Tumor Budding T-cell Graphs: Assessing the Need for Resection in pT1 Colorectal Cancer Patients

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Abstract

Colon resection is often the treatment of choice for colorectal cancer (CRC) patients. However, especially for minimally invasive cancer, such as pT1, simply removing the polyps may be enough to stop cancer progression. Different histopathological risk factors such as tumor grade and invasion depth currently found the basis for the need for colon resection in pT1 CRC patients. Here, we investigate two additional risk factors, tumor budding and lymphocyte infiltration at the invasive front, which are known to be clinically relevant. We capture the spatial layout of tumor buds and T-cells and use graph-based deep learning to investigate them as potential risk predictors. Our pT1 Hotspot Tumor Budding T-cell Graph (pT1-HBTG) dataset consists of 626 tumor budding hotspots from 575 patients. We propose and compare three different graph structures, as well as combinations of the node labels. The best-performing Graph Neural Network architecture is able to increase specificity by 20% compared to the currently recommended risk stratification based on histopathological risk factors, without losing any sensitivity. We believe that using a graph-based analysis can help to assist pathologists in making risk assessments for pT1 CRC patients, and thus decrease the number of patients undergoing potentially unnecessary surgery. Both the code and dataset are made publicly available.

Keywords: Digital Pathology, Graph Neural Networks, Colorectal Cancer

1. Introduction

Thanks to screening programs becoming more common, CRC is getting diagnosed in earlier, and more easily treatable stages. pT1 is such a form of early CRC, only invading the submucosa, but not yet the muscle layer. Thus, defining appropriate treatment guidelines is of high importance. Even though these cancers are minimally invasive, they can still cause lymph node metastasis, which puts patients at risk for distant metastasis (Burt et al., 2010; Argilés et al., 2020). That, however, cannot be assessed just from the polypectomy, but only after surgical colon resection (also referred to as a colectomy). Among pT1 CRC

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patients, less than 15% actually have metastasis present in lymph nodes at the time of diagnosis (Nivatvongs et al., 1991; Kobayashi et al., 2012). Cancer registry data[1] in Bern, Switzerland from 2014 show that 55% of all pT1 CRC patients nonetheless underwent a colectomy. This is due to current clinical guidelines (Bosch et al., 2013; Argilés et al., 2020) commonly recommending that patients should undergo surgery in the presence of just one unfavorable histological risk factor. Hence, improving this risk assessment has a high potential to reduce over-treatment and potential clinical complications (Vermeer et al., 2019).

Deep learning has provided solutions to a variety of challenges in pathology in recent years (Echle et al., 2021; Gurcan et al., 2009), such as tissue segmentation (Abbet et al., 2022), survival analysis (Bychkov et al., 2018; Abbet et al., 2020), and predicting lymph node metastasis (Kiehl et al., 2021; Brockmoeller et al., 2022). Lately, especially the combination of deep learning with spatial analysis has become of high interest (Jaume et al., 2021; Ahmedt-Aristizabal et al., 2021; Pati et al., 2022). Graph-based representations allow us to capture the spatial layout of the tissue and cells of interest and map their interactions in a very concise way. Thus, they make it possible to focus the deep learning algorithm on entities with known histopathological and clinical importance.

Two such factors that are known to play an important role in CRC are tumor budding and CD8+ lymphocytes (also known as cytotoxic T-cells), especially at the invasive front (Lugli et al., 2009). Tumor budding is a well-established prognostic factor in CRC (Lugli et al., 2017; Studer et al., 2021a). Several studies have also highlighted the prognostic power of T-cell scoring (Alwers et al., 2022). Most studies actually investigate the T-cell scoring in relation to tumor budding (Dawson et al., 2020; Nearchou et al., 2021; Lugli et al., 2009; Nearchou et al., 2019; Studer et al., 2022). However, so far the analysis has been limited to creating statistical scores, based on the ratio of counts in areas or within a radius, and other spatial statistics. To our knowledge, this is the first work exploring the interaction between tumor buds and T-cells using a graph-based approach.

The paper is structured as follows: Section 2 describes the used Graph Neural Networks (GNNs) methods, Section 3 introduces the dataset, and Section 4 provides details on the experimental setup and presents the results. Finally, Section 5 summarizes our findings.

