancer site, and type of chemotherapy, demographics, antineoplastic therapy related features.	LR, DT^s ANN	3-Fold CV
[11]	China/2022	Clinical data,	People with cancer	Xerostomia	Hypertension, age, total	RF, DT, XGB	External

		CT image data / 365	receiving RT		radiotherapy dose, dose at 50% of the left parotid volume, mean dose to right parotid gland, mean dose to oral cavity, and course of induction chemotherapy.		Val.
1]	Japan/2022	Clinical data/ 668	People with advanced cancer receiving pharmacological interventions.	Delirium	The baseline Delirium Rating Scale-R98 severity score (cutoff of 15), hypoxia, and dehydration.	DT	5-fold CV
2]	China/2022	Clinical data /80	People with lung cancer receiving CTX	Lung Infection	Age $\geq$ 60 years, length of stay $\geq$ 14 days, surgery history, combined chemotherapy, myelosuppression, diabetes, and hormone application	LR, ANN	Random
3]	USA/2022	Clinical data /40	People with breast cancer	Depressed mood, anxiety	Connectedness, receive support, frequency and duration use of mobile app, physical pain.	RF , XGB	LOOCV ^{ao}
4]	USA/2022	Clinical data, CT image data / 155	People with HNC ^d receiving RT	Xerostomia	N/A	SVM, KNN ^t , NB, RF	Nested
5]	Japan/2021	Clinical data, CT image data/ 69	People with cancer receiving RT	Pain	Age, Numeric rating scale, Biological effective dose 10.	RF	LOOCV
6]	China/2021	Clinical data/386	People with colorectal cancer after CTX	Cognitive Impairment	Age, body mass index, colostomy, treatment complications, Cancer Related Anemia, depression, diabetes, Quality of Life Questionnaire Core 30 score, exercise, hypercholesterolemia, diet, marital status, education level, and pathological stage.	RF, LR , SVM	Random
7]	Canada/2021	Clinical data /46,104	Not mentioned specific cancer site or treatment	Pain, Depression, Well-being	Lung cancer, late-stage cancer, existing chronic conditions such as osteoarthritis, mood disorder, hypertension, diabetes, and coronary disease.	ANN	Random
8]	China/2021	Clinical data /598	People with gastrointestinal tumors after surgery	Postoperative fatigue	Age, higher degree of education, lower personal monthly income, advanced cancer, hypoproteinemia, preoperative anxiety, or depression, and limited social support.	LR, ANN, CART ^v	Random
9]	China/2021	Clinical data/ 533	People with breast cancer	lymphedema	N/A	ANN, LR , C5.0, RF, SVM, CART	10-fold CV
0]	USA/2021	Clinical data/ 823	People with HNC	Pain Taste General Activity	N/A	SVM, KNN, RF, Gaussian NB ^w , MLP ^x , ARIMA ^y , LSTM ^z	Random
1]	USA/2021	Clinical data, CT image data / 138	Not mentioned specific cancer site or treatment	Depression	N/A	Fine-Tree , Medium-Tree , Coarse-Tree, Linear-Discriminant, Quadratic-Discriminant, LR, Gaussian NB, Kernel Naïve Bayes, Linear SVM, Quadratic SVM, Cubic SVM, Fine Gaussian SVM, Medium Gaussian SVM, Coarse Gaussian SVM, Fine KNN, Medium KNN, Coarse KNN, Cosine KNN,	5-fold CV

						Cubic KNN, Weighted KNN, Boosted Trees, Bagged Trees, Subspace Discriminant, Subspace KNN, Random Under sampling Boosted Trees	
7]	USA/2021	Clinical data / 6124	People with cancer receiving CTX	Nausea-vomiting	Smoking, alcohol status, sex, age, and body mass index.	NB, LR, ANN, SVR ^{aa} , DT	10-fold CV
2]	USA/2021	Clinical data / 44	People with pancreatic cancer after surgery	Diarrhea Fatigue Pain	Physical activity bouts, sleep, heart rate, and location.	LR, KNN, SVM, RF, GB ^{ab} , XGB, Light GBM	3-fold CV LOOCV
3]	Greece/2021	Clinical data/ 609	People with breast cancer	Depression	A set of psychological traits (optimism, perceived ability to cope with trauma, resilience as trait, ability to understand the illness), and subjective perceptions of personal functionality (physical, social, cognitive).	RF, SVM , GB	5-fold CV
4]	USA/2021	Clinical data/ 1217	People with cancer receiving CTX	Evening Fatigue	Morning fatigue, lower evening energy, sleep disturbance.	RF , LR (Filtered/Unfiltered), RPART, SVM	10-fold CV
5]	China/2021	Clinical data/ 238	People with non-Hodgkin's lymphoma receiving CTX	Depression	Education level, sex, age, marital status, medical insurance, per capita monthly household income, pathological stage, Suicide Severity Rating Scale, Pittsburgh Sleep Quality Index and Quality of Life Questionnaire Core 30.	SVM, RF, LASSO+LR	Random
5]	Germany/2021	Clinical data/ 496	People with cancer seen in primary care.	Anxiety	Fatigue/weakness, insomnia, and pain appeared.	OLS ^{ac} , RR ^{ad} , LASSO , ENR ^{ae} , RF, and XGB	10-fold CV
7]	USA/2020	Clinical data, CT Images data / 388	People with lung cancer after Intensity-Modulated Radiation Therapy	Weight Loss	Joint Gross tumor volume L1 + L2 + L3 radiomics, Gross tumor volume TV & Esophagus L3 dosiomic.	SVM, DNN ^{af} , Ensemble classifier	Nested CV
8]	Canada/2020	Clinical data / 204	People with breast cancer after surgery	Neuropathic Pain (NP)	Anxiety, type of surgery, acute pain	LS ^{ag} , RR , ENR , RF, GB , ANN	10-fold CV
9]	USA/2019	Clinical data, CT image data / 784	People with HNC receiving RT	Xerostomia	Feature map visualization.	LR, 3D r CNN ^{ah}	Random
0]	USA/2019	Clinical data, CT Images data/ 427	People with HNC	Xerostomia	The patient has Human Papillomavirus, completed chemotherapy, their baseline xerostomia grade, tumor site, N stage, and use of feeding tube.	RR , LASSO, RF	10-fold CV
1]	USA/2019	CT Images data/266	People with HNC	Xerostomia	N/A	Generalized Linear Model	10-Fold CV
2]	USA/2019	Clinical data/ 799	People with cancer receiving CTX.	Sleep Disturbance, Anxiety, Depression	Age, gender, cancer site, the number of prior cancer treatment, initial diagnosis.	SVR (Linear, Polynomial, radial sigma), and n-CCA ^{aj}	10-fold CV, Bootstrap
3]	China/2018	Clinical data/ 375	People with cancer are receiving RT.	Weight loss	Head and neck tumor location, total radiation dose ≥ 70 Gray and without post-surgery.	DT , LR	Random
4]	Denmark/2018	Clinical and CT image / 131	People with lung cancer receive RT.	Odynophagia (painful swallowing)	N/A	Multivariable LR Lasso & Elastic-Net Regularized	10-fold cv

