

TOPICAL REVIEW

Genetic and Epigenetic Predispositions, Shared Mechanisms, and Common Biomarkers Between Cancer and CVD—Machine Learning-Based Insights

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ABSTRACT People affected by cancer are at an elevated risk of cardiovascular disease (CVD)-associated morbidity and mortality; the reverse association is also substantially evident. This bidirectional association can be characterized by their genetic susceptibility, common modifiable and non-modifiable risk factors, shared molecular mechanisms, and diagnostic biomarkers. The root of this intricate relationship between these two disempathetic phenotypes is not clearly understood yet, though their mechanistic correlations and underlying shared pathways are consistently investigated. Along with bioinformatics methods, machine learning capabilities are evolving and may enhance the understanding of this complex relationship through genetic variant and epigenetic modification detection, biological mechanism elucidation, common biomarker discovery, and predictive model development for cancer-related morbidity and mortality in CVD patients and CVD-related events in cancer patients or survivors. In this review, we critically analyze the advancements, contributions, potential, and challenges of machine learning applications. As a relatively new approach, we identify the necessity of optimized computational methods for important feature selection, efficient data imputation algorithms for handling missing data, effective data harmonization pipelines for multi-modal data, computational frameworks for the simultaneous cancer-CVD risk stratification, and explainable algorithms for comprehensive clinical translation. Finally, we recommend machine learning-based causal inference analysis of their interconnections in order to understand their mutual causal effects.

INDEX TERMS Biological association, biomarkers, cancer, cardiovascular diseases (CVD), common pathways, machine learning, molecular mechanisms, predictive modeling.

I. INTRODUCTION

Cancer and cardiovascular disease (CVD) are the top two deadliest chronic diseases worldwide that are among the

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most significant contributors to the global morbidity and mortality [1], [2], [3], [4]. Although independent studies of cancer and CVD are prevalent, substantial evidence highlights the necessity of investigating the complex and shared biological pathways and correlations between these two diseases, given the considerable overlap in risk factors,

pathophysiology, and molecular mechanisms [1], [3], [4], [5], [6]. In addition, mounting evidence addressing cancer-induced risks of CVD development [7], [8], [9], [10], [11], [12], [13], [14] and CVD-influenced risks of cancer growth [15], [16], [17], [18], [19] further underscores the significance of combined approaches to answer a key question more accurately: do they share the same biological origins through overlapping pathways?

The epidemiological similarities are often explained by common modifiable risk factors [1], [3], [4], [20], such as obesity [21], smoking [22], dietary imbalance [23], physical inactivity [24], [25], alcohol consumption [26], [27], [28], diabetes mellitus [29], [30], hypertension [31], [32], [33], [34], hyperlipidemia [35], [36], [37], [38], [39], and social determinants of health factors [1], [40], [41] comprising socio-economic status, healthcare facilities, access to education, surrounding built environment, and neighbourhood quality [1] that usually demonstrate a surface-level understanding of their associations, whereas their genetic and epigenetic predispositions [42], [43], [44], [45], [46], [47], [48], [49], [50], and molecular mechanisms [1], [3], [51], [52], such as chronic systemic inflammation [53], [54], [55], [56], [57], oxidative stress [57], [58], [59], endothelial dysfunction [60], [61], [62], metabolic dysregulation [5], gut microbial dysbiosis [63], [64], cell death mechanisms [65], [66], and angiogenesis [67], [68], [69] provide a deeper insight into their biological intersections. In addition, age is another non-modifiable risk factor, and both these diseases are significantly associated with both biological and chronological age [41], [44], [70], [71], where biological ageing parameters hold an improved picture of their interconnections. However, the paths to the root of their complex associations are yet to be fully understood, though biomedical research has revealed several correlations.

Machine learning (ML) has evolved as an integral methodology in biomedical research with the potential to extract the complex relationships between cancer and CVD. For example, ML can detect the core diagnostic genes from cancer and CVD-specific genetic variants and epigenetic modifications, aiding in potential genetic marker identification that can reveal significant underlying correlations [43], [44], [45], [46], [47], [48], [49], [50]. In addition, ML-based approaches are not only efficient in large-scale genomic data analysis [47], [72], [73], they are also effective in dealing with multi-omics data [48], [49], [50]. Furthermore, they are of importance in multi-modal medical data management [70], [74], [75], [76], [77]. Computational frameworks based on ML can enhance pathway analysis, and innovative approaches report novel pathways [78]; for instance, disulfidptosis-related gene identification for hypertrophic cardiomyopathy detection is a significant contribution, as this newly identified cell death mechanism demonstrates strong correlations with tumor metabolism and is being considered in therapeutic targets for cancers [79], [80], [81], [82], [83], [84]. The contribution of ML is not limited to common biomarker identification

only, but is of importance for identifying novel markers; for example, the integration of retinal image features with clinical data to develop an efficient biological ageing marker is such an approach [70]. Additionally, the role of ML has assisted in the repurposing of cancer screening data (CT scan images, LDCT scans, and mammograms) for CVD-associated marker identification [85], [86], [87], [88]. Therefore, it is no surprise if a framework takes cancer screening data, calculates CVD-associated markers using that data, and predicts CVD events automatically. Moreover, demonstrating urinary heat shock proteins as cancer-specific markers is another notable ML contribution [89].

Limited but significant ML-based attempts are observed in predictive model development, which is a proven strength of machine learning architectures. Promising approaches are evident in predicting cancer events by assessing CVD conditions [90], [91], [92] and predicting CVD events in cancer patients or survivors [40], [74], [93], though most of them are cohort-specific and require external validation for clinical translation. Furthermore, ML-assisted cancer-CVD mortality analysis [70], [94], [95], [96], [97], [98], [99], [100], [101] reveals several significant associations that enhance the comprehensive analysis of the intersections between cancer and CVD. Figure 1 depicts an overview of the role of ML in cancer-CVD association analysis.

This comprehensive review is an attempt to critically analyse the application of ML in enhancing the understanding of the natural and biological associations of cancer and CVD through exploring their shared mechanisms, biological pathways, common biomarkers, and predictive models. Therefore, we intentionally exclude the studies that are solely focused on cardio-oncology because it offers assessment, treatment, and management of cardiovascular conditions in cancer patients, particularly those exposed to treatment and therapies causing cardiotoxicity [102], [103]. Despite several significant contributions of ML, future research directions may be found in addressing the existing challenges observed in data, algorithms, and clinical implementations.

II. SHARED MECHANISMS AND CORRELATIONS

The modifiable and non-modifiable risk factors common to cancer and cardiovascular complications are significant indicators of their biological correlations. Genetic susceptibilities and several signaling pathways demonstrate a vital role in their pathogenesis and enhance the understanding of their co-occurrence. Machine learning can comprehensively analyse the differentially expressed genes, DNA methylation patterns, and other modifications to identify the phenotype-specific signature genes. Additionally, ML can be a useful tool in their shared pathophysiology analysis to extract the potential molecular correlations.