2. Graph Neural Networks

With the introduction of GNNs, the field of deep learning has been expanded into the domain of graph-based analysis. Mathematically, a graph G is defined as a tuple of (N, E, α, β), where N denotes a finite set of nodes (or vertices), and E a set of edges, which are inserted according to a specified edge insertion function, and α and β are the node and edge labelling functions, respectively.

For classification tasks, GNNs architectures can be divided into two phases, a message-passing (MP) and a read-out phase. During the MP phase, information is exchanged between connected nodes, and then aggregated to update their hidden state:

$$\mathbf{a}_i^{k+1} = AGGREGATE_{j \in \mathcal{N}(i)}(\mathbf{x}_i^k, \mathbf{x}_j^k, \mathbf{e}_{ij}^k) \tag{1}$$

$$\mathbf{x}_i^{k+1} = UPDATE(\mathbf{x}_i^k, \mathbf{a}_i^{k+1}), \tag{2}$$

1. https://www.krebsregister.unibe.ch

where $\mathcal{N}(i)$ denotes the neighbouring nodes of node i, x_i the feature vector of node i, e_{ij} the edge feature vector between node i and j. In the first round (or layer) of MP, the hidden node state is the node feature vector of the input graph. By performing k rounds (or layers) of MP, the aggregation range is extended to the k-hop neighbourhood.

In order to perform graph classification, the information of all hidden node states is aggregated and passed to the classification header, which is often a multi-layer perceptron (MLP). This is referred to as the read-out phase:

$$\mathbf{v}_G = READOUT(\mathbf{x}_i^K | i \in G). \tag{3}$$

where $\mathbf{x}_i^K$ is the node state after the last MP round. However, it has been shown to be beneficial to also consider the intermediate representations, i.e. performing a read-out after each layer. These skip connections were introduced by (Xu et al., 2018b) and termed Jumping Knowledge (JK). The different read-out vectors can e.g. be concatenated such as $\mathbf{v}_G = \mathbf{v}^1 \parallel \ldots \parallel \mathbf{v}^K$.

2.1. Message-passing Functions

Over the years, many different MP functions have been introduced, however, the performance of a GNN model is highly dependent on the graph type and the right choice is not trivial (Thomas et al., 2022; You et al., 2020). We use three of the most commonly used ones for graph classification, which are all based on graph convolution.

GraphSAGE (Hamilton et al., 2017) is one of the early proposed MP functions. The hidden node state is updated as follows, using the mean aggregator scheme:

$$\mathbf{x}_i^{k+1} = \mathbf{W}_1^k \mathbf{x}_i^k + \mathbf{W}_2^k \cdot \text{mean}_{j \in \mathcal{N}(i)} \mathbf{x}_j^k \tag{4}$$

GIN (graph isomorphism network) (Xu et al., 2018a) is designed to achieve maximum discriminative power. The hidden state is updated using an MLP, ϵ is either a learnable parameter or fixed between $[0, 1]$:

$$\mathbf{x}_i^{k+1} = \text{MLP}\left((1+\epsilon) \cdot \mathbf{x}_i^k + \sum_{j \in \mathcal{N}(i)} \mathbf{x}_j^k \right) \tag{5}$$

GATv2 (Brody et al., 2021) incorporates an attention mechanism into the convolution, and is able to learn neighbor-specific weights, which can not only consider node but also edge features. The attention coefficients $\alpha_{i,j}$ is defined as

$$\alpha_{ij} = softmax_j(\mathbf{a}^\top \text{LeakyReLU}(\mathbf{W} \cdot [\mathbf{x}_i \parallel \mathbf{x}_j \parallel \mathbf{e}_{i,j}]), \tag{6}$$

where $\parallel$ denotes vector concatenation, and $\mathbf{a} \in \mathbb{R}^{2d'}$ and $\mathbf{W} \in \mathbb{R}^{d' \times d}$ are learned. The hidden representation of node i is thus updated as follows (σ is a non-linearity):

$$\mathbf{x}_i^{k+1} = \sigma(\sum_{j \in \mathcal{N}(i)} \alpha_{ij}^k \cdot \mathbf{W}^k \mathbf{x}_j^k). \tag{7}$$