						Generalized Linear Models, SVM	
5]	Germany/2018	Clinical and CT image / 153	People with HNC after RT	Xerostomia	The parotid gland volume, the spread of the contralateral dose-volume histogram, and the parotid gland eccentricity, sex.	LR-L1 ^{ai} , LR-L2 ^{aj} , LR-EN ^{ak} , KNN , SVM , ET ^{al} , GTB	Single and nested CV
6]	Germany/2018	Clinical data/ 1000	People with breast cancer after surgery	pain	Age, chronic pain of any kind, number of precious operations, body mass index, preoperative pain in the area to be used smoking, psychological factors.	Unsupervised Machine Learning	Random
7]	IRAN/2018	Clinical and CT image / 47	People with HNC receiving CTX	Hearing loss	10 of the 490 radiomic features selected as the associated features with significant sensorineural hearing loss status.	Decision Stump, Hoeffding, C4.5, NB, AdaBoost, bootstrap aggregating, LR	10-fold cv
8]	USA/2018	Clinical and CT image /68	People with HNC	Xerostomia	N/A	LR	External Validation
9]	Serbia/2017	Clinical data/ 84	People with breast cancer	Depression	N/A	ELM ^{am} , ANN, Fuzzy with genetic algorithm	Random
0]	USA/2017	CT image features/249	People with HNC	Xerostomia	N/A	LR	10-Fold CV

^a CT: Computed tomography, ^b CTX: Chemotherapy, ^c RT: Radiotherapy, ^d HNC: Head and Neck Cancer, ^e LR: Logistic Regression, ^f RF: Random Forest, ^g GBDT: Gradient Boosting Decision Tree, ^h XGB: Extreme Gradient Boosting, ⁱ ANN: Artificial Neural Network, ^j EN= Elastic Net, ^k LASSO= Least Absolute Shrinkage and Selection Operator, ^l RPAR: Recursive Partitioning and Regression Trees, ^m SVM: Support Vector Machine, ⁿ NB = Naïve Bayes, ^o MP: Multiple Perceptron, ^p AdaBoost :Adaptive Boosting, ^q Light GBM: Light Gradient Boosting Machine, ^r CNN: Convolutional Neural Networks, ^s DT: Decision Tree, ^t KNN: K-Nearest Neighbor, ^v CART: Classification and Regression Tree, ^w Gaussian NB= Gaussian Naïve Bayes, ^x MLP: Multi-Layer Perceptron, ^y ARIMA: Autoregressive Integrated Moving Average, ^z LSTM: Long Short-Term Memory Neural Network, ^{aa} SVR: Support Vector regression, ^{ab} GB: Gradient Boosting, ^{ac} OLS= Ordinary Least Square, ^{ad} RR= Ridge Regression, ^{ae} ENR= Elastic Net Regression, ^{af} DNN: Deep Neural Network, ^{ag} LS: Least-Squares, ^{ah} n-CCA: Non-linear Canonical Correlation Analysis by Neural Networks, ^{ai} L1LR: L1 penalized Logistic Regression, ^{aj} L2LR: L2 penalized Logistic Regression, ^{ak} LR-EN: Logistic Regression- Elastic Net, ^{al} ET: Extra Tree, ^{am} ELM: Extreme Linear Machine, ^{an} CV: 3- Fold Cross validation, ^{ao} LOOCV: Leave-One-Out-Cross-Validation, ^{ap} Bolded letters in this column indicate the best results used in the study.

Primary Database Information

The studies selected were published between 2017 and 2023 and were conducted in North America (18/42, 43%), Asia (16/42, 38%), and Europe (8/42, 19%). Methods of data collection varied, with studies originating from individual centers (23/42, 55%) and multiple centers (19/42, 45%). The average sample size was 1686; and the studies varied in sample size: fewer than 100 participants (8/42, 19%), between 100 to 1,000 participants (27/42, 64%), and more than 1,000 participants (7/42, 17%). Most of the studies relied on clinical data (28/42, 67%), though some integrated clinical data with computed tomography (CT) images (14/42, 33%). The study designs were diverse, including retrospective (18/42, 43%), cross-sectional (15/42, 38%), prospective (5/42, 12%), and longitudinal (4/42, 10%) approaches.

Cancer Primary Sites and Predicted Symptoms

Various primary cancer sites were studied, with head and neck cancers being the most prevalent (9/42, 21%). Breast cancer was the focus of 8 studies (19%), and lung cancer was studied in 3 cases (17%). The included studies included participants undergoing a range of treatments, including

chemotherapy (9/42, 21%), radiotherapy (9/42, 21%), surgery (4/42, 10%), and investigations into post-treatment survivors (2/42, 5%). Of the 42 included studies, 10 unique symptoms were reported as outcome variables in predictions. Those included were xerostomia (9/42, 14%) [27, 30, 34, 49-51, 55, 58, 60], depression (8/42, 13%) [22, 33, 37, 41, 43, 45, 52, 59], pain (8/42, 13%) [20, 25, 26, 35, 37, 40, 42, 56], fatigue (6/42, 10%) [23, 24, 29, 38, 42, 44], anxiety (3/42, 5%) [33, 46, 52], sleep disturbance/insomnia (3/42, 5%) [26, 28, 52], nausea/vomiting (3/42, 5%) [17, 26, 29], weight loss (2/42, 3%) [47, 53], cognitive impairment (2/42, 3%) [21, 36], and diarrhea (2/42, 3%) [29, 42].

One study reported multiple symptoms, including hypersensitivity [29], stomatitis [29], hand-foot syndrome [29], peripheral neuropathy [29], constipation [29], and neuropathic pain [48]. Another study delved into taste and general activity [40]. Individual studies were dedicated to each of the following symptoms: delirium [31], lung infection [32], lymphedema [39], well-being [37], odynophagia [54], social distress [26], spiritual pain [26], dyspnea [26], and hearing loss [57]. The distribution of these symptoms is depicted in Figure 3.