A. GENETIC AND EPIGENETIC CORRELATIONS

Differentially expressed genes (DEGs) resulting from genomic alterations, including single nucleotide polymorphisms (SNPs) or epigenetic modifications such as DNA

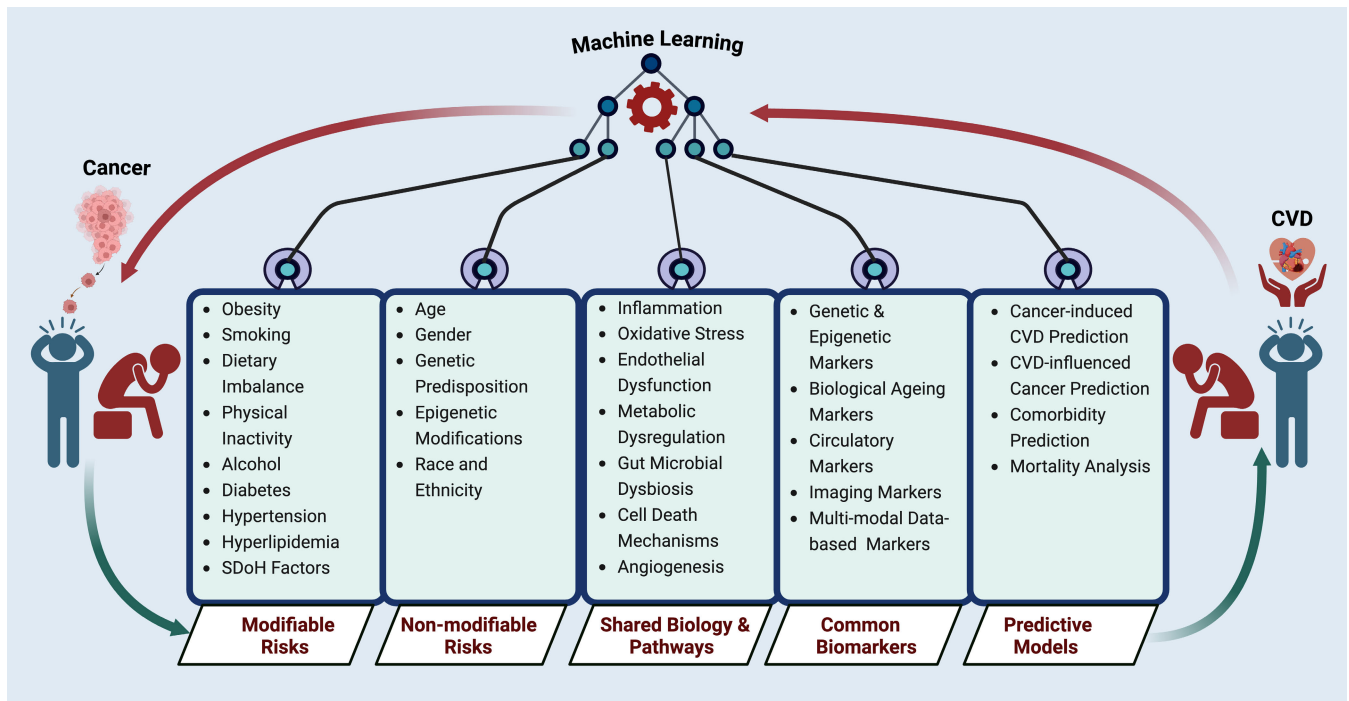


FIGURE 1. ML can significantly elevate risk stratification, shared pathophysiology revelation along with bioinformatics methods, common biomarker detection and validation, and efficient predictive model development.

methylation require advanced analysis (gene ontology, enrichment analysis, pathway analysis, functional analysis, etc.) to understand the biological process, cellular ingredients, molecular mechanism, and pathways underlying cancers and various CVD conditions, where machine learning has evolved as an instrumental tool alongside transcriptomics [104], [105], [106], [107], [108], [109] in analyzing gene expression patterns and revealing the key diagnostic genes and molecular connections [43], [45], [46], [49]. For instance, methyltransferase-like 7B (METTL7B) is one of the four core diagnostic genes of heart failure (HF) identified from a set of DEGs using LASSO regression-based feature selection technique, support vector machine (SVM), and random forest (RF) classifiers [43], which was previously found to be involved in several types of cancers, including lung adenocarcinoma [110] and non-small cell lung cancer [111]. In immune and functional analysis, METTL7B was overexpressed in two specific lung cell lines (A549 and PC9) where both mRNA and protein levels were found significantly higher, suggesting the potential role of METTL7B in the simultaneous occurrence of heart failure and cancer in lung cells, though further investigations are required, especially in myocardial cells [43]. Similarly, Ficolin-3 (FCN3), MAP2K1, AP-3 complex subunit mu-2 (AP3M2), and Cadherin-19 (CDH19) are the four core co-diagnostic genes for HF and hepatocellular carcinoma (HCC) identified from a set of 88 DEGs leveraging random forest with LASSO regression [46]. Furthermore, epigenetic modification through DNA methylation at CpG (Cytosine-

phosphate-Guanine) sites can regulate gene expression, influencing cancer-CVD pathways, as several CpGs were marked as strongly associated with both cancer and CVD-related outcomes [44]. In addition, some immune, methylation, and autophagy-associated genes (IMAAGs) not only enhanced the genetic risk scores to predict the recurrence risk of breast cancer but were also observed to activate the inflammatory coagulation network, endothelial shear stress, and atherosclerosis pathways [45].

Methods utilizing ML can extract the intricate patterns and associations from large-scale genomic data [44], [47], [72], [73]. Topic modeling using non-negative matrix factorization (NMF) [112], an unsupervised ML approach, has validated a known positive association between rs10455872—a specific SNP in the Lipoprotein(a) (LPA) gene—and CVD risks [113], [114], while revealing a novel negative correlation of rs10455872 with lung cancer [47], which was unidentified in a previous genome-wide association analysis [115]. Genomic and transcriptomic data combined together essentially increase the dimension of the data, and ML methods are not only indispensable in such scenarios but are also found to be efficient in finding complex associations from high-dimensional data [48]. Analysis aided by ML techniques on genetic inference data from a genome-wide association analysis and single-cell transcriptomic data has detected the F3 gene, also known as CD142, as a key regulator in both glioma and coronary heart diseases [48]. Another approach involving multi-omics data has revealed that hypertrophic cardiomyopathy (HCM) and various cancers share a genetic