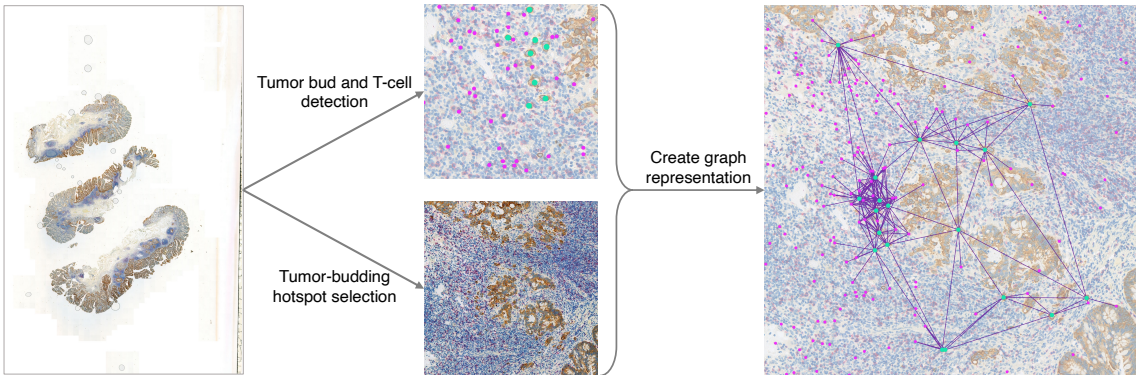

Figure 1: Overview of the graph extraction workflow. The tumor buds and T-cells are automatically detected on the WSIs using CNNs. The hotspot annotations are created by an expert pathologist. To create the graph, all detected objects are added as nodes.

3. The pT1 Hotspot Tumor Budding T-cell Graph (pT1-HBTG) Dataset

Figure 1 shows the workflow of the creation of the pT1-HBTG dataset, which is available open-source[2]. Figure 2 shows an example image for each graph representation and class. Additional details on the dataset and more example images can be found in Appendix B.

3.1. pT1 Patient Cohort

Our pT1 cohort consists of patients that, after the polypectomy, either (A) underwent resection, and thus have a known lymph node status, or (B) have at least 36 months of follow-up information about local/distant recurrence. We categorize the patients as either high- or low-risk, according to the clinical question of whether, in retrospect, they required the colectomy. Patients (A) without lymph node metastasis (N0) and patients (B) without recurrence are considered low-risk. Thus, patients (A) with lymph node metastasis (N+) and patients (B) with a recurrence are grouped into the high-risk class.

In total, we have 626 WSIs of polyps from 575 pT1 CRC patients collected from eight different pathology institutes and selected by expert pathologists. The WSIs are double-stained for CD8-AE1/AE3 using immunohistochemistry (AE1-AE3 pan-cytokeratin for the tumor, and CD8 for the cytotoxic T-cells). They are digitized using a Pannoramic 250 scanner at $0.243\mu m/pixel$. The class distribution is unbalanced, with 541 versus 85 for the low-risk and high-risk groups, respectively.

3.2. Graph Representations

The pT1-HBTGs represent the tumor budding hotspot of a slide according to the IT-BCC (Lugli et al., 2017) recommendations (area of highest budding at the invasive front, $0.785mm^2$), selected by an expert pathologist. As introduced in section 2, a graph consists

2. We are currently working on getting the ethics approval for the release of the clinical and image data. We hope to have this finalized by the time of publication.