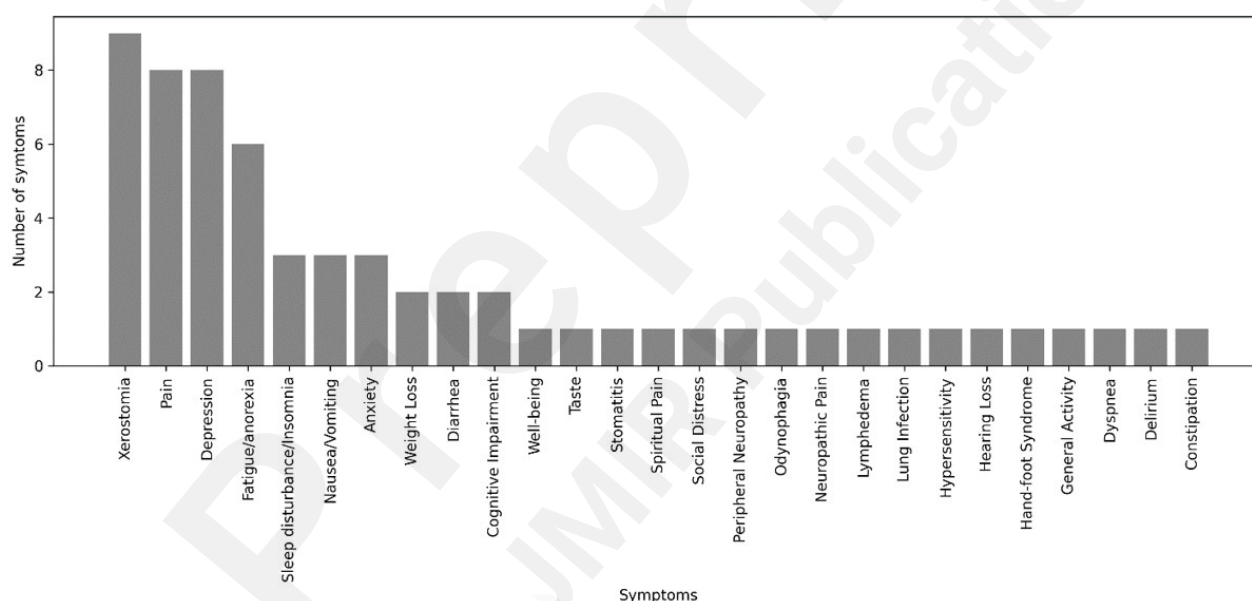


Figure 3. Number of studies per cancer symptoms

Significant Candidate Predictors of Symptoms

Numerous predictors were frequently utilized for predicting symptoms, which can be grouped into demographic features and clinical characteristics.

Demographic Features: Age, sex, body mass index (BMI), income, medical insurance, education, marital status, and Zip code level of poverty.

Clinical Characteristics: Smoking and alcohol use, initial diagnosis, presence of cancer, stage of cancer, cancer course, tumor site, type and number of prior treatments, chemotherapy type, and radiotherapy dose and volume. Health conditions such as comorbidity, diabetes, hypertension,

osteoarthritis, and coronary disease also play a significant role. Additionally, psychological factors like depression and anxiety, fatigue, sleep disturbance, and pain are considered. Other influential predictors encompass care fragmentation, polypharmacy, hormone levels, physical activity, diet, heart rate, and social support factors.

In our comprehensive analysis of 42 studies, all detailed findings on common cancer symptoms are visually compiled in Figure 4. We provide a detailed analysis of the predictors for the four most frequently reported cancer symptoms identified in this study: xerostomia, pain, depression, and fatigue. In a detailed analysis of 42 studies, various predictors for four common cancer symptoms - xerostomia, pain, depression, and fatigue - have been identified, each with its distinct set of influencing factors.

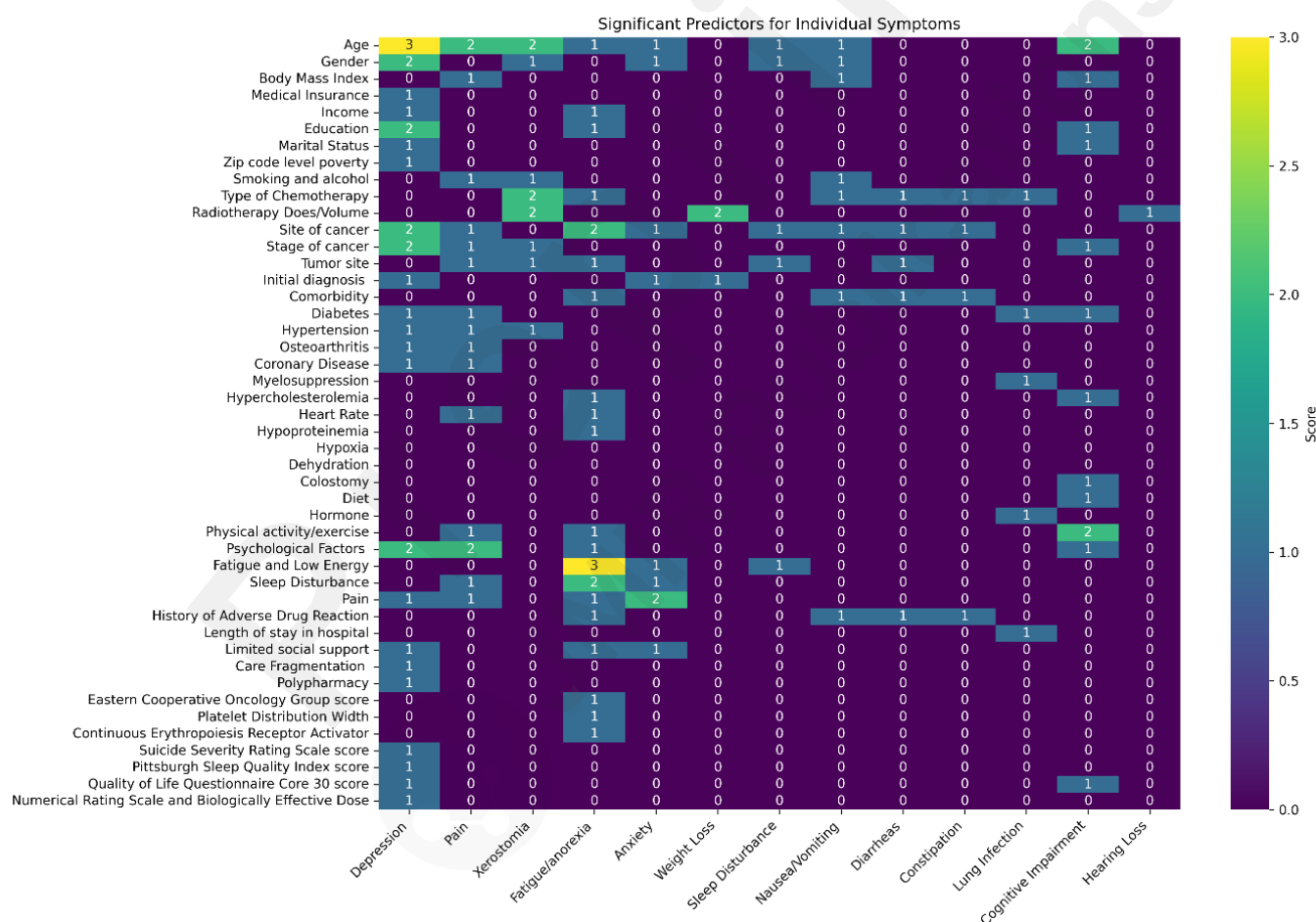


Figure 4. Significant predictors for individual symptoms

For xerostomia, age, gender, chemotherapy type, radiotherapy dose and volume, cancer stage, tumor site, and hypertension are crucial predictors. In the case of pain, factors such as age, BMI (Body Mass Index), smoking and alcohol habits, cancer site and stage, tumor site, diabetes, hypertension, osteoarthritis, coronary disease, physical activity, psychological factors, sleep disorders, and existing

pain conditions emerge as significant. Significant Predictors for depression include age, gender, education, cancer site and stage, economic factors like insurance, income, and poverty level, marital status, initial diagnosis impact, comorbidities (diabetes, hypertension, osteoarthritis, coronary disease), pain, social support, care fragmentation, polypharmacy, and various scale scores. Finally, for fatigue, the key predictors are existing fatigue and low energy, cancer site, sleep disturbances, age, income, education, chemotherapy type, tumor site, comorbidities, hypercholesterolemia, heart rate, hypoproteinemia, physical and psychological factors, pain, adverse drug reaction history, limited social support, Eastern Cooperative Oncology Group score, platelet distribution width, and erythropoiesis.

