

BIOFUSIONNET: DEEP LEARNING-BASED SURVIVAL RISK STRATIFICATION IN ER+ BREAST CANCER THROUGH MULTIFEATURE AND MULTIMODAL DATA FUSION

Raktim Kumar Mondol¹, Ewan K.A. Millar², Arcot Sowmya¹, and Erik Meijering^{1,*}

¹School of Computer Science and Engineering, University of New South Wales, Sydney, Australia

²Department of Anatomical Pathology, NSW Health Pathology, St. George Hospital

*Correspondence: erik.meijering@unsw.edu.au

ABSTRACT

Breast cancer is a significant health concern affecting millions of women worldwide. Accurate survival risk stratification plays a crucial role in guiding personalised treatment decisions and improving patient outcomes. Here we present BioFusionNet, a deep learning framework that fuses image-derived features with genetic and clinical data to achieve a holistic patient profile and perform survival risk stratification of ER+ breast cancer patients. We employ multiple self-supervised feature extractors, namely DINO and MoCoV3, pretrained on histopathology patches to capture detailed histopathological image features. We then utilise a variational autoencoder (VAE) to fuse these features, and harness the latent space of the VAE to feed into a self-attention network, generating patient-level features. Next, we develop a co-dual-cross-attention mechanism to combine the histopathological features with genetic data, enabling the model to capture the interplay between them. Additionally, clinical data is incorporated using a feed-forward network (FFN), further enhancing predictive performance and achieving comprehensive multimodal feature integration. Furthermore, we introduce a weighted Cox loss function, specifically designed to handle imbalanced survival data, which is a common challenge in the field. The proposed model achieves a mean concordance index (C-index) of 0.77 and a time-dependent area under the curve (AUC) of 0.84, outperforming state-of-the-art methods. It predicts risk (high versus low) with prognostic significance for overall survival (OS) in univariate analysis ($HR=2.99$, 95% CI: 1.88–4.78, $p<0.005$), and maintains independent significance in multivariate analysis incorporating standard clinicopathological variables ($HR=2.91$, 95% CI: 1.80–4.68, $p<0.005$). The proposed multifeature and multimodal data fusion approach not only improves model performance but also addresses a critical gap in handling imbalanced data. This advancement has the potential to substantially influence therapeutic decision-making, leading to improved clinical outcomes for patients.

Keywords Multimodal Fusion · Breast Cancer · Whole Slide Images · Deep Neural Network · Survival Prediction

1 INTRODUCTION

Breast cancer poses a significant global health concern, with a high incidence rate and substantial impact on morbidity and mortality [1, 2]. The incidence of breast cancer varies across different regions and populations, with higher rates observed in developed countries [1]. The prevalence of breast cancer in Australia, affecting 1 in 8 women up to the age of 85, is a cause for concern due to its rising incidence rate over the past decade [3]. This trend highlights the crucial need for accurately predicting survival risks to identify high-risk patients who may benefit from more intensive treatment or monitoring, thereby potentially improving outcomes [2].

In breast cancer, the estrogen receptor (ER) status plays a critical role in determining treatment strategies and predicting patient prognosis. ER+ breast cancer, which includes Luminal A and Luminal B subtypes, is distinguished by the presence of ERs on cancer cells, making it responsive to hormonal therapies such as tamoxifen [4]. While Luminal A tumours are usually low-grade with a favorable prognosis ($Ki-67<14\%$), Luminal B tumours are usually higher grade and pose a higher recurrence risk and worse outcome ($Ki-67\geq14\%$) [4, 5]. The inherent heterogeneity

of breast cancer poses challenges for prediction of prognosis and treatment decisions, particularly in post-menopausal ER+ breast cancer, with previous studies reporting conflicting results on the survival difference between Luminal A and B metastatic breast cancer patients [6, 7]. A common critical clinical dilemma is the selection of those early ER+ breast cancer patients at high risk of recurrence who may benefit from the addition of chemotherapy to endocrine therapy. Therefore, accurate survival risk prediction models specifically tailored for ER+ breast cancer are essential for personalised treatment decisions.

Traditional methods for survival risk prediction often rely on clinicopathological risk factors (such as age, tumour size, grade, lymph node metastasis and clinical stage), which may fail to fully capture the complex biology of cancer [4, 7–10]. To address this issue, molecular markers and gene expression profiles have been identified as potential prognostic factors that provide valuable insights into tumour biology and potential therapeutic targets [11–15]. Over the past decade, the integration of genomic testing into treatment decision-making processes has been enhanced by the utilisation of several commercial gene panels, such as Prosigna/PAM50, OncotypeDx and Endopredict

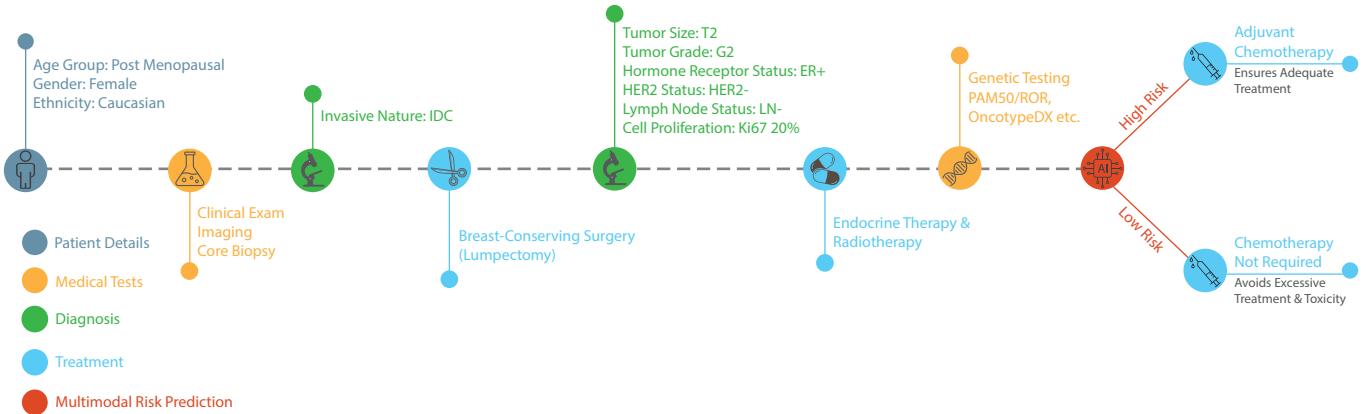


Figure 1: Illustration of the clinical management pathway in treating breast cancer patients. This example concerns a postmenopausal patient who has been diagnosed with breast cancer, specifically invasive ductal carcinoma (IDC). The process begins with an initial diagnosis through clinical examination, imaging and core biopsy. Following this, surgery is performed to completely excise the tumour, and postoperative tumour histopathological classification is performed to assess key factors including tumour size (e.g. T2), grade (e.g. G2), hormone receptor status (e.g. ER+), HER2 status (e.g. HER2-), lymph node status (e.g. LN-), and proliferation index (e.g. Ki67 20%). Subsequent treatments may include hormone therapy and radiotherapy. Additional molecular tests, like genetic testing, are utilised to determine specific cancer molecular subtypes and further assess risk of recurrence. The proposed final step in this pathway is the application of our BioFusionNet model. This model combines tumour characteristics, pathology and genetic testing to determine high and low risk patients, thereby guiding personalised treatment decisions and efficiently preventing both under-treatment and over-treatment. For example, low-risk patients might undergo lumpectomy with hormone therapy and radiotherapy, whereas high-risk patients are advised to have chemotherapy in addition to these treatments. Whilst this pathway mirrors current clinical practice, our study streamlines the integration of all available critical data to derive an automated single risk prediction score.

among others. In addition, histopathological imaging, which offers in-depth insights into the cellular and tissue characteristics of tumours, plays a vital role in both the diagnosis and prognosis of breast cancer [16]. However, to address the varied nature of the disease effectively, it is essential to consider all available data modalities. Therefore, integrating imaging, genetic and clinicopathological information into a single risk prediction model could potentially enhance risk prognostication in the clinic [9]. In this study, we propose a novel multimodal survival risk prediction model to enhance the prognosis of ER+ breast cancer. The model uniquely integrates histopathology images, genetic profiles and clinical data, enabling the prediction of risk scores that categorise patients into distinct risk groups aligned with their survival outcomes. The model is thoroughly evaluated using metrics such as the concordance index (C-index) and time-dependent area under the curve (AUC) score, and its performance is compared to existing methods to establish its efficacy. Additionally, we analyse the interpretability of the model, providing insights into how different genes and clinical factors influence the risk prediction, thereby enhancing our understanding of the underlying predictive mechanisms.