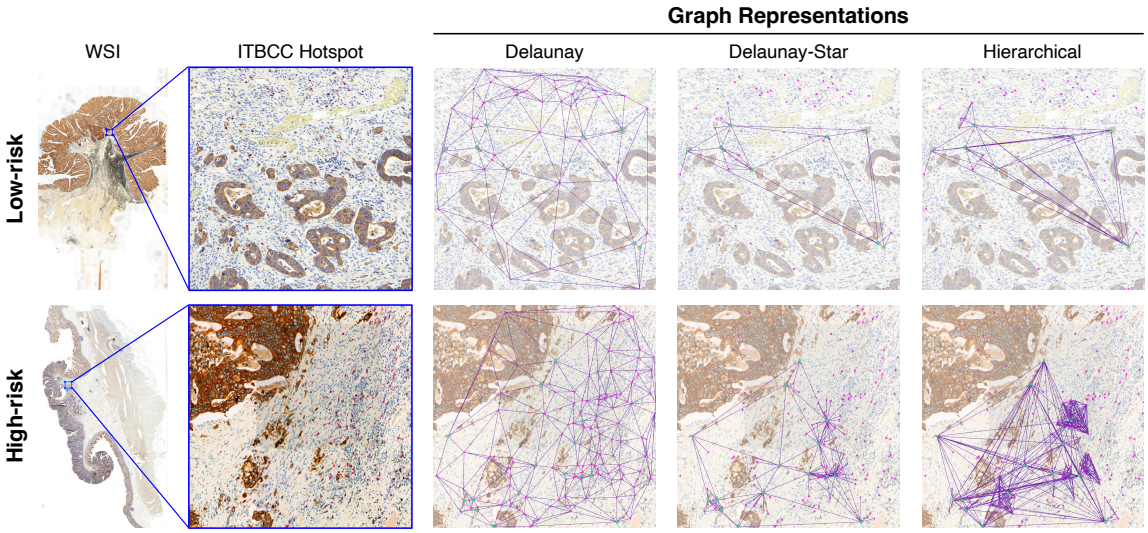

Figure 2: Example graph representations for a low- and a high-risk patient. The nodes are color-coded based on the *type* node label, tumor buds in green and T-cells in pink. The blue rectangle on the WSI shows the annotation of the ITBCC hotspot.

of *nodes* and *edges*, which are inserted according to a specified edge insertion function. Both nodes and edges can have additional information attached to them, also referred to as *labels*.

3.2.1. Node Detection and Node Labeling

Since our graphs map the interaction of tumor buds with T-cells, they build the nodes of our graphs. T-cells are single cells, whereas a tumor bud is defined as a cluster of 1-4 tumor cells. The tumor bud detection is performed using a student-teacher CNN (Bokhorst et al., 2022) model, which is available on Grand Challenge[3]. The algorithm used for the T-cells is based on U-Net, with additional post-processing (Swiderska-Chadaj et al., 2019). Color deconvolution is performed as a pre-processing step as the algorithm is trained on single-stain immunohistochemistry (IHC). The quality of the output was manually assessed on a subset (Studer et al., 2020), with a precision of 89.9% and recall of 93.0%.

We define three different types of node features. First, the *type* of the node, i.e. tumor bud or T-cell, which is one-hot encoded. Second, we use the *coordinates* of the node, normalized to the center of the hotspot using zero centering: $x' = x - \bar{x}$. Third, we compute the *embedding vector* of crops ($200x200$ *pixels* centered on the node coordinates) using the ImageNet (Deng et al., 2009) pre-trained DINO model (Caron et al., 2021). Using the ViT-16 backbone, we get a feature vector of size 384.

3.2.2. Edge Insertion and Edge Labelling

As an edge label, we use the distance between the nodes in μm. We define three different edge insertion functions. As a baseline, we use the *Delaunay* triangulation (Delaunay

3. https://grand-challenge.org/algorithms/colon-budding-in-ihc/

Table 1: Options for the experimental setups. In total, this results in 144 setups for all combinations of graph configurations, node labels, message passing functions, and with/without JK and additional clinical information.

Graph Options	Edge Configuration	Delaunay, Delaunay-Stars, Hierarchical
	Node Labels	Type (tumor bud or T-cell), coordinates, ViT-16 embedding
GNN	MP Functions	GraphSAGE, GIN, GATv2
	Jumping Knowledge (JK)	With and without
Additional Data	Clinical Information (SGG Criteria)	With and without

and Spherevide, 1934) (without distinguishing between the two node types), which is very commonly used in histopathology, especially for cell graphs (Sharma et al., 2015).

Since we only consider two cell (cluster) types as nodes and not all cells, and are especially interested in the interaction of the T-cells within close proximity of the tumor buds, we define two more edge insertion functions. We create a *Hierarchical* representation, where all T-cells nodes are connected to their closest tumor bud node, with a cut-off of $100\mu m$. Then, all T-cell nodes connected to the same tumor bud are fully-connected. Lastly, the tumor bud nodes are fully-connected as well. We also propose the *Delaunay-Star* representation, the tumor bud nodes are connected using Delaunay triangulation, and the T-cell nodes are connected to all tumor bud nodes within a radius of $100\mu m$.