When examining the commonalities across these predictors for xerostomia, pain, depression, and fatigue, several factors stand out as particularly influential across multiple symptoms: Age, gender, Cancer Site and Stage, treatment-related factors like the type of chemotherapy and radiotherapy, comorbidities conditions like diabetes, hypertension, and coronary disease, physical and psychological factors, socioeconomic factors like income and education level, demonstrating the impact of cancer treatments on symptom development. These common predictors underscore the complex, multifactorial nature of symptom manifestation in cancer patients, necessitating a comprehensive approach to their management and care.

ML algorithms and Validation Metrics

Out of the 42 studies analyzed, 7 (17%) utilized a single ML algorithm, whereas 35 (83%) employed multiple algorithms. The most effective models, in terms of performance, were Logistic Regression (LR) (9/42, 17%), Random Forest (RF) (7/42, 13%), Artificial Neural Networks (ANN) (5/42, 9%), Decision Trees (DT) (5/42, 9%), and Extreme Gradient Boosting (XGB) (3/42, 6%). As for validation methods, the 10-Fold Cross Validation was the most used (14/42, 31%), followed by 5-Fold Cross Validation (5/42, 11%), 3-Fold Cross Validation (2/42, 4%), and 8-Fold Cross Validation (1/42, 2%). The primary evaluation metric across these studies was the Area Under the Curve (AUC), adopted in 26 of the studies (24%). Figure 5 presents a visual representation of the leading machine learning models along with the validation and evaluation metrics used in the study.

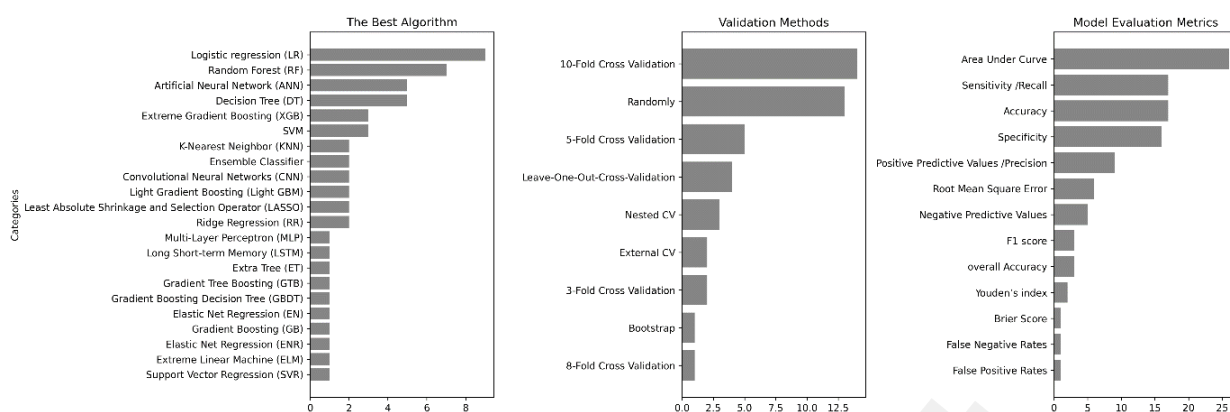


Figure 5. Visual overview machine learning models and metrics

Discussion

In this review, we present the first systematic analysis of ML applications in predicting the development of cancer symptoms. We explore the most frequently studied cancer sites and delve into the intricacies of ML procedures. Breast, head/neck, and lung cancers are the most frequently studied sites in current research, with xerostomia, depression, pain, and fatigue being prominent symptoms. The application of various ML techniques is on the rise, with data acquisition and preprocessing being pivotal for successful ML models. While a range of algorithms, from traditional methods like LR and DT to advanced ones like DL, are utilized, there is a growing emphasis on data quality, external validation, and a standardized approach to model evaluation. The future of ML in cancer symptom prediction looks promising, with a need for collaborative efforts among oncologists, data scientists, and patient groups, combined with more comprehensive research on lesser-studied cancer sites and standardized methodologies.

Regarding the cancer sites covered in the studies, breast, head/neck, and lung cancers emerged as the most frequently researched primary cancer sites. The range of symptoms and side effects that patients experienced varied from one study to another. Some symptoms depended on the specific cancer site and the treatments patients received. For example, xerostomia, which can either arise from the tumor itself or manifest as a treatment side effect, has a significant impact on patients' dental health and compromises antimicrobial functions [61]. However, most symptoms were not directly attributed to a particular cancer site or treatment.

Our review revealed a notable emphasis on predicting xerostomia in 14% of the studies, despite head and neck cancers being less prevalent. Interestingly, even with the lower prevalence of head and neck cancers, our review underscored a pronounced focus (9 out of 42 studies, 14%) on predicting

xerostomia. The notable emphasis on predicting xerostomia in ML research, despite the lower prevalence of head and neck cancers, is likely due to the advancements in integrating ML with CT imaging. CT imaging is a pivotal tool in the diagnosis and treatment planning for head and neck cancers. The integration of ML with CT imaging has opened new possibilities for more accurately predicting side effects like xerostomia. ML techniques, when applied to CT images, can potentially identify patterns and indicators that are not easily discernible to human observers. This capability can lead to earlier and more precise predictions of xerostomia, enabling better preventive measures and treatment planning to mitigate this side effect. Therefore, the focus on xerostomia in ML research, in the context of head and neck cancers, is likely driven by the opportunities presented by combining ML with advanced imaging techniques.

Depression, a widespread emotional challenge for people with cancer [62, 63], was the focus of prediction in many studies (8/24, 13%). Similarly, pain, a recurrent concern for palliative care patients [64] and survivors of cancer [65, 66], was the subject of prediction in over (8/24, 13%) of studies. Fatigue, prevalent across all age groups with cancer [67, 68], was highlighted in 6 out of 42 the studies (10%) reviewed.