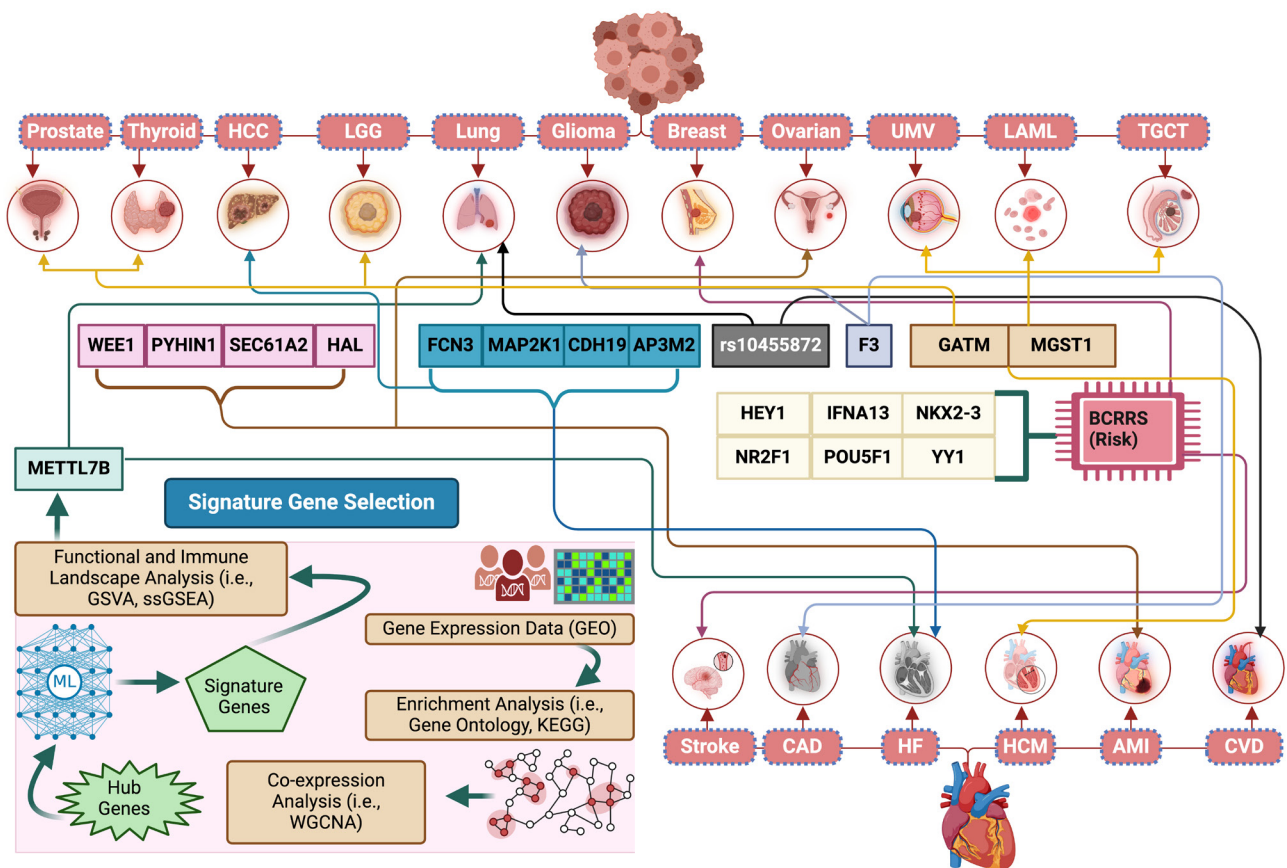


FIGURE 2. The signature gene selection process is adapted from [43] that identified *METTL7B* as a potential regulator in both heart failure and lung cancer. Studies [43], [45], [46], [47], [48], [49], [50] revealed potential genetic links among several types of cancers (prostate, thyroid, hepatocellular carcinoma (HCC), low-grade gliomas (LGG), lung, glioma, breast, ovarian, uveal melanoma (UVM), acute myeloid leukemia (LAML), and testicular germ cell tumors (TGCT)) and cardiovascular diseases (stroke, coronary artery diseases (CAD), heart failure (HF), hypertrophic cardiomyopathy (HCM), and acute myocardial infarction (AMI)). Breast cancer recurrence risk score (BCRRS) influenced by *HEY1*, *IFNA13*, *NKX2-3*, *NR2F1*, *POU5F1*, and *YY1* was associated with stroke [45].

link via *GATM* (Glycine AmidinoTransferase) and *MGST1* (Microsomal Glutathione S-Transferase 1) that have been found heavily involved in the xenobiotic metabolism and epithelial-mesenchymal transition pathways [49]. Furthermore, *WEE1* (a protein kinase), *PYHIN1* (Pyrin and HIN Domain Family Member 1), *SEC61A2* (*SEC61* Translocon Alpha Subunit 2), and *HAL* (Histidine Ammonia-Lyase) are monocyte-derived genes identified through multi-omics analysis that have been seen responsible for a shared activation of the notch signaling pathway, and consequently, they have been identified as potential diagnostic and prognostic markers of acute myocardial infarction (AMI) and cancers [50]. Figure 2 depicts the typical process of signature gene selection and the potential connections of the core diagnostic genes with several cancers and CVDs. The associated biological pathways are highlighted in Section II-B. The full potential of ML is yet to be explored for understanding the combined genetic predisposition of both these disease conditions, though significant advancements are evident in the individual studies of cancer and CVD.

B. SHARED PATHOPHYSIOLOGY AND MOLECULAR PATHWAYS

Recent evidence strongly suggests a bidirectional association between cancer and CVD, highlighting the influence of shared pathophysiological processes in addition to the traditional shared risk factors, because the biological mechanisms driving CVD conditions can play a significant role in cancer growth [18], [49]. On the other hand, adverse cardiac events may be triggered by oncogenic conditions, as they are influenced by several common mechanisms [50]. The relationship is even more intricate as they share a wide range of biological processes (see Table 1) alongside the mostly studied ones, such as chronic inflammation, oxidative stress, endothelial dysfunction, and angiogenesis. Oncogenic inflammation influences tumor progression and metastasis as anti-tumor immunity is effectively suppressed by the inflammatory mediators [116], and this down-regulated immune system affects the cardiovascular system due to chronic inflammation, often exacerbated by oxidative stress [117], [118], causing endothelial dysfunction and

inducing vulnerability in atherosclerotic plaques, resulting in adverse cardiovascular events [119]. Inflammatory cytokines and chemokines promote angiogenesis [120] and immune evasion that are closely associated with the prognosis and progression of both disease conditions [121].