2 BACKGROUND

Cancer risk prediction is of paramount importance due to its potential for guiding personalised screening, prevention and treatment strategies, ultimately leading to improved patient outcomes and reduced mortality (Fig. 1). This approach is especially vital in the context of ER+ breast cancer, where accurate risk prediction is essential for identifying individuals at higher recurrence risk. These patients may benefit from more aggressive treatments like chemotherapy [17–20]. On the other hand,

risk models are equally critical in recognising lower-risk patients, potentially sparing them from unnecessary treatments and their side effects [21]. Online algorithms such as Predict¹ and Adjuvant² are used clinically to estimate the risk of recurrence and the benefit of adding chemotherapy to endocrine therapy, which is a major treatment dilemma.

Developments in deep learning, such as the Cox proportional hazards deep neural network, have revolutionised cancer research by improving survival data modeling and treatment recommendation systems [22]. Multimodal data fusion, which combines information from diverse sources such as imaging, genomics and clinical data, has gained attention in cancer research due to its ability to provide a comprehensive understanding of the disease and improve predictive outcomes [23–25]. Cross-attention transformer mechanisms that integrate histopathological images and genomic data capture complementary information from different modalities, leading to improved survival prediction [26].

In this evolving landscape, models such as MultiDeepCox-SC [27], MCAT [28], MultiSurv[29], HFSurv [30], Pathomic Fusion [31], and TransSurv [32] exemplify significant progress in multimodal analysis. Pathomic Fusion, for instance, employs a gating-based attention mechanism that modulates the expressiveness of features from each modality. This approach is particularly effective in mitigating the impact of noisy unimodal features, ensuring that the model integrates and emphasises the most pertinent information from each data source [31]. Similarly, HFSurv decomposes the fusion problem into different levels and integrates and passes information progressively

¹<https://breast.predict.nhs.uk/tool>

²<https://oncoassist.com/adjuvant-tools/>

from lower to higher levels. This hierarchical framework, with modality-specific and cross-modality attentional factorised bilinear modules, captures and quantifies complex relations in multimodal data while reducing computational complexity [30]. Moreover, the significance of deep autoencoders in constructing nonlinear mappings between 2D images and 3D poses has also been emphasised, further highlighting the potential of these methods in cancer research [33].

Despite these advances, the integration of multimodal data, marked by its inherent heterogeneity and dimensional variability, remains a significant challenge, underscoring the need for advanced methodologies to effectively integrate and leverage diverse data sources for robust survival risk assessment [34–36]. A previous study has addressed ER+ breast cancer risk stratification using pathology image analysis, focussing on Nottingham grading components such as mitotic rates, nuclear pleomorphism and tubule formation [37]. However, multimodal approaches that thoroughly integrate diverse data types to accurately predict survival risks for ER+ breast cancer are currently lacking. This research gap emphasises the need for novel multimodal fusion techniques for risk prediction in ER+ breast cancer.

3 MATERIALS AND METHODS

3.1 Data Collection

Our study used hematoxylin-and-eosin-stained (H&E) formalin-fixed paraffin-embedded (FFPE) digital slides from The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA). Whole-slide images (WSIs) from the TCGA-BRCA data collection were downloaded from the [GDC Portal](#) (accessed 25 August 2023). In this work, we chose a subset of 249 cases from the TCGA-BRCA dataset, specifically focussing on two molecular subtypes: Luminal A comprising 149 samples, and Luminal B with 100 samples. Additionally, we obtained transcriptome-wide RNA-sequencing data representing mRNA expression levels for a total of 20,438 genes in the reference genome from the TCGA dataset. These data were processed using RNA-sequencing by expectation maximisation (RSEM) and were downloaded from the [cBioPortal](#) platform[38]. This dataset included a range of clinical information for each patient, such as tumour grade, tumour size, lymph node status, age at diagnosis and molecular subtypes. Overall, patients who had WSIs, RNA-sequencing and clinical data available were included in the study.

3.2 Data Preparation

3.2.1 Slide Annotation

An expert breast pathologist manually annotated the selected slides using QuPath [39]. The annotation was performed for localization of the tumour outline, excluding any necrosis but including stroma and tumour infiltrating lymphocytes (TILs). The pathologist was blinded to any molecular or clinical features during annotation.

3.2.2 Image Data Preparation

The images were first downsampled to 0.25 $\mu\text{m}/\text{pixel}$, corresponding to approximately 40 \times magnification. The annotated tumour regions were processed semi-automatically with QuPath to create 224 \times 224-pixel patches, resulting in approximately 500 nonoverlapping patches per sample. To address staining inconsistencies, vector-based color normalization was applied [40].

3.2.3 RNA-Sequencing Data Preparation

From the extensive set of 20,438 genes, we selected genes featured in various commercial assays, namely Oncotype DX, Mammaprint, Prosigna (PAM50), EndoPredict, BCI (Breast Cancer Index), and Mammostrat [41–46], as these are the most relevant genetic markers to our study's objectives. This resulted in a subset of 138 genes.

3.2.4 Clinical Data Preparation

From the clinical data, we selected variables based on their established relevance in breast cancer prognosis and treatment outcomes [47–50]. Specifically, we included tumour grade (categorised as grade 1&2 versus grade 3), tumour size (>20 mm versus ≤ 20 mm), patient age (>55 versus ≤ 55) and lymph node status (positive versus negative).

3.3 Proposed Model

The proposed deep learning model, which we call BioFusionNet, is an innovative feature extraction and multimodal fusion framework designed to leverage and integrate diverse data types, including histology images, genomic features and clinical data for enhanced cancer outcome prediction (Figs. 2 and 3). The essence of BioFusionNet lies in its capability to fuse these data modalities into a cohesive tensor representation, effectively capturing both bimodal and trimodal interactions. This approach is aimed at surpassing the performance of traditional unimodal and existing multimodal representations in survival risk prediction.

3.3.1 Feature Extraction Using DINO and MoCoV3

Histopathological images, rich in phenotypic information, are pivotal for understanding cancer pathology. BioFusionNet utilises two advanced self-supervised learning models, DINO (self-DIstillation with NO labels) and MoCoV3 (Momentum Contrast version 3), both based on the Vision Transformer (ViT) architecture, to extract morphological features from histology images crucial for identifying cancer-related patterns.