In terms of ML approaches utilized in the studies, a plethora of techniques were employed to construct these predictive models, spanning all phases of the ML process, from data collection and preprocessing to feature and algorithm selection, model training, testing, and evaluation. The process of data acquisition is pivotal for the development of ML models, thereby emphasizing the importance of an adequate sample size. Upon reviewing 42 studies, we discerned that the most frequent sample sizes for ML applications ranged between 100 and 1000 samples. More advanced ML techniques necessitate larger datasets to bolster robustness and mitigate the risk of overfitting. Alarming, certain studies in our review utilized ML with comparably smaller datasets, introducing the risk of model overfitting and potential biases in the subsequent performance metrics [69]. Challenges tied to sample size might impede the creation of sturdy and trustworthy ML models [70]. Data preprocessing is indispensable to yield clean and interpretable data, a cornerstone for proficient ML models. Data cleaning approaches encompass addressing missing values, tackling data noise, and data normalization. Within healthcare datasets, noisy or absent data are frequently a byproduct of inaccuracies in manual entries or instrument recordings made by medical personnel or ancillary staff [71]. Yet, most of the reviewed studies lacked comprehensive descriptions of their data cleaning methodologies or strategies for handling noisy data and normalization, constrained by word or page limits in publications.

Given the crucial importance of data quality in developing machine learning models, it's essential for

researchers to focus equally on effective data preparation and choosing suitable algorithms. Future endeavors would benefit from exhaustive procedural documentation made available on public platforms like GitHub. In a research context, GitHub can be used for sharing and collaborating on various aspects of a research project, including but not limited to code. It allows researchers to maintain version control of their scripts, data analysis procedures, and even documentation. This feature is particularly beneficial for replicating studies and verifying results, as it provides a transparent view of the methodologies and analyses used.

Overloading an ML model with excessive features can undermine its ability to differentiate between pertinent data and superfluous noise, leading to the challenge often referred to as the 'curse of dimensionality.' The goal of feature engineering is to mitigate model complexity, expedite the training process, reduce the data's dimensionality, and avert overfitting [72]. By streamlining the model with a curated set of predictors, it becomes more accessible and transparent, emphasizing the importance of feature selection during data preparation. Our review pinpointed the most frequently used significant predictors in cancer symptom prediction. The efficacy of prediction models is heavily influenced by the number and interplay of relevant predictors. Factors such as age, gender, the type and number of previous treatments, cancer location, cancer stage, chemotherapy type, dosage and volume of radiotherapy, chronic conditions like diabetes and hypertension, concurrent diseases, and symptoms including depression, anxiety, fatigue, pain, and sleep disturbances have consistently featured as determinants in numerous predictive frameworks. Our review of cancer symptom prediction underscored age as a pivotal factor, associated with predominant symptoms like depression, pain, xerostomia, and fatigue. While numerous elements, from gender to type of treatment and cancer stage, influence the predictive models, it is the prominence of age that consistently emerges as a cornerstone predictor. As we delve deeper into this field, even with the introduction of newer determinants and correlations, the centrality of age in these frameworks remains indisputable.

When it comes to algorithm selection, traditional methods often struggle with handling high-dimensional data and processing extensive information. To tackle these challenges, researchers have increasingly shifted towards innovative ML algorithms renowned for their robust predictive power and strong generalization capacities. These sophisticated algorithms excel at delving deep into data and discerning intricate interrelationships among variables. For navigating the multifaceted landscape of modeling challenges, it is advantageous for researchers to leverage a diverse array of ML algorithms. Most studies employed multiple predictive models, with techniques like LR, RF, ANN, DT and consistently delivering stellar results. The introduction of advanced ML techniques,

such as DL and Ensemble classifiers, provides promising opportunities to elevate prediction accuracy in upcoming research.

After their design, ML models undergo training and testing on different datasets. However, these models can grapple with issues like overfitting and underfitting. Overfitting occurs when a model becomes overly complex, which leads to increased variance and reduced clarity. In contrast, underfitting results from an oversimplified model, causing it to overlook key data patterns and diminish its predictive capacity. Therefore, the ideal learning model should strike a balance between optimal variance and justifiable bias. To mitigate these issues, the common strategy is to divide the dataset into training and testing subsets, followed by internal or external validation. While most studies in our review utilized internal validation, only one study reported external validation [58] which was demonstrated on a small cohort of 25 head and neck cancer patients. Even though its performance is typically lower than evaluations using the original datasets, external validation remains crucial for gauging ML models [72]. It's a crucial step in ensuring that the model's performance is not just limited to the conditions and data it was originally trained on, but also applicable and reliable in broader, real-world clinical settings. This approach serves to verify the model's efficacy and generalizability across different patient populations and settings.

Understanding and interpreting ML models continue to pose challenges. Determining the variables that significantly impact symptom prediction can be elusive due to the intricate prediction processes. Many studies gauge the performance of ML models using metrics that examine their ability to distinguish between two classes. From our systematic review of 42 studies, the area under the curve (AUC) emerged as the predominant metric for prediction models. Other metrics included accuracy, sensitivity, specificity, positive predictive value (PPV), root mean square error (RMSE), and negative predictive value (NPV). These metrics provide a holistic view of a model's efficacy, facilitating its refinement and enabling more precise predictions. Yet, the diverse emphasis on distinct metrics in numerous studies underscores the need for a uniform approach to evaluating ML models in cancer symptom prediction.

As interest grows in using ML for predicting cancer symptoms, there are several areas that merit deeper investigation. A crucial area is broadening the range of studied cancer sites and more comprehensively correlating symptoms with various treatment methods. To fully understand symptom prediction, it is essential that future studies delve into lesser-explored or infrequently studied cancer sites. Furthermore, the methodologies used for data preprocessing and cleaning should

be documented more thoroughly, focusing on best practices to ensure data integrity. Since data is foundational to ML models, transparent and detailed preprocessing can improve the reliability and repeatability of these models. Although our analysis highlighted common predictors for symptom forecasting, examining potentially underrepresented or emerging indicators could refine these models further. On the algorithmic front, exploring hybrid ML methods that merge the strengths of multiple algorithms might be particularly beneficial for cancer symptom prediction. Standardizing evaluation metrics across studies would also bring clarity and facilitate a more accurate comparison of various ML techniques. To genuinely progress, collaborations among oncologists, data scientists, and patient advocacy groups are vital to ensure the developed models are technically robust and clinically pertinent. With these insights, ML stands poised to transform cancer care, creating treatment plans based on patient-focused and accurate symptom prediction models.

Limitations

This review is not without its limitations. Although we established clear inclusion and exclusion criteria, potential biases in the studies we analyzed could inherently limit our review. We might have missed or excluded relevant studies due to inadequate information or absent keywords in their titles or abstracts. Many of the studies we reviewed did not specify the cancer site, potentially limiting the accuracy and applicability of our findings to specific cancer types. The broad range of predictors used across the studies also made it difficult to draw definitive conclusions about the most influential factors in predicting cancer symptoms using ML algorithms. As such, readers should interpret these results cautiously given this variability.