Immune and inflammatory response-related pathways are evident in the pathophysiology of heart failure (HF) and hepatocellular carcinoma (HCC) [122], [123], [124], [125]. In a recent study [46], four core co-diagnostic genes (FCN3, MAP2K1, AP3M2, and CDH19) of HF and HCC have been detected using a machine learning approach incorporating XGBoost algorithm with Bayesian sequence model-based hyperparameter optimization, and the involvement of metabolic pathways and co-altered immune cells has been unveiled through the association analysis of these four genes with 50 classical pathways from a molecular pathway database (MSigDB) [126] using GSVA—a gene set variation analysis technique [127] and ssGSEA—a single sample-based variant of gene set enrichment analysis [128]. Similarly, the involvement of oxidative stress and immune landscape in HF and lung cancer has been determined through the further functional and immune landscape analysis, such as GSVA and ssGSEA on the genes identified using machine learning-based methods [43], whereas lipoprotein metabolism has been revealed as a shared channel between lung cancer and cardiovascular conditions [47]. In addition, cellular signaling pathways (notch signaling, WNT signaling, and TGF- β), interferon response, epithelial-mesenchymal transition, epigenetic modifications such as RNA methylation, and stem cell regulations are observed to be shared by breast cancer and stroke risk [45]. Furthermore, Angiogenesis, vascular endothelial dysfunction, and TNF- α signaling via NF- κ B has revealed a potential connection between glioblastoma and coronary artery diseases [48], whereas a shared activation of the notch signaling pathway has unveiled an association underlying acute myocardial infarction and various cancers [50].

C. CAN DISULFIDPTOSIS BE A SHARED MECHANISM?

Disulfidptosis [129] is a recently identified cell death mechanism that destroys the cytoskeleton structure of the cell as a result of induced disulfide stress and actin collapse, where the disulfide stress is induced by the aberrant accumulation of intracellular disulfides due to glucose starvation with overexpressed SLC7A11 [78]. This newly identified programmed cell death mechanism has garnered significant attention, particularly in cancer research, due to its complex relationship with tumor metabolism and potential as a therapeutic target [79], [80], [83], [84]. However, it remains largely understudied in the context of cardiovascular disease (CVD), whereas other regulated cell death pathways, such as apoptosis, necroptosis, cuproptosis, and ferroptosis are already recognized as crucial in the pathophysiology of both cancer and CVD.

Machine learning applications addressing disulfidptosis in CVD research have opened up a range of research opportunities, potentially finding a strong shared pathway to minimizing the cancer and CVD-related burdens. A computational framework incorporating four ML algorithms (SVM, RF, Extreme Grading Boosting (XGBoost), and Generalized Linear Model (GLM)) has identified 16 disulfidptosis-related genes that are significantly associated with hypertrophic cardiomyopathy (HCM) occurrence, where SVM has been optimal (with a ROC value of 0.853) in finding the top five markers of them (GYS1, MYH10, SLC3A2, CAPZB, and PDLIM1) and a predictive model with these five core markers for HCM has exhibited an outstanding prediction accuracy [78]. In HCM patients, GYS1, MYH10, and PDLIM1 have been found upregulated, whereas SLC3A2 and CAPZB have demonstrated decreased expression levels, and in immune infiltration analysis, B cells, regulatory T cells, gamma delta T cells, resting NK cells, and M2 macrophages have been presented with increased infiltration patterns, whereas monocytes and activated dendritic cells have been reflected with decreased infiltration. Additionally, in drug prediction targeting these core genes, resveratrol (RSV) has been revealed as a potential therapeutic solution on HCM, whose effectiveness in cancer has already been widely reported [130], [131].

III. INVESTIGATING COMMON BIOMARKERS

Genetic and epigenetic drivers of cancer and CVD highlighted in Section II-A and Section II-B underscore the involvement of ML approaches for such biomarker discovery and validation. Several genes and genetic variants, such as lipoprotein (a), have been crucial in revealing the correlations between various cancers and cardiovascular diseases [43], [45], [46], [47], [48], [49], [50]. Furthermore, CpGs are significant biomarkers as they hold molecular-level information of genetic influence and environmental exposures [132], [133]. For instance, five CpGs in European ancestry and eight CpGs in African ancestry were found common in both cancer and CVD mortality, and these mortality-specific CpGs were reported to be strongly associated with several cancers and CVD-oriented risk factors through immune and cancer-associated pathways [44].

Furthermore, ML can aid in non-invasive and cost-effective biomarker discovery with the already demonstrated potential of deep learning architectures, specifically in imaging data processing. Biological age shows a stronger correlation with disease phenotypes than chronological age, as the associated markers are mostly blood parameters (albumin, glucose, C-reactive protein, etc.) in biological age calculation [134]. Retinal photographs can significantly enhance the biological age estimation as they provide data on neural tissue and microvasculature responses [135], [136] in a non-invasive manner. A deep convolutional neural network model has been developed [70] that combines retinal image features, mainly focusing on the macula, optic disc, and retinal vessels, with clinical features to produce a comparatively better composite

TABLE 1. Genetic variants and SNPs, the associated molecular pathways, and the revealed associations with cancer and CVD are highlighted here. Abbreviations: ROS-Reactive Oxygen Species, BCPRS-Breast cancer prognosis risk score, BCRRS-Breast cancer recurrence risk score.

Genetic Variants/SNPs	Biological Pathways/Mechanisms	Cancer Association	CVD Association	Key ML Methods	Study
METTL7B	ROS (Oxidative stress immune response)	Overexpressed in two lung cell lines (A549 and PC9)	Core diagnostic genes for HF	SVM, LASSO, RF	[43]
HEY1 IFNA13 NKX2-3 NR2F1 POU5F1 YY1	LINC00276&MALAT1/miR-206/FZD4-Wnt7b	Involved in BCPRS and BCRRS estimation. (High expressions of HEY1, IFNA13, NKX2-3, and NR2F1, and low expressions of YY1 and POU5F1 are associated with poor breast cancer prognosis.)	BCRRS is associated with high stroke risk	RF, LASSO, Neural Networks	[45]
FCN3	Immune dysregulation, inflammatory signaling and metabolic pathways: Xenobiotic Metabolism, UV Response Up, Complement, TNF- α Signaling via NF- κ B, KRAS Signaling Up, IL-6-JAK-STAT3 Signaling, IL-2-STAT5 Signaling, TGF- β Signaling, Inflammatory Response, and p53 Pathway	Strong positive association across the pathways, except UV Response Up (weak correlation)	Strong positive association, except KRAS Signaling Up (no correlation); TGF- β , TNF- α Signaling via NF- κ B, and IL-2-STAT5 Signaling show weak correlations	RF, LASSO, XGBoost	[46]
MAP2K1 (MEK1)		Strong positive association across the pathways	Strong positive association, except Xenobiotic Metabolism (no correlation)		
CDH19		Strong positive association across the pathways, except UV Response Up (weak correlation)	Strong positive association across the pathways		
AP3M2		Strong negative association across the pathways, except TGF- β (weak correlation)	Strong negative association across the pathways		
rs10455872 (LPA SNP)	Lipoprotein Metabolism	Negative correlation with lung cancer ($r = -0.039$, $p = 8.5 \times 10^{-6}$)	Positive correlation with CVD ($r = 0.072$, $p = 5.8 \times 10^{-16}$)	LR, Topic Modeling (NMF), t-SNE and PCA	[47]
F3 (CD142)	Angiogenesis, Vascular Endothelial Dysfunction, Inflammatory Response (TNF- α Signaling via NF- κ B)	Highly expressed in gliomas, contributing to the development, progression, and prognosis.	Statistically significant positive correlation with CAD ($r = 0.825$, $p = 3.3 \times 10^{-3}$)	SVM, LASSO, RF, XGBoost, MR	[48]
GATM MGST1	Xenobiotic Metabolism, Epithelial Mesenchymal Transition (EMT)	Substantial correlations with key immune checkpoint genes across various cancers; Positive correlations with cancer-associated signals (apoptosis, hypoxia, inflammation, metastasis, and stemness)	Highly expressed in HCM tissues; involved in immune landscape alterations in HCM.	LASSO, SVM-RFE, RF, Boruta, XGBoost	[49]
WEE1 PYHIN1 SEC61A2 HAL	Notch Signaling Pathway (shared activation)	Elevated expression at both mRNA and protein levels Overexpressed at mRNA level Upregulated at mRNA level Upregulated at protein level	Downregulated in AMI samples Downregulated in AMI samples Downregulated at AMI samples Upregulated at AMI samples	LASSO, LR	[50]