DINO: The DINO framework employs a dual-network architecture, consisting of a student and a teacher network, both being ViTs. The student network learns by attempting to replicate the output of the teacher network, which in turn is an exponential moving average of the student's parameters. The core process involves generating multiple augmented views (I_1, I_2, \dots, I_k) of a given input image (I), which are then processed by these networks. The resultant feature vectors from the student (F_s) and teacher (F_t) networks are utilised to compute the distillation loss as follows:

$$\mathcal{L}_D = \sum_{i=1}^k \text{CrossEntropy}\left(F_s(I_i), \text{Softmax}\left(\frac{F_t(I_i)}{\tau}\right)\right), \quad (1)$$

where τ represents the temperature scaling parameter. Notably, DINO is pretrained on a broad range of datasets, including BACH, CRC, MHIST, PatchCamelyon and CoNSeP, comprising 33 million patches (DINO33M), and 2 million patches from TCGA-BRCA (DINO2M) [51, 52]. The output functions for DINO33M and DINO2M, denoted as $f_{\text{DINO33M}}(x)$ and $f_{\text{DINO2M}}(x)$ respectively, convert an input image x of size $224 \times 224 \times 3$ into a 1×384 feature vector. We utilised these two models for feature extraction: DINO33M trained on diverse datasets providing a broad perspective and enabling the model to recognise a wide array of general histopathological features, and

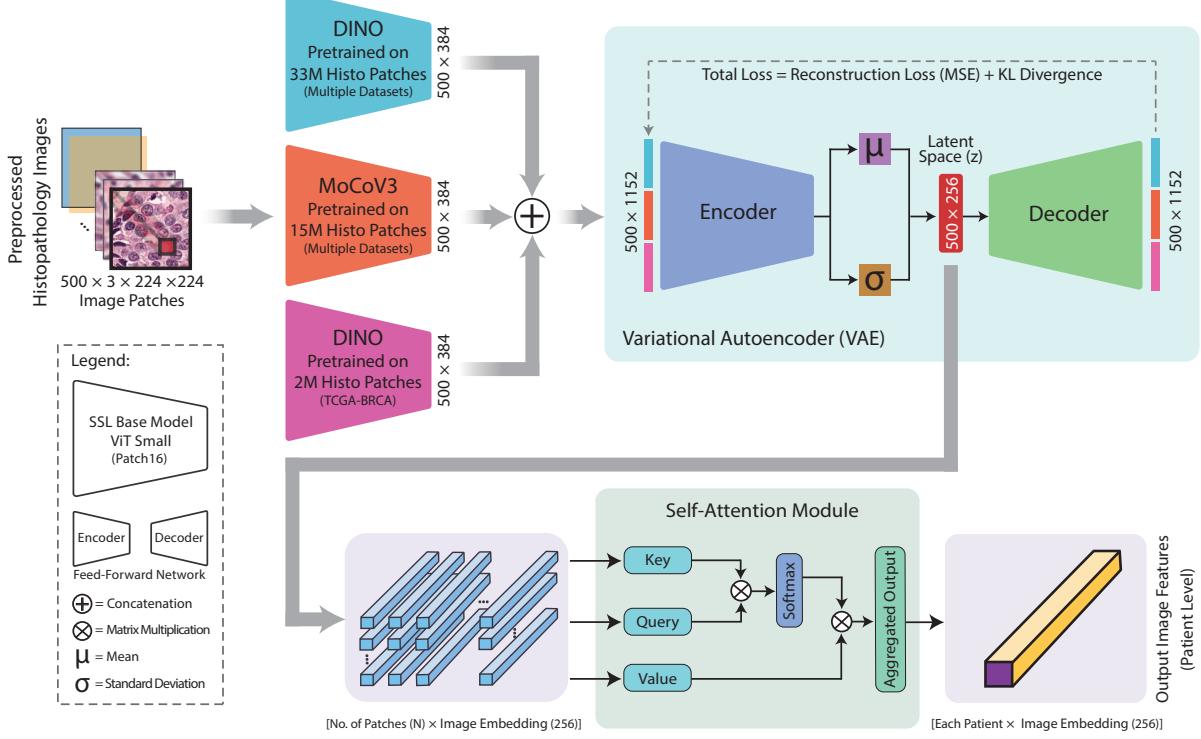


Figure 2: BioFusionNet Stage 1: The proposed model integrates self-supervised image feature extraction methods, namely DINO and MoCoV3, pretrained on three distinct datasets. Features are concatenated and fed to a Variational AutoEncoder (VAE). Subsequently, the latent space of the VAE is utilised to feed a self-attention network, which aggregates patch-level features into a comprehensive patient-level representation.

DINO2M specifically trained on breast cancer data for more specialised and precise feature extraction relevant to breast cancer pathology.

MoCoV3: The MoCoV3 framework, which incorporates ViTs, represents a significant advancement in self-supervised learning through its adoption of the momentum contrast (MoCo) approach [53]. At the heart of this framework lies the contrastive learning mechanism, designed to differentiate between positive and negative pairs, thereby enhancing the model’s feature learning capabilities. MoCoV3’s architecture is defined by two main components: a query encoder that processes the current batch of images, and a key encoder updated via a momentum-based moving average of the query encoder’s parameters:

$$\theta_k \leftarrow m\theta_k + (1 - m)\theta_q, \quad (2)$$

where θ_k and θ_q are the parameters of the key and query encoders respectively and m is the momentum coefficient. This enables the key encoder to maintain a queue of encoded keys representing previously seen images, thus enhancing the model’s ability to maximise agreement between differently augmented views of the same image (positive pairs) and minimise similarity with other images (negative pairs). The framework uses the InfoNCE loss [54]:

$$\mathcal{L}_{\text{InfoNCE}} = -\log \frac{\exp(q \cdot k^+ / \tau)}{\sum_{i=0}^K \exp(q \cdot k_i / \tau)}, \quad (3)$$

where q and k^+ are the query and positive key feature vectors, k_i are the negative key vectors, K is the number of negative keys and τ is the temperature parameter. MoCoV3 has been

pretrained on an extensive collection of 15 million histology patches from over 30 thousand WSIs derived from the TCGA and Pathology AI Platform (PAIP) datasets, encompassing a wide variety of cancer types and histological features. This endows the model with a robust and versatile capability to extract meaningful features from histopathological data [55]. Similar to DINO, the output function of MoCoV3, $f_{\text{MoCoV3}}(x)$, transforms an input image x of dimensions $224 \times 224 \times 3$ into a 1×384 feature vector.

3.3.2 Unimodal Feature Integration

Extracted features from DINO33M, DINO2M and MoCoV3 are concatenated to form a comprehensive 1×1152 feature vector $f_{\text{cat}}(x) = f_{\text{DINO33M}}(x) \oplus f_{\text{DINO2m}}(x) \oplus f_{\text{MoCoV3}}(x)$ (Fig. 2). Following this, we employ a VAE to encode the integrated image features into a 256-dimensional feature in latent space. The latent feature vector is then passed through a self-attention model and aggregated using sum pooling to generate patient-level features.