4. Experimental Evaluation

In this section, we provide the details of the experimental setups and present the results of the best-performing ones. As a baseline, we use the risk assessment guidelines defined by the Swiss Society of Gastroentrologists (SGG) (Dieter, 2022), which define the current treatment recommendations for pT1 polyps for Swiss pathologists. For more details on the SGG criteria see Appendix A.

Because the dataset is unbalanced, we use the following metrics to assess the performance: Average F1Score (average of per-class score), the True Negative Rate (TNR), and the True Positive Rate (TPR). The TNR is the recall for the low-risk class and is also called specificity or selectivity. The TPR is the recall for the high-risk group, also known as sensitivity.

4.1. Experimental Setup

We use a 5-fold cross-validation (CV) setup. The data is split so that patients do not overlap, and the distribution between the two classes is roughly the same in each fold (see Table C5). The evaluation is done per patient, if there are multiple graphs per patient, the classification is based on $max(softmax(\mathbf{z}_i), ..., softmax(\mathbf{z}_n))$ with n being the number of

Table 2: Best results for all node label and graph configuration combinations are presented here (10-model ensemble, average and standard deviation over 5-fold CV). For the complete result tables see Appendix D. As a baseline, we report the classification based on the guidelines by the SGG (see Figure 3). True Negative Rate (TNR): recall for the low-risk group. True Positive Rate (TPR): recall for the high-risk group). The top three are indicated in bold.

Node Label	Edge Config	GNN	Clin. Info	Average F1Score	TNR	TPR
Type	Delaunay	GraphSAGE-JK	Yes	$35.2_{\pm 3.3}$	$31.4_{\pm 4.7}$	$\mathbf{88.3_{\pm 5.1}}$
	Delaunay-Star	GraphSAGE-JK	Yes	$39.5_{\pm 8.1}$	$40.2_{\pm 13.1}$	$79.9_{\pm 13.5}$
	Hierarchical	GIN-JK	No	$30.4_{\pm 14.4}$	$27.9_{\pm 20.7}$	$83.7_{\pm 13.5}$
Type Coord.	Delaunay	GIN-JK	No	$27.1_{\pm 11.2}$	$24.1_{\pm 22.1}$	$83.0_{\pm 21.4}$
	Delaunay-Star	GraphSAGE-JK	Yes	$37.2_{\pm 6.6}$	$35.9_{\pm 8.2}$	$80.2_{\pm 5.6}$
	Hierarchical	GraphSAGE	Yes	$33.5_{\pm 4.9}$	$30.0_{\pm 8.4}$	$84.4_{\pm 14.3}$
Type ViT-16.	Delaunay	GATv2	Yes	$36.3_{\pm 8.7}$	$32.6_{\pm 10.8}$	$\mathbf{90.5_{\pm 9.6}}$
	Delaunay-Stars	GIN-JK	Yes	$\mathbf{40.9_{\pm 13.2}}$	$\mathbf{41.5_{\pm 18.6}}$	$84.2_{\pm 6.1}$
	Hierarchical	GATv2	Yes	$\mathbf{41.1_{\pm 12.7}}$	$\mathbf{40.7_{\pm 15.6}}$	$84.8_{\pm 8.4}$
Type Coord. ViT-16	Delaunay	GIN-JK	No	$35.2_{\pm 10.7}$	$32.9_{\pm 14.9}$	$83.3_{\pm 9.8}$
	Delaunay-Star	GraphSAGE-JK	Yes	$39.7_{\pm 4.2}$	$38.4_{\pm 4.8}$	$\mathbf{85.7_{\pm 9.9}}$
	Hierarchical	GraphSAGE-JK	Yes	$\mathbf{41.9_{\pm 5.4}}$	$\mathbf{42.5_{\pm 8.9}}$	$84.0_{\pm 8.2}$
SGG Criteria Classification				$28.2_{\pm 4.4}$	$22.2_{\pm 4.3}$	$85.0_{\pm 7.6}$

slides. We create an ensemble of 10 models per experimental setup, the final classification decision is based on the average of the softmax output.