biological ageing marker (RetiPhenoAge), which has been found to be significantly associated with cancer and CVD-related morbidity and mortality.

Blood and biochemical investigations are competitively more reasonable and also non-invasive in nature, but they contain significant information that can be exploited using ML methods for finding disease indices. SHAP (SHapley

Additive exPlanations) analysis of feature importance on a model which is built with logistic regression (LR), SVM, RF, and XGBoost algorithms, integrating routine blood and biochemical test data, has revealed the crucial markers of chronic diseases, including cancer and CVD [137]. Neutrophil levels have been noticed as significantly elevated in CVD patients, and the levels are observed even higher

in CVD patients with tumors than in CVD patients without tumors [137].

In addition, opportunistic value can be added to the computed tomography (CT) scan images of the asymptomatic cancer screening population by utilizing them for predicting future adverse CVD events [88], as CT scans are highly enriched with additional body composition data sufficient for quantifying several CVD markers, such as aortic calcification, muscle density, liver fat contents, and visceral and subcutaneous fat ratio [138], [139], [140], [141], [142]. Low-dose computed tomography (LDCT) scans of lung cancer screening have been repurposed to calculate coronary artery calcification (CAC) score more accurately [143], which is a significant marker of CVD, and additionally, juxtacardiac fat has been identified as another marker in that study. The composition of CAC and juxtacardiac fat has been found to contribute significantly to their model to enhance CVD risk score because the correlation between epicardial or pericardial fat and various CVD risks is already reported in several studies [144], [145]. Moreover, the hierarchical learning capabilities of convolutional neural network (CCN)-based deep learning models and the robustness of ensemble learning mechanisms are not only found in breast cancer detection on mammography images [146], [147] but are also observed to transform mammography images into a potential source of CVD markers such as breast arterial calcification (BAC) [85], [86] and CAC [87], [148]. Figure 3 highlights the dual-purpose use of cancer screening data (CT, LDCT, and mammograms) in the CVD context and depicts how CVD risk can be stratified using these markers with no additional cost and radiation.

Heat shock proteins (HSPs) serve as molecular chaperones that are observed at a higher level in plasma, serum, and tissue biopsies of a vast category of cancer patients, and the overexpressions of HSPs are found to have a link with tumor aggressiveness and metastasis [89], [149]. Note that HSPs are also observed to demonstrate abnormal expressions in patients with cardiovascular diseases [150], [151]. Moreover, HSPs secreted in urine, rather than plasma, serum, or tissue biopsies, have been analyzed, and a machine learning approach using XGBoost with a tree booster has been developed to predict cancer based on specific cancer-type HSP signatures, which have been identified as cancer-specific [89]. This novel approach further attests to the capability of machine learning in biomarker discovery and validation.

IV. PREDICTIVE MODELS

The identification and appreciation of the intersections of cancer and CVD provide a rationale for the early detection and better risk stratification of both these disease phenotypes, where ML-based predictive models incorporating deep learning, ensemble learning and hybrid approaches can be unparalleled in predicting cancer prevalence from CVD conditions and vice versa, as machine learning-based

approaches are already found crucial in their individual studies [152], [153], [154], [155], [156], [157], [158], [159], [160]. Importantly, ML-driven predictive models with causal inference capability can be even more pivotal, as exposing their cause-and-effect relationship may reveal critical insights to enhance the understanding of their internal mechanisms. Although adequate evidence is yet to be reported, a promising study conducted recently has developed the first ML-based causal inference model using a Bayesian network to predict the risk of CVD incidents in breast cancer survivors during adolescence and young adulthood [161], though several applications of causal inference analysis based on Mendelian randomization [162] are reported to efficiently extract some causal effects [44], [48], [163], [164].

Beyond Bayesian networks and Mendelian randomization, several emerging ML-based causal inference models can be adapted because of their demonstrated strong potential in biomedical research. For example, causal forests can be developed by extending random forest algorithm to estimate heterogeneous causal effects, meta learners built on random forests, Bayesian additive regression trees, or neural networks can be a significant inclusion in estimating conditional causal effects, double machine learning (DML) can be effective in providing debiased causal parameters in high-dimensional data scenarios, deep neural networks-based architectures can be designed to capture balanced data representation from complex observational datasets to generate counterfactual predictions, and differentiable causal discovery methods are capable of scalable data-driven identification of causal graphs without imposing a predefined structure. The integration of these ML-based causal inference models into cancer-CVD research can be a significant step to quantify their bidirectional influences.

A. ML PREDICTING CANCER FROM CVD CONDITIONS

Cancer is one of the major comorbidities of stroke, and cancer prevalence in stroke patients has increased significantly in recent times, whereas 4.3% of stroke patients without any previous cancer history are unaware of having occult cancer [90]. Venous thromboembolism (VTE) is the third leading cause of death in CVD patients [165], which can also be the initial indication of an occult cancer [92]. Patients eligible for cancer screening often demonstrate poor cardiovascular health (CVH) profiles [91]. Hence, the role of ML may be crucial in uncovering various malignancy events influenced by numerous cardiovascular abnormalities, though this concept is still underexplored by ML. See Table 2 for the ML approaches and key insights from the relevant studies.