3.3.3 Feature Fusion Using Variational Autoencoding

Our VAE consists of an encoder and a decoder. The encoder function f_{enc} maps the concatenated feature vector $f_{\text{cat}}(x)$ to the latent space by generating the mean μ and standard deviation σ of the latent representation:

$$(\mu, \sigma) = f_{\text{enc}}(f_{\text{cat}}(x)). \quad (4)$$

With 500 patches per patient, the latent space is structured as a matrix of size 500×256 . This is achieved by sampling z using

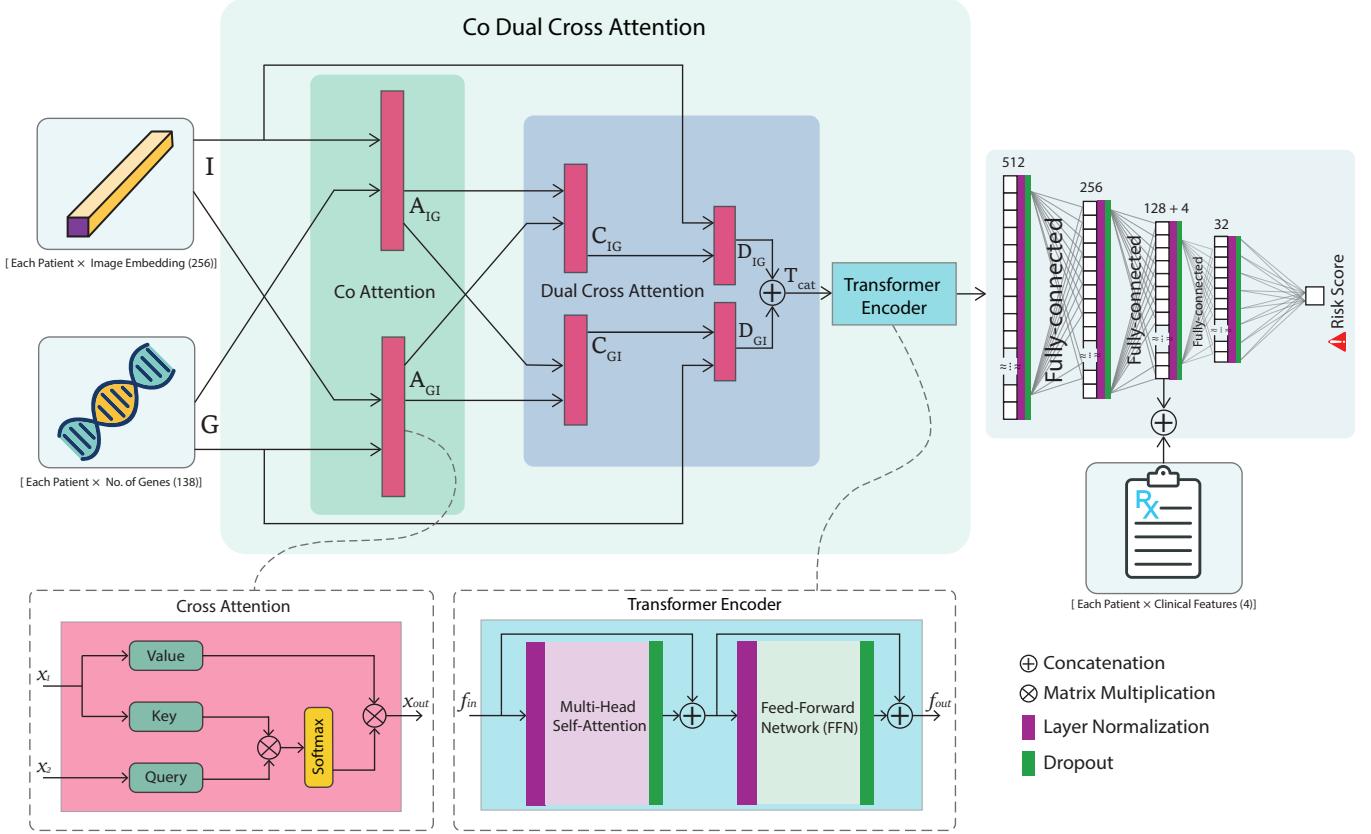


Figure 3: BioFusionNet Stage 2: The proposed model fuses image embeddings generated from Stage 1 with genetic data through a co-dual-cross-attention mechanism. This fusion is subsequently combined with clinical data using a feed-forward network (FFN), leading to the generation of the final risk score output.

the reparameterization trick:

$$z = \mu + \sigma \cdot \epsilon, \quad \epsilon \sim \mathcal{N}(0, I), \quad z \in \mathbb{R}^{500 \times 256}. \quad (5)$$

The decoder f_{dec} then attempts to reconstruct the input from the latent variable z :

$$\hat{x} = f_{\text{dec}}(z). \quad (6)$$

The VAE is optimised using a loss function that combines mean squared error (MSE) for reconstruction accuracy and Kullback-Leibler (KL) divergence for distribution regularisation:

$$\mathcal{L}_{\text{VAE}} = \text{MSE}(\hat{x}, x) + \beta \cdot \text{KL}(\mathcal{N}(\mu, \sigma^2) || \mathcal{N}(0, I)), \quad (7)$$

where β balances the reconstruction and regularisation terms. The MSE term ensures that the reconstructed image closely resembles the original input, while the KL divergence term encourages the latent distribution to approximate a standard normal distribution. This enables BioFusionNet to effectively blend the features from the different self-supervised models, enhancing the overall feature representation.

3.3.4 Patch-to-Patient Aggregation

To aggregate the patch-level features from the latent space of the VAE into a comprehensive patient-level representation capturing the interdependencies among image patches, our model uses self-attention (Fig. 2). The self-attention module computes a

weighted sum of the key (K), query (Q), and value (V) vectors:

$$y_i = \sum_{j=1}^{500} \text{Softmax}(s(Q_i, K_j)) V_j, \quad (8)$$

where $s(Q_i, K_j)$ is the attention function that determines the relevance between each query and key pair. This offers two significant benefits. First, by leveraging the VAE's latent vectors, the model focusses on the most pertinent image features, resulting in a more precise feature representation. Second, by considering all latent representations, the self-attention mechanism contextualises each patch within the broader histopathology of the patient.

3.3.5 Multimodal Fusion Using Co Dual Cross Attention

To integrate patient-level image embeddings with genetic feature data, our model uses a co-dual-cross-attention mechanism (Fig. 3). This is achieved using a complex architecture comprising co-attention and dual-cross-attention modules.

The co-attention module applies linear transformations to the image embeddings I and genetic features G , yielding their respective query (Q), key (K), and value (V) vectors, and computes the co-attention scores between them as:

$$A_{IG} = \text{Softmax}(Q_I K_G^T) V_G, \quad (9)$$

$$A_{GI} = \text{Softmax}(Q_G K_I^T) V_I, \quad (10)$$

where A_{IG} represents the attention from images to genetic features, and A_{GI} the attention from genetic features to images. The Softmax function normalises these scores, facilitating an effective weighting of feature importance in the fusion process. This bidirectional attention prepares the ground for more complex interactions in the subsequent stage of the co-dual-cross-attention mechanism.

Subsequently, the dual-cross-attention module further refines the integration of the image and genetic features in two distinct stages. The first stage concerns the interaction between the co-attended image features (A_{IG}) and co-attended genetic features (A_{GI}). The cross attention is computed as:

$$C_{IG} = \text{Softmax} \left(A_{IG}(A_{GI})^T \right) A_{IG}, \quad (11)$$

$$C_{GI} = \text{Softmax} \left(A_{GI}(A_{IG})^T \right) A_{GI}, \quad (12)$$

where C_{IG} represents the cross-attention output when image features attend to genetic features, and C_{GI} the reverse. This stage is crucial for enhancing each modality by integrating contextually relevant information from the other. In the second stage, the outputs from the first stage are further refined by reapplying them to their respective original features. This enhances the depth of the multimodal integration:

$$D_{IG} = \text{Softmax} \left(C_{IG} I^T \right) I, \quad (13)$$

$$D_{GI} = \text{Softmax} \left(C_{GI} G^T \right) G, \quad (14)$$

where D_{IG} and D_{GI} denote the refined cross-attention outputs, further enhancing the original image and genetic data with additional contextual insights.