Table 1 shows the different options for the experimental setups (total of 144 experiments). The additional clinical information used as input for the classification header is based on the SGG criteria: lymphovascular invasion yes/no (one hot encoded), tumor grade (1-3), $\log_{10}(number\ of\ tumor\ buds)$ and $\log_{10}(invasion\ depth)$ in mm. The numerical variables are $log10$ transformed to be near normal distributed. The implementation details can be found in Appendix C and the code is available on GitHub[4].

4.2. Results and Discussion

Table 2 shows the best results for each graph structure and node label combination. To choose the best model, we consider the best three in terms of average F1Score and average Recall (average between TNR and TPR) and choose the one with the highest TPR among them. Models that perform lower than the baseline in terms of TNR are also not considered. The complete result (with additional metrics) can be found in Appendix D.

4. https://github.com/LindaSt/GraphNeuralNetworkExperiments

When selecting the overall best model, one has to determine which metric is the most relevant. If the main goal is to prevent unnecessary surgeries, a high TNR is important. If we choose the model with the highest average F1Score, we select a model that shows an increased performance for both the TNR and TPR compared to the baseline. For both of these metrics, the GraphSAGE-JK architecture trained on the *Hierarchical-Type-Coordinate-ViT16* graphs, and using the additional clinical information, shows the best performance. If not missing any high-risk patient is of high importance, and a moderate improvement in the TNR is acceptable, the GATv2 trained on the *Delaunay-Type-ViT16* graphs, and using the additional clinical information, should be considered.

Adding more node labels seems to generally improve the performance. However, it is notable that training a GraphSAGE-JK model on the *Delaunay-Type* graphs, the most simple representation, combined with the additional clinical patient information shows, an improvement over the baseline. Ockham's razor would thus suggest, that this model is preferred due to its simplicity. This setup also shows good resilience, having the lowest standard deviation over the 5-fold CV.

As observed in (You et al., 2020), the architecture of the GNN depends heavily on the graph. We can see this here, in that different architectures perform best for different graph structures and node label combinations. However, using a variation of *Delaunay* triangulation to create graphs seems to be a generally good choice to perform spatial analysis in digital pathology, not only when using cell graphs. Interestingly, GraphSAGE shows good performance, even though it is the simplest MP function. This is likely due to the size of our dataset, as large models are more prone to overfitting on small datasets. Using JK seems to be preferred for both GraphSAGE and GIN, but not for GATv2.

5. Conclusion

In this study, we explore the potential of analyzing the interaction between the tumor and the immune system at the invasive front using graph-based deep learning for risk assessment of pT1 CRC patients. We introduce our publicly available pT1 Hotspot Tumor Budding T-cell Graph (pT1-HBTG) dataset, which contains three different graph representations, as well as three different node feature options. Using GNN models, especially when combined with known histopathological risk factors (tumor grade, tumor budding, invasion depth, and lymphovascular invasion), we are able to outperform the risk stratification according to current treatment recommendations and decrease the number of falsely identified high-risk patients by 20%, without a decrease in sensitivity. For future work, we hope to validate our proposed methods on an external cohort and extend our findings to other cancer patient groups of interest, such as stage II CRC.

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Appendix A. Guidelines by the Swiss Society of Gastroentrologists

Figure 3 shows the risk assessment workflow recommended by the SGG for pT1 polyps. The criteria vary slightly between sessile and pedunculated polyps, as some of the scoring methods are different. In essence, however, they both cover tumor grade, infiltration depth, lymphovascular invasion, and tumor budding.