Conclusion

ML offers an intriguing potential for predicting cancer symptoms, thereby preemptively mitigating the associated challenges. Predicting the symptoms that people with cancer might experience and determining their onset throughout their treatment journey is a pivotal clinical issue that can enhance patients' quality of life. Notably, all studies in our review were published post-2017, highlighting the nascent nature of this research area. Our investigation primarily sought to outline the ML methodologies harnessed for symptom prediction in people with cancer. While ML techniques hold an edge over traditional statistical approaches by virtue of their prowess in analyzing vast datasets and gauging the efficacy of diverse prediction models, certain impediments like a limited pool of symptoms, suboptimal data preparation, challenges in feature engineering, and complexities in ML algorithm design, validation, and evaluation can constrain the broad applicability of these predictive

models. Forthcoming research should pivot towards amplifying the efficacy of ML strategies. This enhancement can be achieved by harnessing expansive, high-caliber datasets, tapping into innovative technologies for data refinement, and sculpting refined models. Harnessing ML can potentially free healthcare practitioners – including doctors, nurses, and clinic personnel – to accentuate the human touch in managing cancer symptoms.

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Multimedia Appendix 1

The detailed databases search strategy, which employs Boolean expressions. [Multimedia Appendix 1](#)

Multimedia Appendix 2

The data extracted from 42 studies. [Multimedia Appendix 2](#)

Conflicts of Interest

None declared.

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Abbreviation:

ANN= Artificial Neural Network

DL =Deep Learning

DT = Decision Tree

LR= Logistic Regression

ML= Machine Learning

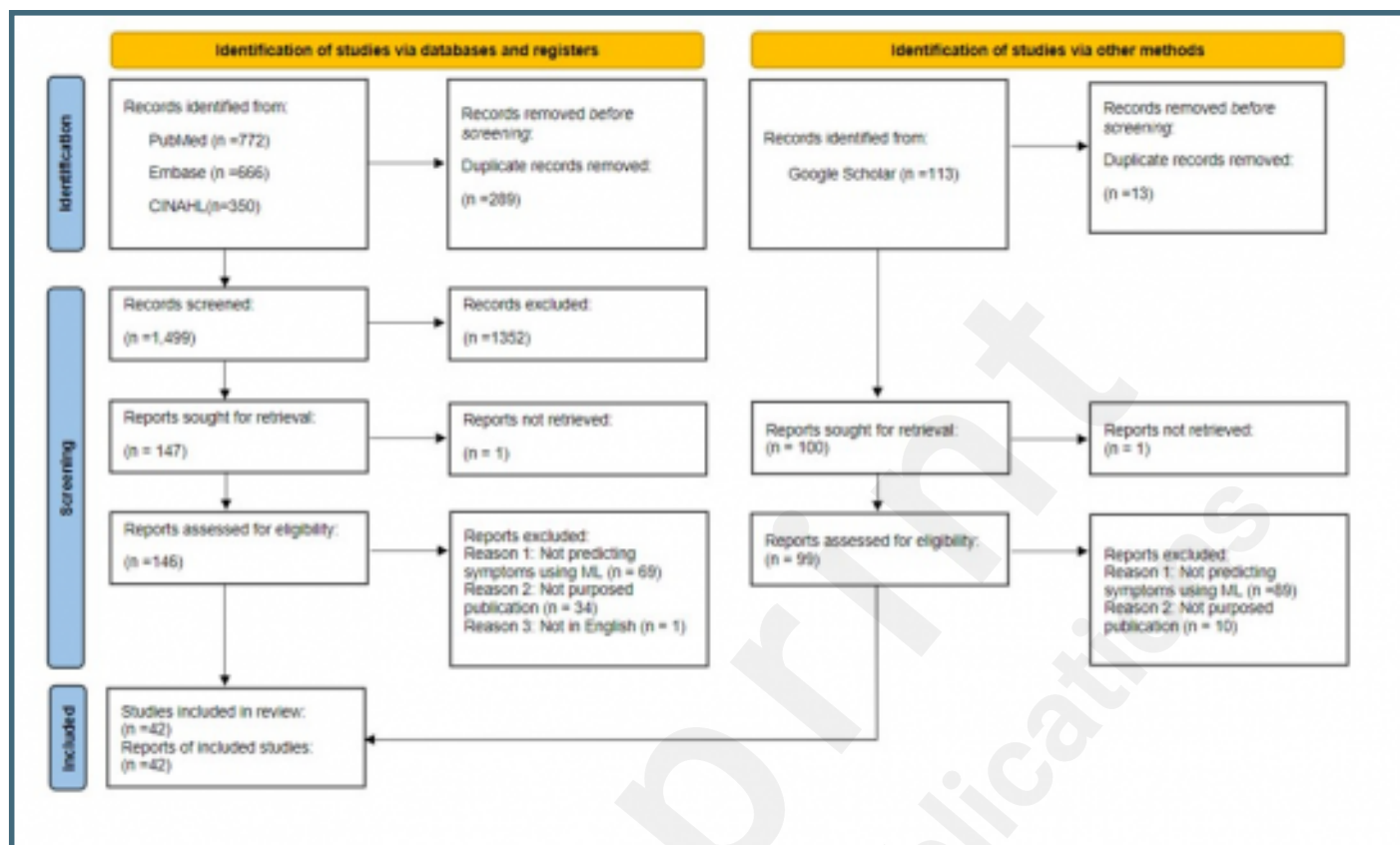
PRISMA =Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RF= Random Forest