By sequentially processing the attended features, the model achieves a richer and more contextually informed representation of the fused image and genetic data, suited for complex tasks like risk prediction. The concatenated output $T_{\text{cat}} = D_{IG} \oplus D_{GI}$ is fed to a Transformer Encoder, which employs multiple layers of self-attention and a feed-forward network (FFN) to achieve a deeper assimilation and transformation of the fused features. The output of the Transformer Encoder is then processed by four fully-connected layers, the third of which also integrates the clinical information (Fig. 3). The integration of clinical variables at this stage is crucial due to their dimensionality and characteristics. Clinical data, comprising only four features, may be overshadowed by the higher-dimensional features from histopathological images and genetic profiles if introduced earlier in the model. By embedding these variables in a later layer, their impact is more directly and effectively mapped onto the model's output, preserving their significant influence on survival risk prediction.

This multimodal integration results in a holistic representation of both the phenotypic and genotypic information of ER+ breast cancer. Finally, the network employs a linear output layer that predicts the survival risk score.

3.4 Proposed Loss Function

For training BioFusionNet, we propose a novel loss function termed the weighted Cox loss (computed by Algorithm 1), which is tailored to address the challenges of imbalanced survival data (a common issue in survival analysis):

$$\mathcal{L}_{\text{WCox}} = -\frac{1}{\sum_{i=1}^N w_i e_i} \sum_{i=1}^N w_i e_i (r_i - \log(H_{w_i})), \quad (15)$$

Algorithm 1 Weighted Cox Loss

Require: r : risks (log hazard ratios), e : events, w : weights
Ensure: $\mathcal{L}_{\text{WCox}}$: negative log likelihood loss

- 1: Compute $E_w = \sum_{i=1}^N w_i e_i$ as total weighted events
- 2: Sort samples by descending r and align e, w
- 3: **for** $i \in 1, \dots, N$ **do** ▷ N is the number of samples
- 4: Compute hazard ratio $h_i = \exp(r_i)$
- 5: **end for**
- 6: Init weighted cumulative hazard $H_{w_0} = 0$
- 7: **for** $i \in 1, \dots, N$ **do**
- 8: Update cumulative sum $H_{w_i} = H_{w_{i-1}} + w_i h_i$
- 9: **end for**
- 10: **for** $i \in 1, \dots, N$ **do**
- 11: Compute uncensored log likelihood $u_i = w_i(r_i - \log(H_{w_i}))$
- 12: **end for**
- 13: Compute $c = u \odot e$ ▷ \odot is the element-wise product
- 14: Compute loss $\mathcal{L}_{\text{WCox}} = -\frac{1}{E_w} \sum_{i=1}^N c_i$
- 15: **return** $\mathcal{L}_{\text{WCox}}$

where e_i denotes the event occurrence, w_i the assigned weight, r_i the log hazard ratio, H_{w_i} the weighted cumulative hazard and N the number of samples. Unlike the traditional Cox proportional hazards loss (\mathcal{L}_{Cox}) [22], the proposed loss uses weighting to mitigate the effects of uneven distribution of events within the dataset. In this work we used $w_i = 3$, considering that censored data (denoted as '0') is almost three times as prevalent as event data (denoted as '1'), and thus the sensitivity of the loss function to the latter should be enhanced accordingly, mitigating the bias towards censored data.

3.5 Model Training

The training of BioFusionNet is divided into two distinct stages as follows (Figs. 2 and 3):

Stage 1: Feature Extraction: The self-supervised pretrained models DINO33M, MoCoV3 and DINO2M extract features from histopathology image patches, which are concatenated and then fed into a VAE to produce embeddings, which in turn are processed by a self-attention module to produce a patient-level feature vector (Fig. 2). The VAE was optimised using AdamW with a learning rate of 0.0001 and a batch size of 12. The employed loss function is a combination of MSE and KL divergence, targetting the construction of an advanced latent space to generate detailed patient-level features.

Stage 2: Risk Prediction: The proposed co-dual-cross-attention mechanism, followed by multiple FFNs and a final output node that uses a linear activation function, predicts the patient-level risk from the image-based, genetic and clinical information (Fig. 3). Here, training was performed using the proposed weighted Cox loss ($\mathcal{L}_{\text{WCox}}$), which was optimised using the Adam algorithm with a learning rate of 0.001 and a batch size of 12. To mitigate overfitting, an early stopping mechanism based on the validation loss was implemented. This involved halting the training process after a patience period of 10 epochs if no improvement was observed.

Both training stages used a dataset comprising 199 training samples and 50 validation samples within a five-fold cross-validation framework. The trained model predicts a continuous risk score for every patient within each validation fold. For survival analy-

Table 1: Performance comparison of multimodal and unimodal models for cancer risk prediction using C-index.

Fold	Imaging+Genetic+Clinical		Imaging+Genetic		Imaging		Clinical		Genetic+Clinical	
	BioFusionNet	BioFusionNet	BioFusionNet	BioFusionNet	CoxPH	RSF	CoxPH	RSF	CoxPH	RSF
1	0.78		0.73		0.58		0.60		0.60	
2	0.71		0.72		0.69		0.69		0.58	
3	0.72		0.69		0.61		0.65		0.52	
4	0.81		0.75		0.70		0.72		0.62	
5	0.82		0.65		0.69		0.70		0.64	
Mean ± Std	0.77 ± 0.05		0.71 ± 0.04		0.67 ± 0.04		0.58 ± 0.11		0.60 ± 0.13	
									0.59 ± 0.04	
										0.52 ± 0.18

sis, we employed the median risk score θ_{opt} , derived from each training set, as a threshold to classify patients in the validation set into two categories: high risk (risk score $> \theta_{\text{opt}}$) and low risk (risk score $< \theta_{\text{opt}}$).

3.6 Evaluation Metrics

To quantitatively evaluate survival risk score prediction, we employed the concordance index (C-index) and the area under the curve (AUC) as our primary metrics. The C-index assesses the concordance between predicted survival times and observed outcomes, especially in the presence of censored data:

$$\text{C-index} = \frac{\sum_{i=1}^n \sum_{j=1}^n \mathcal{I}(y_i < y_j, \delta_i = 1) \mathcal{I}(\hat{f}(x_i) < \hat{f}(x_j))}{\sum_{i=1}^n \sum_{j=1}^n \mathcal{I}(y_i < y_j, \delta_i = 1)}. \quad (16)$$

where n is the number of patients, y_i and y_j denote the observed survival times, δ_i indicates whether the event was observed (not censored), $\hat{f}(x_i)$ represents the predicted risk for the i th patient, and \mathcal{I} is the indicator function that returns 1 when its condition is true and 0 otherwise. The time-dependent AUC offers a dynamic view of the model accuracy over time t and incorporates weights ω_i , and is calculated using the following formula:

$$\text{AUC}(t) = \frac{\sum_{i=1}^n \sum_{j=1}^n \omega_i \mathcal{I}(y_i \leq t) \mathcal{I}(y_j > t) \mathcal{I}(\hat{f}(x_j) \leq \hat{f}(x_i))}{\sum_{i=1}^n \omega_i \mathcal{I}(y_i \leq t) \sum_{i=1}^n \mathcal{I}(y_i > t)}. \quad (17)$$

Both the C-index and AUC values range from 0 to 1, with higher values indicating better performance.

4 EXPERIMENTAL RESULTS

4.1 Comparison Across Modalities

The effectiveness of BioFusionNet in cancer risk prediction was evaluated by comparing its C-index performance across different modality configurations. The results (Table 1) show that the mean performance in the cross-validation experiments consistently increased from using only imaging data, to using imaging and genetic data, to combining imaging, genetic and clinical data. Two traditional methods, namely Cox Proportional Hazards (CoxPH) and Random Survival Forests (RSF), were also evaluated, showing no consistent advantage in using genetic and clinical data as opposed to only clinical data, and performing worse than BioFusionNet.