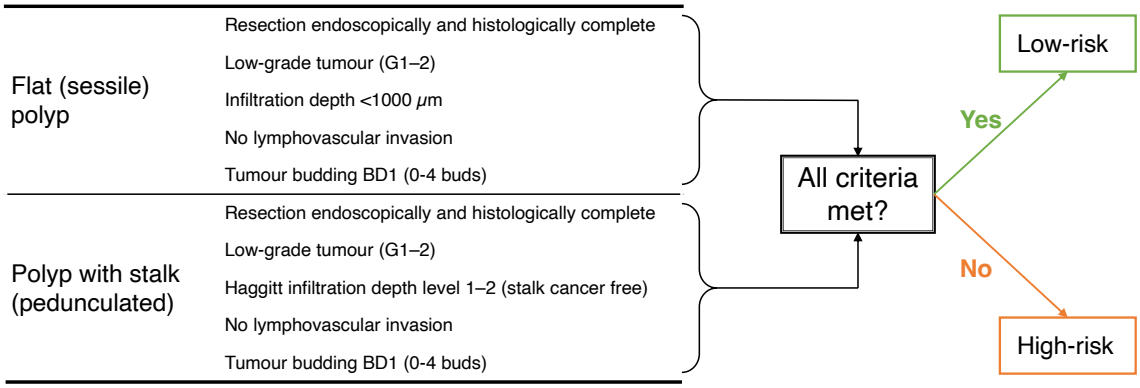


Figure 3: Prognostic classification criteria set forth by the SGG for risk assessment of pT1 polyp biopsies (Dieter, 2022). High-risk patients usually undergo colon resection, and low-risk patients follow a watch-and-wait strategy.

Appendix B. Additional Details on pT1-HBTG Dataset

Figure 4 shows more example images of the different graph types. See Table 4 for key statistics on the graphs in the different graph configuration datasets, and Table 3 for the clinical information within the high- and low-risk groups. A previous version of a subset of this dataset is described in (Eloy and Campelos, 2020). The code used to create the graph representations is available on GitHub[5].

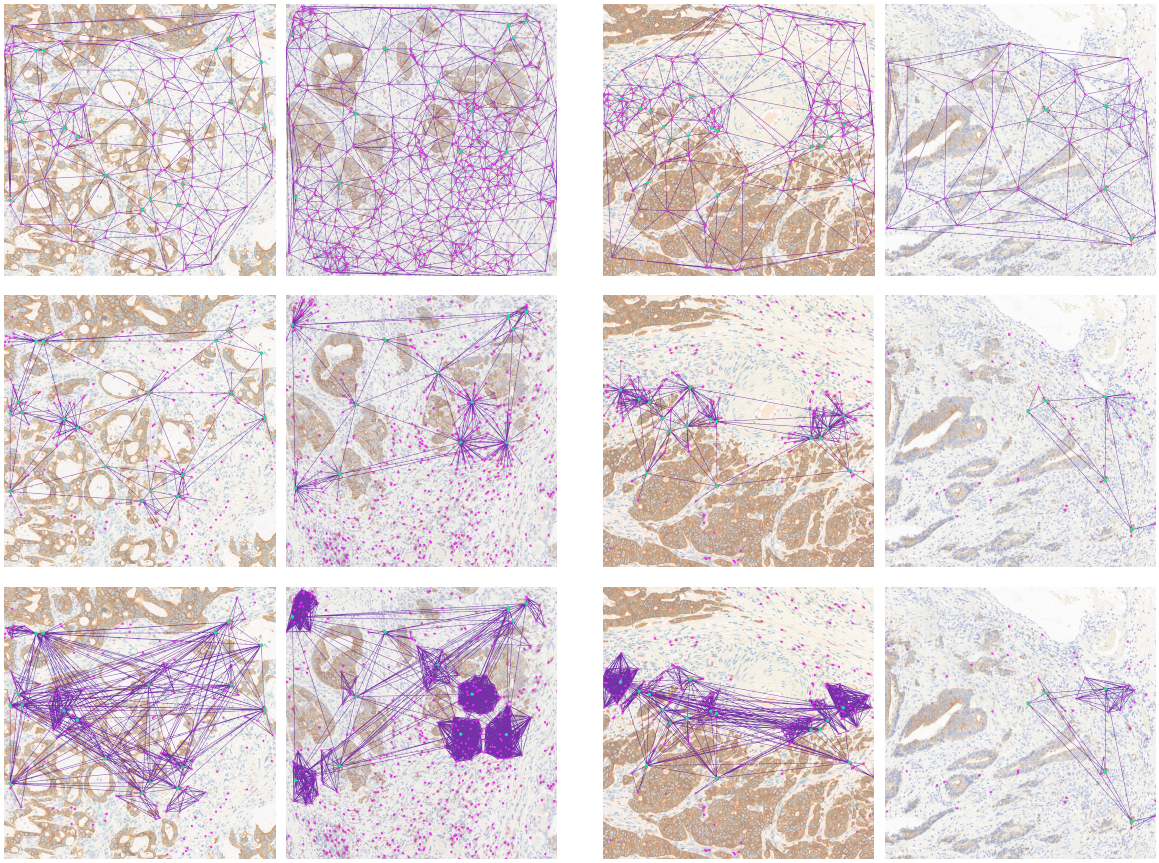
Table 3: Statistics on the pT1 patient cohort per group of interest in regards to the clinical information.