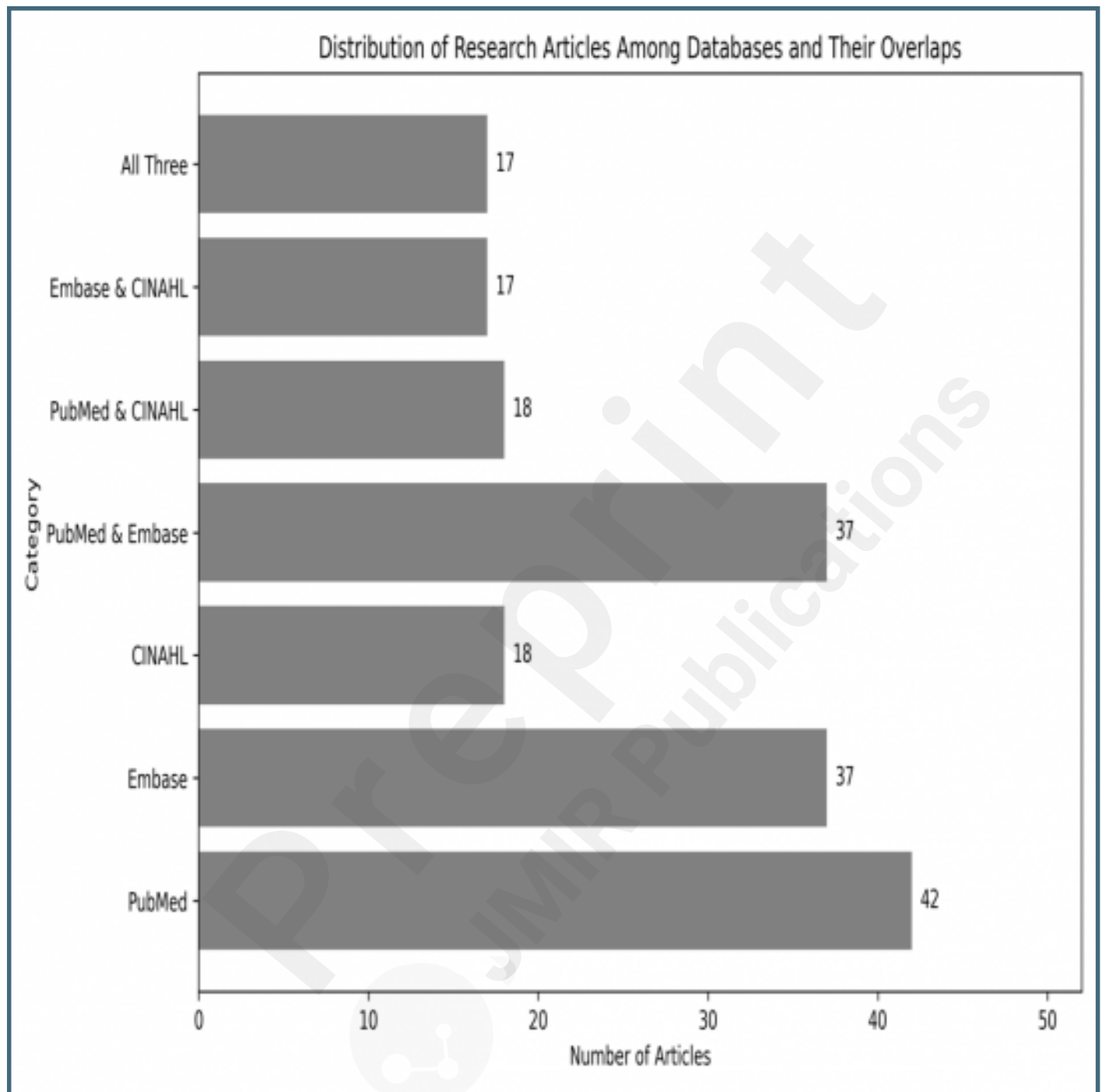
Supplementary Files

Figures

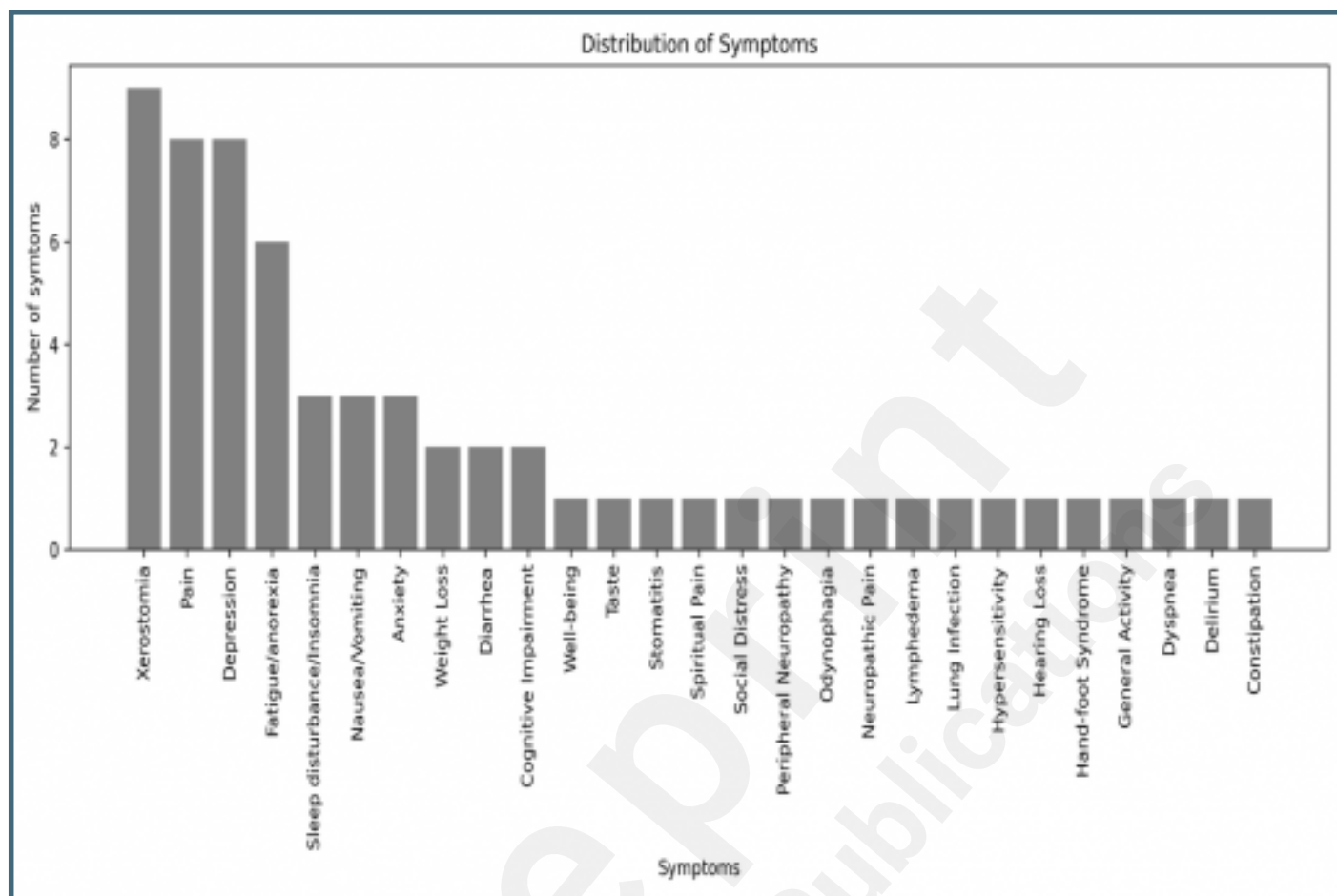
PRISMA Flowchart.