4.2 Comparison With State-of-the-Art Fusion Methods

The performance of BioFusionNet was compared with several state-of-the-art multimodal fusion methods for cancer risk prediction in terms of both C-index and AUC (Table 2). For this experiment we included methods using concatenation (MultiSurv), hierarchical attention (HFBSurv), gating attention (PathomicFusion), co-attention (MCAT) and cross attention (TransSurv). The AUC was calculated using average values over 5-year and 10-year periods. The proposed model consistently outperformed all these previous methods, showing substantial improvements in both metrics.

4.3 Evaluation of Loss Functions

The performance of two different loss functions was compared using the C-index across five cross-validation folds for BioFusionNet and MoCoV3 (Table 3). The results show that the mean performance improved for both methods when using the

Table 2: Performance comparison of multimodal fusion methods for cancer risk prediction.

Method	Fold	C-index		AUC	
		Value	Mean ± Std	Value	Mean ± Std
MultiSurv [29, 56, 57]	1	0.71		0.74	
	2	0.59		0.52	
	3	0.60	0.63 ± 0.07	0.61	0.63 ± 0.09
	4	0.69		0.70	
	5	0.54		0.57	
HFBSurv [30]	1	0.58		0.51	
	2	0.47		0.51	
	3	0.56	0.54 ± 0.07	0.45	0.49 ± 0.04
	4	0.45		0.44	
	5	0.62		0.53	
PathomicFusion [31]	1	0.63		0.68	
	2	0.43		0.10	
	3	0.56	0.52 ± 0.08	0.54	0.47 ± 0.23
	4	0.50		0.63	
	5	0.46		0.38	
MCAT [28]	1	0.71		0.70	
	2	0.69		0.67	
	3	0.64	0.70 ± 0.04	0.65	0.71 ± 0.04
	4	0.70		0.69	
	5	0.76		0.72	
TransSurv [32][26]	1	0.70		0.68	
	2	0.61		0.60	
	3	0.69	0.69 ± 0.04	0.65	0.66 ± 0.04
	4	0.69		0.67	
	5	0.74		0.72	
BioFusionNet (Proposed)	1	0.78		0.82	
	2	0.71		0.93	
	3	0.72	0.77 ± 0.05	0.79	0.84 ± 0.05
	4	0.81		0.81	
	5	0.82		0.83	

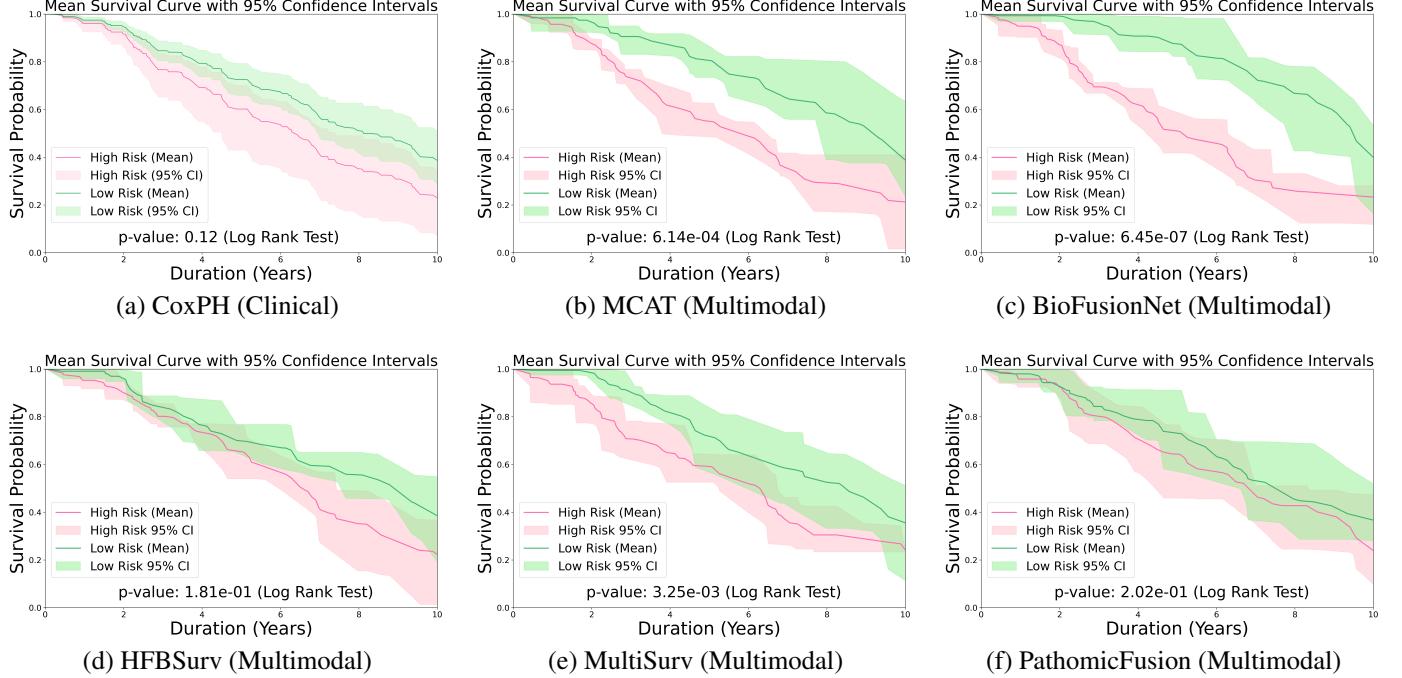


Figure 4: Performance comparison of BioFusionNet and other methods using Kaplan-Meier survival curves.

Table 3: Performance comparison of loss functions for cancer risk prediction using two different methods.

Loss	Method	C-index (Fold)					Mean \pm Std
		1	2	3	4	5	
\mathcal{L}_{Cox}	BioFusionNet	0.69	0.54	0.59	0.75	0.80	0.67 ± 0.10
	MoCoV3	0.66	0.57	0.57	0.78	0.80	0.67 ± 0.11
$\mathcal{L}_{\text{WCox}}$ (Proposed)	BioFusionNet	0.78	0.71	0.72	0.81	0.82	0.77 ± 0.05
	MoCoV3	0.70	0.66	0.66	0.77	0.72	0.70 ± 0.04

weighted Cox loss ($\mathcal{L}_{\text{WCox}}$) proposed in this paper, compared to the traditional Cox loss (\mathcal{L}_{Cox}).

4.4 Univariate and Multivariate Hazard Analysis

A comprehensive hazard analysis was conducted to evaluate the overall survival (OS) in the TCGA dataset of ER+ patients. Both univariate and multivariate analyses were performed (Table 4). The analysis encompassed various parameters, including tumour grade, tumour size, age, lymph node (LN) status, subtype and the risk predictions made by BioFusionNet. In the multivariate analysis, positive LN status was associated with a hazard ratio (HR) of 1.87 (95% CI: 1.32–2.64), demonstrating a significant effect on survival ($p < 0.005$). Additionally, patients over the age of 55 had a HR of 1.77 (95% CI: 1.07–2.91), also showing a significant impact on survival ($p = 0.03$). However, no significant associations were found between tumour grade, size, or subtype and survival outcomes in this analysis. Notably, the BioFusionNet-predicted risk group (high vs. low) demonstrated a significant correlation with OS, with a HR of 2.91 (95% CI: 1.80–4.68) ($p < 0.005$). Univariate analysis indicated that tumour grade, size, age, and subtype were not statistically significant, whereas LN status (HR of 1.84, 95% CI: 1.33–2.55, $p < 0.005$)

and BioFusionNet risk group (HR of 2.99, 95% CI: 1.88–4.78, $p < 0.005$) were significant predictors of survival. We note that the LN status had 51 missing values, which were imputed using a fixed value of 2. Kaplan-Meier survival analysis further supported the results, showing a significant difference in survival probabilities between the high- and low-risk groups as predicted by BioFusionNet (log-rank test $p = 6.45e-7$) (Fig. 4c).