Three instances of a CNN-based model were built on the platelet-stained, fibrin-stained, and erythrocyte-stained immunohistochemical slide images of thrombi collected from thrombectomy in stroke patients to extract features, and logistic regression-based binary classifiers trained on each feature set determined whether a patient belonged to the

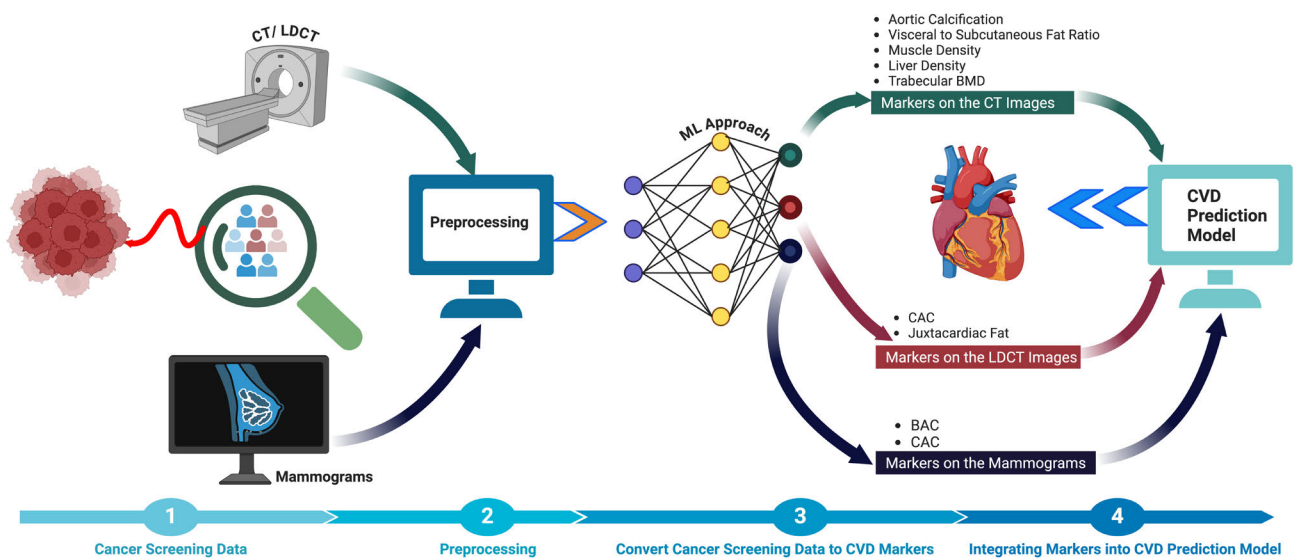


FIGURE 3. Aortic calcification, visceral to subcutaneous fat ratio, muscle density, liver density, and trabecular bone mineral density (BMD) can be quantified from body computed tomography (CT) scan images [88]. Coronary artery calcification (CAC) and volumetric juxtacardiac fat are extracted from low-dose computed tomography (LDCT) images [143]. Two significant CVD markers, CAC and breast arterial calcification (BAC), can be quantified from mammograms [85], [86], [87]. CT, LDCT, and mammograms are collected from the cancer screening population. The role of ML is also highlighted in this figure.

TABLE 2. Overview of the ML approaches applied to predict cancer events in CVD patients. Several key insights are also highlighted in this table. CVH – Cardiovascular Health, BMI – Body Mass Index, BP – Blood Pressure, A1C – Hemoglobin A1C, LDL – Low-Density Lipoprotein, ALT – Alanine Aminotransferase, TG – Triglycerides, VTE – Venous Thromboembolism.

ML Methods	Data	Key Predictors	Best Model	Best Performance	Key Insights	Validation Status	Study
Transfer Learning (CNN and LR)	Histopathologic Images of Thrombi (Total 70561 images) Availability: Restricted	Extracted Thrombus Features	anti-CD42b (Platelet)	AUROC: 0.954 (Internal); AUROC: 0.949 (External)	- Thrombi from stroke and active cancer patients are platelet-rich. - ML can differentiate cancer-related thrombi. - Occult cancer can be a cause of ischemic stroke.	External Validation in 5 Centers (63 patients)	[90]
LSTM	EHR Data of CVH Risk Factors (Total 362,533 patients) Availability: Upon reasonable request	Smoking Status, BMI, BP, A1C, LDL	LSTM	AUROC: 0.70 for cervical cancer	- A poor CVH profile increases the likelihood of receiving cancer screening (mainly poor A1C). - Cancer screening helps improve the CVH measures. - ML can analyse time-series CVH metrics to decrease the overall cancer-CVD burden.	Internal Validation (20% test data)	[91]
XGBoost, LightGBM, CatBoost	Clinical and Laboratory Data from VTE Patients (Total 815 patients) Availability: Upon reasonable request	Age, D-dimer, Systolic BP, ALT, Hb, Creatinine, Cholesterol, Platelet, TG, Leukocytes, Weight, Chronic lung diseases, Heart rate, Gender, Previous VTE	CatBoost	AUROC: 0.86 (Test data: 25%)	- ML can identify patients who are vulnerable to occult cancer among VTE patients. - CatBoost is optimal while dealing with a large amount of categorical data. - First ML application to predict occult cancer in VTE patients.	3-fold cross-validation (External validation required)	[92]

cancer group or the other cause group, where platelet-stained images were observed to produce the best features [90]. The extended application of this approach also predicted occult cancer in stroke patients. In addition, [92] demonstrated an

ML method incorporating variants of the gradient boosting techniques, such as XGBoost, LightGBM and CatBoost, suitable for handling categorical data to predict occult cancer between 30 days and 24 months of the first VTE event.

TABLE 3. Overview of the ML approaches applied to predict CVD events in cancer patients and survivors. Several key insights are also highlighted in this table. NN – Neural Network, CM – Cardiomyopathy, CHF – Congestive Heart Failure, CAD – Coronary Artery Diseases, MI – Myocardial Infarction, TIA – Transient Ischemic Attack, AR – Arrhythmia.