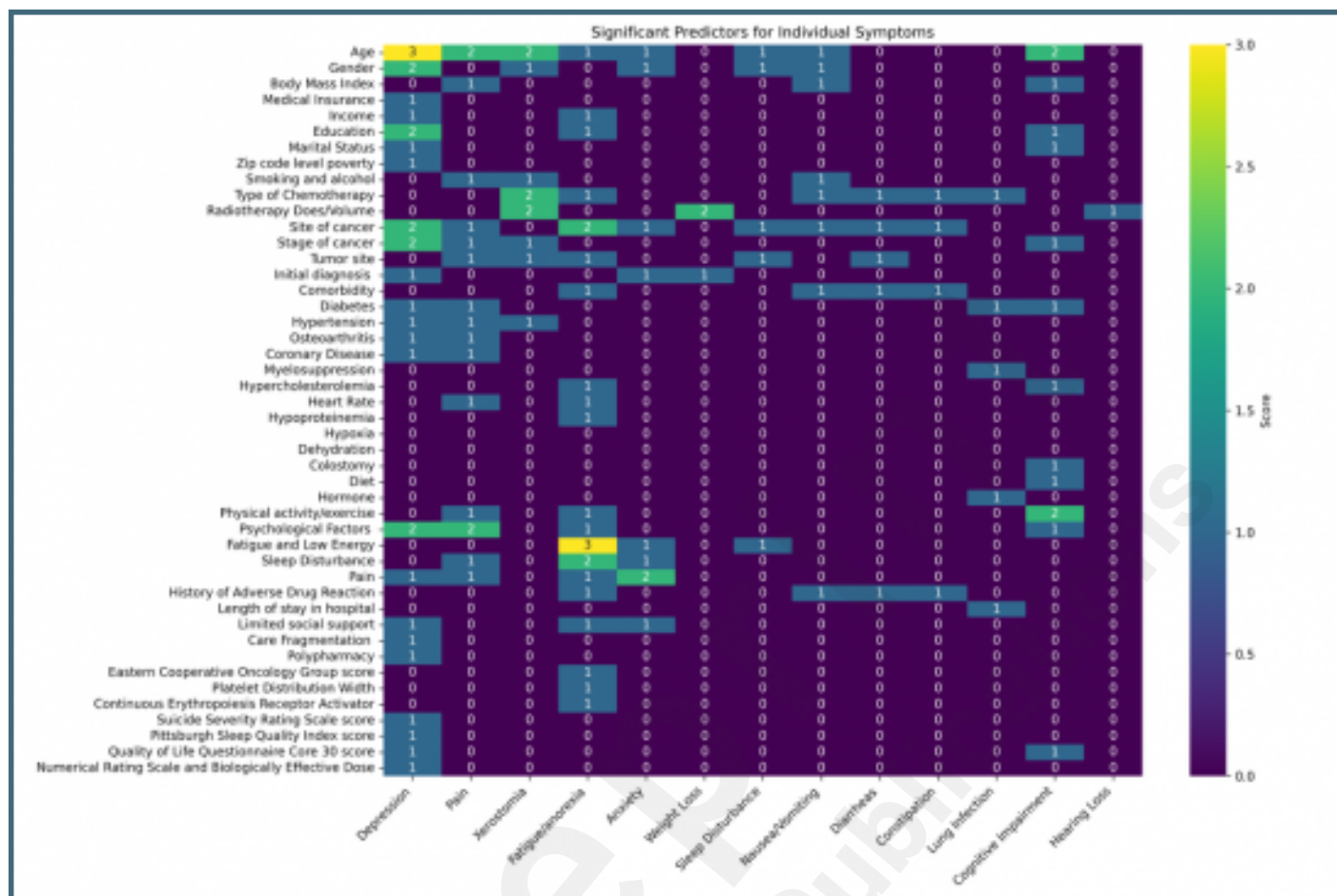
Distribution of research articles among databases and overlaps.



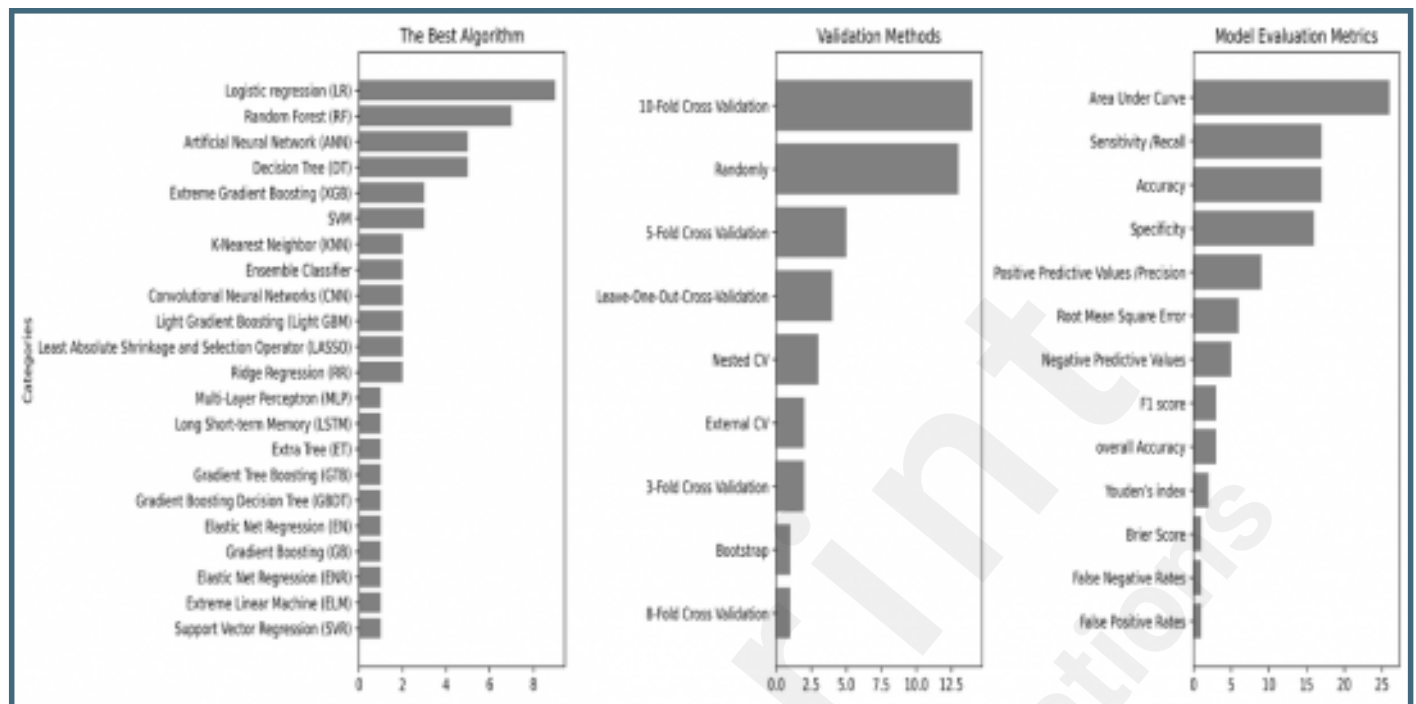
Number of studies per cancer symptoms.



Significant predictors for individual symptoms.



Visual overview machine learning models and metrics.



Multimedia Appendixes

The detailed databases search strategy and employs Boolean expressions.

URL: <http://asset.jmir.pub/assets/7c5a0fd56d5d3e616d5a33f7f27e680b.docx>

The data extracted from 42 studies.

URL: <http://asset.jmir.pub/assets/e1565a555906cadeee93832162b50df0.docx>

PRISMA_2020_checklist.

URL: <http://asset.jmir.pub/assets/594fb5de598913fc85b839deb0a9a94d.pdf>