4.5 Ablation Study

We also evaluated the performance of various versions of BioFusionNet for ER+ breast cancer risk stratification. The results (Table 5) show that the base model, BioFusionNet-B0 (MoCoV3, ViT Small) with $\mathcal{L}_{\text{WCox}}$, achieved the lowest C-index, and incorporating single cross-attention (SCA), dual cross-attention (DCA), or co-attention (CoA) yielded slight improvements, as did BioFusionNet-B1 (DINO33M, ViT Small) and BioFusionNet-B2 (DINO2M, ViT Small), both with DCA and $\mathcal{L}_{\text{WCox}}$. Combining BioFusionNet-B0, B1, and B2 with just $\mathcal{L}_{\text{WCox}}$ also resulted in slightly better performance than the base model, as did the inclusion of SCA and VAE. More substantial improvements of the combined model were obtained with the inclusion of DCA or CoA instead of SCA. The best performance was achieved by the combined model using VAE, CoA and DCA with $\mathcal{L}_{\text{WCox}}$, which clearly outperformed the same model using the traditional Cox loss \mathcal{L}_{Cox} .

4.6 Interpretability of BioFusionNet

BioFusionNet utilises a self-attention mechanism to analyse histopathological image patches, identifying regions of high and low attention within both high-risk and low-risk patient profiles. Visual inspection of the results (Fig. 5) reveals that regions with high attention contain distinct cellular patterns crucial for synthesising features from patch-level to patient-level, whereas

Table 4: Univariate and multivariate analysis for overall survival (OS) in the TCGA dataset of ER+ patients.

Parameter	Risk Group Cutoff	#Patients/Group	Multivariate (n=249)			Univariate (n=249)		
			HR	95% CI	p	HR	95% CI	p
Tumour Grade	3 vs. 1 & 2	64 vs. 185	0.83	0.46–1.49	0.54	1.13	0.67–1.91	0.65
Tumour Size	>20 vs. ≤20 (mm)	167 vs. 82	1.45	0.88–2.37	0.14	1.37	0.86–2.19	0.19
Age	>55 vs. ≤55	159 vs. 90	1.77	1.07–2.91	0.03	1.47	0.91–2.36	0.11
LN Status*	pos. vs. neg.	110 vs. 88	1.87	1.32–2.64	<0.005	1.84	1.33–2.55	<0.005
Subtype	lum B vs. A	100 vs. 149	1.43	0.88–2.34	0.15	1.38	0.88–2.18	0.16
BioFusionNet	high vs. low	132 vs. 117	2.91	1.80–4.68	<0.005	2.99	1.88–4.78	<0.005

*LN Status had 51 missing values which were imputed with a fixed value for both multivariate and univariate analysis.

Table 5: Ablation study of BioFusionNet.

Model	C-index
BioFusionNet-B0 (MoCoV3, ViT Small) + $\mathcal{L}_{\text{W Cox}}$	0.65 ± 0.05
BioFusionNet-B0 (MoCoV3, ViT Small) + SCA + $\mathcal{L}_{\text{W Cox}}$	0.69 ± 0.04
BioFusionNet-B0 (MoCoV3, ViT Small) + DCA + $\mathcal{L}_{\text{W Cox}}$	0.70 ± 0.03
BioFusionNet-B0 (MoCoV3, ViT Small) + CoA + $\mathcal{L}_{\text{W Cox}}$	0.70 ± 0.04
BioFusionNet-B1 (DINO33M, ViT Small) + DCA + $\mathcal{L}_{\text{W Cox}}$	0.68 ± 0.02
BioFusionNet-B2 (DINO2M, ViT Small) + DCA + $\mathcal{L}_{\text{W Cox}}$	0.67 ± 0.03
BioFusionNet-Concat(B0+B1+B2) + $\mathcal{L}_{\text{W Cox}}$	0.67 ± 0.04
BioFusionNet-Concat(B0+B1+B2) + SCA + $\mathcal{L}_{\text{W Cox}}$	0.69 ± 0.03
BioFusionNet-Concat(B0+B1+B2) + VAE + SCA + $\mathcal{L}_{\text{W Cox}}$	0.68 ± 0.04
BioFusionNet-Concat(B0+B1+B2) + VAE + DCA + $\mathcal{L}_{\text{W Cox}}$	0.75 ± 0.04
BioFusionNet-Concat(B0+B1+B2) + VAE + CoA + $\mathcal{L}_{\text{W Cox}}$	0.70 ± 0.03
BioFusionNet-Concat(B0+B1+B2) + VAE + CoA + DCA + \mathcal{L}_{Cox}	0.67 ± 0.10
BioFusionNet-Concat(B0+B1+B2) + VAE + CoA + DCA + $\mathcal{L}_{\text{W Cox}}$	0.77 ± 0.03

areas of low attention typically exhibit less cellular atypia. This shows the model capacity to pinpoint clinically relevant features within tissue morphology. Additionally, SHAP analysis (Fig. 6) reveals the influence of individual genes on the model predictions, ranked from high to low, providing interpretability of the risk assessment process. From this analysis, gene SLC39A6 (an estrogen regulated Zinc transporter protein with a role in epithelial to mesenchymal transition (EMT)) was identified as the most important predictor, with high expression levels producing high SHAP values, indicating positive impact on the model’s cancer risk prediction. Other influential genes include ERBB2 (the gene for HER2), ESR1 (the gene for ER), with low expression levels producing high SHAP values therefore positive impact on the model. Moreover, the distribution of SHAP values for clinical features (Fig. 7) indicates that higher values of clinical parameters—such as positive LN status, higher tumour grade, increased tumour size, and postmenopausal age group—tend to have a positive impact on the model’s output. In this context, a ‘positive impact’ implies that the model associates these values with a higher likelihood of predicting patients at high risk.

5 DISCUSSION AND CONCLUSION

As demonstrated by the experimental results, the proposed BioFusionNet is highly effective for cancer risk prediction, showing superior performance compared to alternative approaches. Clearly, the multimodal fusion of imaging, genetic and clinical data allows the model to achieve substantially higher C-index scores compared to unimodal and dual-modal configurations, as well as compared to the traditional Cox Proportional Hazards and Random Survival Forests methods. Furthermore, BioFu-

sionNet outperforms existing multimodal fusion methods such as MultiSurv, HFBSurv, PathomicFusion, MCAT and TransSurv, and achieves the highest mean C-index (0.77 ± 0.05) and AUC (0.84 ± 0.05). Partly, the superior performance of BioFusionNet is due to the introduction of the proposed weighted Cox loss function instead of using the traditional Cox loss. Univariate and multivariate analyses showed the significant impact of age and BioFusionNet predictions on survival outcomes, while other clinical parameters such as tumour grade, size, lymph node status and subtype did not exhibit a significant correlation with survival outcomes. Kaplan-Meier analysis revealed a distinct separation in survival probabilities between the high-risk and low-risk groups identified by BioFusionNet. In addition, the results of the ablation experiment confirmed the importance of attention mechanisms in improving prediction accuracy, with the combined model configuration utilising VAE, CoA and DCA and the weighted Cox loss showing the highest performance. BioFusionNet also presents a significant advancement in the interpretation of histopathological images, leveraging a self-attention mechanism to distinguish critical regions in patient profiles. A key contribution is the model’s ability to align high-attention areas with distinct cellular patterns, crucial for transitioning from patch-level to patient-level analysis, thereby enhancing the diagnostic process. SHAP analysis amplifies this by clarifying the influence of specific genes and clinical features on the model’s predictions. We observed that elevated SLC39A6 gene expression correlates with a high-risk prediction in ER+ breast cancers, where previous studies have shown conflicting findings, associating high SLC39A6 levels with good prognosis [58, 59], while others associated it with increased proliferation and lymph node involvement [60–62]. Similarly, our model identified high ESR1 expression as indicative of low risk, aligning with literature that associates ESR1 positivity with enhanced responsiveness to endocrine therapy and, consequently, a better prognosis in ER+ breast cancer patients [63]. In contrast, our analysis revealed an unexpected association between ERBB2 overexpression and a favorable prognosis in ER+ breast tumours, contrasting with the established view that ERBB2 overexpression indicates a poor prognosis [64, 65]. As our study was specifically tailored to analyze ER+ samples, excluding the HER2-enriched subtype (known for its high ERBB2 expression and aggressiveness) likely influenced the findings. Moreover, the SHAP analysis for clinical factors (LN positivity, higher tumour grade and size, and postmenopausal age) significantly influences our model’s ability to identify patients at increased risk, highlighting the critical role of these factors in breast cancer prognosis. Our analysis provides a transparent understanding of