ML Methods	Data	Key Predictors	Best Model	Best Performance	Key Insights	Validation Status	Study
XGBoost	EHR and SDoH (4309 breast cancer patients) Availability: Open-source	Number of CVD history/risk factors, age at diagnosis, Prior cardiomyopathy, time to surgery, neighbourhood median household income	Race-agnostic model	C-index: 0.79 (Race-agnostic model)	- ML can predict 2-year MACE in post-breast cancer patients. - Non-Hispanic Black (NHB) women are more prone to CVD. - Social determinants can influence CVD risk in post-cancer.	10-fold cross-validation on independent validation data	[40]
Adaptive LASSO and RF	EHR, Lifestyle, and SDoH Availability: Restricted	Age, prior CVD, and SDoH	RF for CM, CHF, CAD, and LASSO for MI, TIA, AR	RF C-index: 0.752 (CAD), LASSO C-index: 0.745 (MI)	- ML can integrate heterogeneous multi-modal data into the prediction model. - Including an additional data modality does not always improve model performance. The performance can also be degraded.	Internal Validation (30% validation data)	[74]
Elastic Net, RF, XGBoost, SVM, and NN	EHR and Epidemiology (18,388 patients) Availability: Upon reasonable request	Prior stroke, socio-economic status, cancer characteristics	RF	RF AUROC: 0.916 (Ischemic Stroke)	- The SMOTE resampling approach cannot always improve the model performance. - The inclusion of socio-economic factors and cancer characteristics enhances stroke prediction. - Tree-based models (RF, XGBoost) are better in non-linear interactions.	10-fold cross-validation (30% validation data)	[93]

Another approach [91] presented a long short-term memory (LSTM) neural network with one input layer that takes a 32-dimensional feature vector embedding the cardiovascular health (CVH) metrics, one hidden layer with 100 dimensions, and an output layer activated by a sigmoid activation function to predict the receipt of breast, cervical and colon cancer screening using the CVH measures.

B. ML PREDICTING CVD IN CANCER PATIENTS

Cardiovascular diseases are the primary contributor to cancer-associated mortality [166], and thus, ML can significantly contribute to enhancing CVD event prediction in various oncogenic conditions. Note that CVD complications are mainly driven by metabolic disruption and treatment-induced cardiotoxicity in cancer patients and survivors [167], [168], [169], [170]. Thus, it is inevitable to consider the cardiotoxicity effects while predicting CVD events in cancers. The role of treatment-induced cardiotoxicity is beyond the scope of this review, as the aim is to highlight the natural biological correlations. Hence, we have selected studies with minimal cardiotoxicity focus, and instead, we concentrate more on the ML approaches in this section. The application of ML is also underexplored here (see Table 3 for the ML approaches and key insights from the selected studies).

An ML approach using the XGBoost algorithm has been implemented [40] as the XGBoost algorithm was found to outperform a deep learning approach when dealing with

categorical data [171]. The approach is capable of predicting 2-year major adverse cardiac events (MACE), including heart failure, acute coronary syndrome, atrial fibrillation, and ischemic stroke integrating social determinants of health data (SDoH) that mainly represent neighbourhood information and the surrounding environment with the electronic health records (EHR) of breast cancer survivors or sufferers [40]. The poorer the SDoH condition, the higher the risk of MACE. It is worth mentioning that SDoH data cannot predict CVD outcomes independently but can be crucial when integrated with other data modalities.

Multi-modal data integration is a challenging task that can have multifaceted impacts on the model's performance. A multi-modal data integration pipeline to predict six subtypes of CVD outcomes in breast cancer survivors has been developed and validated [74], incorporating three independent feature sets: EHR data only, EHR and lifestyle data, and EHR, lifestyle, and SDoH data into LASSO and RF. Adaptive LASSO is found to enhance feature selection in heterogeneous data, where RF has been superior in structured clinical data. Furthermore, ML models are well-adapted to high-dimensional complex data structures and efficient in extracting the non-linear associations between predictors and model outcomes [172], [173]. Again, RF has been found superior in predicting 1-year stroke from a more complex and non-linear landscape that has considered demographics, socio-economic factors, comorbidities, cancer

characteristics, cancer treatment, and medication history in cancer patients with atrial fibrillation, although several linear and non-linear ML approaches, including RF, are observed to fail in achieving high performance metrics while predicting the major bleeding events in those patients [93].

C. LIMITATIONS AND CHALLENGES

ML-based predictive models offer strong potential for bidirectional risk stratification of cancer and CVD, though ensuring their interpretability and clinical translation has been challenging because of some constraints. First, data heterogeneity and missingness are pervasive in clinical setups, which risk selection bias when records are presented based on availability [40], [92]. Excluding cancer patients with conditions other than stroke also raises bias concerns, as real-world patients may be exposed to multiple health conditions simultaneously [90]. Second, inadequate samples and class imbalance in outcome often limit statistical capabilities; thus, models are required to train and evaluate on sufficiently large datasets before clinical translation [90], [91], [92]. In addition, rigorous methodologies are essential to address class imbalance, as cancer events in CVD patients or CVD events in cancer patients are historically rare, producing highly skewed outcome distributions. Third, losing outcome granularity due to aggregating heterogeneous cardiovascular diagnoses into a class can significantly degrade model performance in various clinical situations [74]. Fourth, the lack of external validation impedes the generalization of the models. Only one model [90] underwent external validation among those in sections IV-A and IV-B, although the validation was restricted to a single ethnicity. Therefore, independent, prospective, multi-center validation and periodic model updating are essential for clinical adaptability [40], [74], [91], [92], [93]. Fifth, the lack of self-explainability of the models, due to their black-box architectures, limits clinical trust [90], [92]. Finally, suboptimal discriminatory performance (e.g., low AUROC) reduces clinical utility, as demonstrated by the model in [91].

V. CANCER-CVD MORTALITY ANALYSIS

Cancer-associated CVD mortality and CVD-associated cancer mortality contribute significantly to the overall cancer-CVD mortality worldwide. Cancer and CVD risk factors are positively correlated in both directions and often influence comorbidity [95]. It is known that CVD patients demonstrate a higher probability of cancer development [15], [16], [17], [18], [19], and conversely, cancer patients and survivors are at an elevated risk of developing CVD events [7], [8], [9], [10], [11], [12], [13], [14], thus substantially increasing the overall risk of cancer-CVD mortality. Machine learning applications are demonstrating promising potential in cancer-CVD morbidity, comorbidity, and mortality analysis, considering a wide range of aspects, such as ageing-related factors, clinical risk parameters, genetic and epigenetic signatures, chemical and environmental exposures, etc.

Epigenetic age, or DNAm age derived from DNA methylation, is a crucial predictor of several age-associated diseases and mortality [174], [175], [176]. For instance, CpGs are DNAm age markers that can significantly elevate all-cause, CVD and cancer mortality prediction when integrated with clinical risk factors [44]. Another deep learning approach has been applied, integrating retinal photographs with clinical phenotypic data to produce a better biological ageing marker that has been reported to demonstrate a stronger association with cancer and CVD mortality [70]. Chronological age is also identified as the principal contributing factor of all-cause and CVD-specific mortality [41].