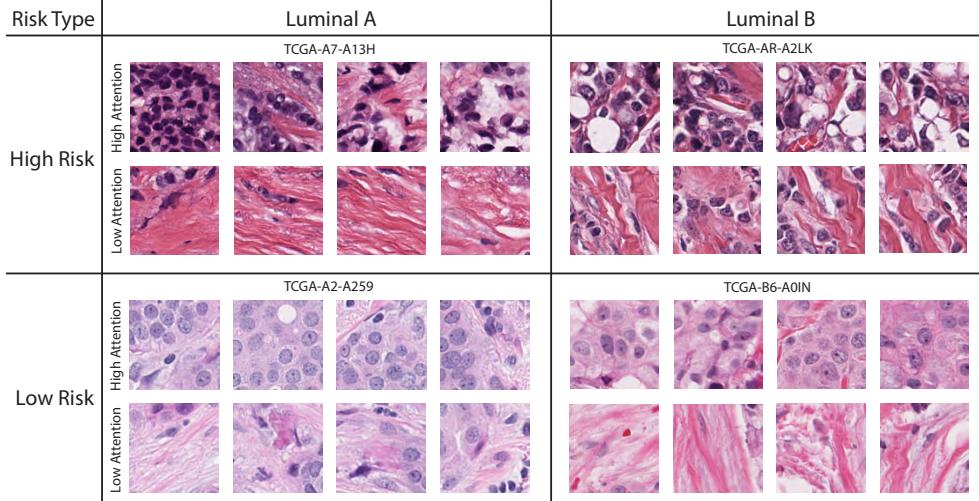


Figure 5: Visualisation of model-derived attention regions and associated risk types in Luminal A and Luminal B breast cancer patients. The figure presents raw histopathological image patches processed with BioFusionNet, which identifies areas of high and low attention, subsequently categorising patients into high and low risk.

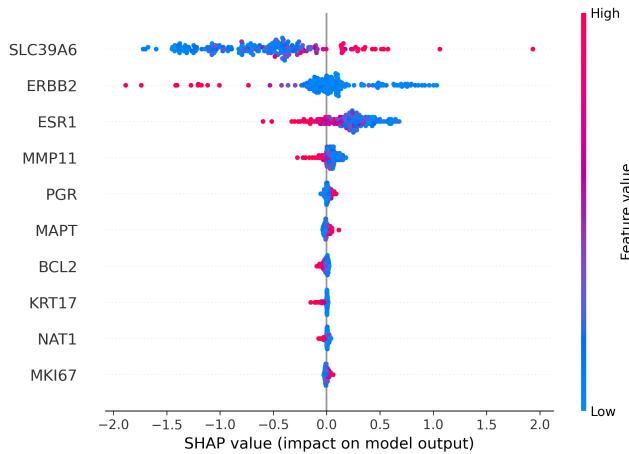


Figure 6: SHAP analysis of genetic features. The x-axis represents the SHAP value; colour intensity indicates gene expression level. The plot is sorted vertically by the features' overall importance.

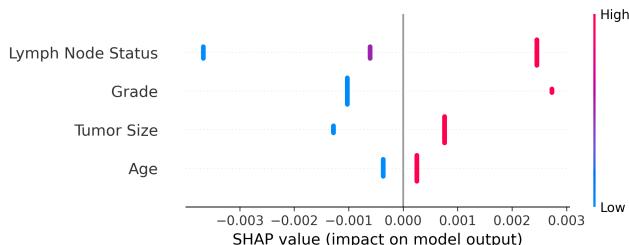


Figure 7: SHAP value distribution of clinical features. In this distribution, higher clinical values showing positive impact on the model, as indicated by its SHAP values.

how each gene and clinical feature contributes to the model's predictions, providing actionable insights for clinical decision-

making. While the risk assessment process mirrors current clinical practice, BioFusionNet streamlines the integration of all available data (patient features, tumour features and molecular features) to derive an automated single risk prediction score as a potential clinical oncology tool of the future.

While insightful, this study has certain limitations. We primarily opted for OS as the key outcome measure, instead of disease-free survival (DFS). This choice was made because DFS presented challenges such as a lower rate of events and a higher degree of data censorship, which could have limited the depth of the analysis. While OS is a feasible choice, it potentially overlooks critical insights into early-stage disease progression, typically highlighted by DFS. Moreover, the study's reliance on specific datasets such as TCGA for ER+ patients may affect the broad applicability of our findings. Another shortcoming of this study is the inherent limitations of the clinical data, which, during univariate analysis, identified tumour size, grade, and age as insignificant while only LN Status emerged as significant. Despite its limitations, the effectiveness of deep learning algorithms in analysing this clinical data arises from their ability to uncover complex patterns and interactions within dataset. Future research should therefore aim to validate these findings across a wider range of datasets to bolster the model's generalisability. Incorporating organ-level data, such as mammograms, could further enhance the predictive accuracy of our model. Additionally, extending the application of BioFusionNet to other cancer types and clinical scenarios could yield more comprehensive insights, making the research more universally relevant and applicable.

DATA AVAILABILITY

TCGA image data and clinical data are publicly available at <https://portal.gdc.cancer.gov/>.

CODE AVAILABILITY

Our work is fully reproducible and source code is publicly available on GitHub at <https://github.com/raktim-mondol/BioFusionNet>.

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Raktim Kumar Mondol is a PhD candidate in Computer Science and Engineering, specializing in computer vision and bioinformatics. He completed his MEng in Engineering with High Distinction from RMIT University, Australia. Mondol’s research interests include histopathological image analysis, clinical prognosis prediction, and enhancing clinical understanding through the interpretability of computational models.



Ewan Millar is a Senior Staff Specialist Histopathologist with NSW Health Pathology at St George Hospital Sydney with expertise in breast cancer pathology and translational research and a strong interest in AI and digital pathology applications.



Arcot Sowmya is Professor in the School of Computer Science and Engineering, UNSW. Her major research interest is in the area of Machine Learning for Computer Vision and includes learning object models, feature extraction, segmentation and recognition based on computer vision, machine learning and deep learning. In recent years, applications in the broader health area are a focus, including biomedical informatics and rapid diagnostics in the real world. All of these areas have been supported by competitive, industry and government funding.



Erik Meijering (Fellow, IEEE), is a Professor of Biomedical Image Computing in the School of Computer Science and Engineering. His research focusses on the development of innovative computer vision and machine learning (in particular deep learning) methods for automated quantitative analysis of biomedical imaging data.