Cancer-induced CVD mortality and CVD-induced cancer mortality underscore the interplay between them. A deep learning approach has been made combining ML-extracted features and clinically measured features from low-dose CT (LDCT) images of lung cancer patients to predict not only lung cancer mortality but rather all-cause mortality [101]. In addition, random survival forest (RSF) has been implemented to predict the atherosclerosis CVD (ASCVD) risk score as the most significant factor of survival in brain metastases, and further multivariate Cox regression analysis has revealed that higher ASCVD scores (>25.1) imply worse survival possibility [99]. While most of the ML applications are focused on mortality prediction, the multi-cause mortality in patients with lung cancer has been investigated by applying ML algorithms to clinicopathologic factors [97], and it has been reported that 5.35% of deaths among 42,257 patients occurred due to CVD events. In another study, among hospitalized cancer patients, only lung and breast cancers were found to contribute significantly to stress cardiomyopathy (SC) development, and importantly, the co-occurrence of cancer and SC was observed not to demonstrate any significant association with increased mortality overall; rather interestingly, the concomitance of breast cancer and stress cardiomyopathy was seen to reduce the mortality significantly [94].

Machine learning has also identified several environmental chemicals that are significantly associated with all-cause, cancer and CVD mortality. Fine particulate matter (PM_{2.5}) refers to the small environmental pollutants (aerodynamic diameter $\leq 2.5 \mu\text{m}$) that can influence cellular oxidative stress and DNA damage, endothelial dysfunction, chronic inflammation, and elevate cancer progression [96]. Long-term exposure to PM_{2.5} is associated with overall and cause-specific mortality outcomes, including cancer and CVD, and this association varies disproportionately across cause of death, age, and sex [96]. Analysis aided by ML on the elemental components of PM_{2.5} has identified that higher environmental concentrations of iron, zinc, nickel, and vanadium are significantly associated with lung cancer mortality, where potassium and silicon concentrations in ambient air have been reported to be most consistently correlated with overall mortality in Denmark [98]. Furthermore, people are exposed to toxic cadmium mainly via food, water,

and smoking [177], and higher cadmium concentrations in urine and blood significantly elevate the overall mortality risk from all causes, including cancer and CVD-associated mortality [100]. Another interpretable machine learning approach has also detected the positive association between serum cadmium and all-cause mortality while revealing a negative association with the urine concentration of methyl paraben (MP) and 2-naphthol (2-NAP) [41]. In addition, a positive association between urinary bisphenol A (BPA) and CVD mortality is also identified.

VI. DISCUSSION AND CONCLUSION

We critically appraise the role of ML in deciphering the sophisticated correlations between cancer and CVD revealed in the recent past, addressing the associated genetic variants and epigenetic modifications, pathway analysis, biomarker detection, and developing cancer-CVD morbidity and mortality prediction models. Machine learning has been instrumental in genetic marker identification through efficient feature selection algorithms and high-dimensional genomic data analysis. Note that METTL7B is a heart failure diagnostic gene that was found overexpressed in A549 and PC9, indicating an association with lung cancer. Future research, especially in myocardial cells, may strengthen this connection. The CpGs integrated with clinical risk factors were tested on one Cox regression-based statistical model that was regularized with elastic net penalty (Elastic-coxph [178]) and three ML models, including ensemble tree-based random survival forest (RSF [179]), artificial neural network-based survival analyzer (Cox-nnet [180]), and deep learning-based survival predictor (DeepSurv [181]), and surprisingly, ML-based models could not outperform the statistical model and were also found to struggle in several instances, specifically when the input feature set was relatively smaller [44].

In addition, the breast cancer prognosis and recurrence scoring system provided a comprehensive understanding of the association between several genes (immune, methylated, and autophagy-associated) and tumor microenvironment in breast cancer [45], where an association between breast cancer recurrence score and stroke was revealed, though the models need to be verified in independent cohorts. Four genes (FCN3, MAP2K1, CDH19, and AP3M2) were found at the root of the comorbidity of heart failure and hepatocellular carcinoma through immune cell and metabolic pathways, though the findings were from bioinformatics methods without experimental validation [46]. Identifying disulfidptosis-associated genes for HCM prediction is an outstanding achievement, and increasing the sample size may significantly improve the model performance [78]. However, further research should also focus on the evaluation of the therapeutic effects. Topic modeling via NMF demonstrated significant potential to extract latent information from disease phenotypes, and integrating more features (i.e., clinical data and medication information) from electronic health records may result in a more stable model [47].

Moreover, the F3 gene was seen to express immunogenic and angiogenic features in tumor microenvironment, and future *in vivo* analysis and clinical trials may establish the role of the F3 gene in the treatment of glioma and coronary artery diseases [48]. Two genes (GATM and GMST1) were identified as novel biomarkers of HCM and cancers using machine learning methods that were also validated by conducting relevant experiments [49]. However, prospective cohort validation is still essential, and hybrid machine learning approaches may be more beneficial. In addition, WEE1, PYHIN1, SEC61A2, and HAL were also identified as cancer and acute myocardial infarction prognosis markers in a retrospective study, requiring validations in prospective cohorts [50]. In a nutshell, the identified genetic and epigenetic signatures can be considered for intensive molecular biology validation for an improved understanding of their functional mechanisms. Machine learning-driven causal inference models for association analysis can be a significant inclusion in enhancing the causal analysis and understanding of the associated pathways.

RetiPhenoAge [70]—a machine learning-based biological ageing biomarker that demonstrated outstanding performance in several cardiovascular events, such as stroke and myocardial infarction, though the performance in cancer event detection required significant improvements. The application of retinal photographs in cardiovascular risk stratification is further attested by [182] as they applied a deep learning architecture to predict coronary artery calcium (CAC) scores from retinal images. CNN-based deep learning architectures were found to be efficient in extracting image-based features, resulting in several applications that analysed image-based cancer screening data, such as CT, LDCT scans, and mammograms, and identified CVD markers using the same data. Interestingly, human-level expertise was found inadequate for some instances compared with such model performances [90]. This opportunistic screening for CVD risk using cancer screening data can be a cost-effective and life-saving approach. Future research can concentrate on the complete automation of the entire process.

We identify the scarcity of ML-based predictive models for predicting cancer incidents in CVD patients and CVD events in cancer patients. Although several approaches are reported, most of them require external validation. Along with cancer-CVD mortality prediction models, their comorbidity prediction models are also crucial for shedding some significant light into their interplay conditions [95]. Overall, this area is severely underexplored and offers numerous research opportunities in the morbidity, comorbidity, and mortality analysis. Machine learning-based approaches can significantly contribute to minimizing the challenges: addressing the data heterogeneity issues in medical data, developing effective data imputation algorithms for handling missing values, which is a common issue in medical data, handling imbalanced datasets using ML-based techniques, creating multi-modal data integration pipelines to ensure a

holistic assessment of the disease conditions, and integrating self-explainability features into the ML models, which can play a crucial role in clinical translation. The most critical deficiency from the ML perspective to date is the absence of adequate ML-based causal inference models in uncovering the bidirectional correlations between cancer and CVD.

This review underscores the capabilities of ML approaches and identifies several areas that need significant attention to extract the biological root of these two disease phenotypes using machine intelligence. The figures are conceptualized from the relevant studies and created at <https://BioRender.com>.

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