	Average Invasion Depth (mm)	Lymphovascular Invasion		Tumor Grade		
		Yes	No	1	2	3
Low-risk	5.00	79	434	140	333	40
High-risk	6.02	18	44	10	44	8
Total	5.11	97	478	150	377	48

5. https://github.com/LindaSt/BT-graph-creation

Table 4: Graph configuration overview: median of graph feature in the pT1-HBTG. The low-risk group has a median number of 171 nodes (7 for tumor buds, 157 for T-cells), and the high-risk group 193 (16 tumor buds, 180 T-cells).

	Delaunay		Delaunay-Star		Hierarchical	
	Low-risk	High-risk	Low-risk	High-risk	Low-risk	High-risk
Edges	496	561	63	192	224	622
Connected Nodes	171	193	65	100	65	100
Isolated Nodes	0	0	106	93	106	93



(*a*) Low-risk (*b*) High-risk

Figure 4: More examples from the pT1-HBTG datasets. The nodes are color-coded based on the *type* node label, tumor buds in green and T-cells in pink. The edges are in purple according to the edge insertion function described in Section 3.2.2: *Delaunay* (top), *Delaunay-Star* (middle), *Hierarchical* (bottom).

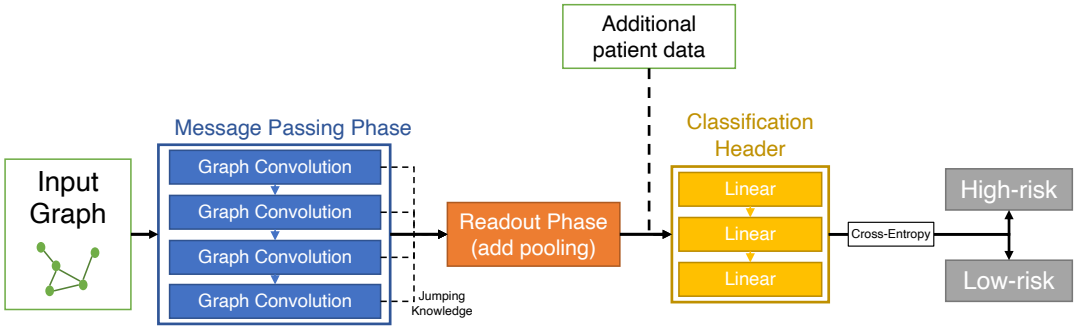


Figure 5: Schematic overview of the GNN architecture. We employ drop-out after each layer and graph-level normalization after each graph convolution layer. Jumping Knowledge increases the size of the embedding vector by a factor of 4, as the read-out of all layers is concatenated.

Appendix C. Additional Details on the Experimental Setup

The implementations are all done in PyTorch (Paszke et al., 2019), specifically, PyTorch Lightning, using the PyTorch Geometric (PyG) (Fey and Lenssen, 2019) library. Table 5 shows data distribution between the CV-folds, Figure 5 gives an overview of the overall GNN architecture, and Table 6 shows the number of parameters for each model.

We use a setup with four MP layers with 196 neurons each, and a three-layer MLP classification header, and between each layer, we add a dropout layer ($p = 0.3$). We also employ the GraphNorm (Cai et al., 2021) normalization implemented in PyG between each MP layer to stabilize training. GraphNorm normalizes the node representations across all nodes per graph using a learnable shift α, which determines how much information to keep in the mean. We use the default $\alpha = 0.00001$

After the read-out phase (global add-pooling), the graph embedding vector has a size of 196 or 784 neurons, as the output of all 4 MP layers are concatenated when using JK. The second MLP layer has double as many neurons, the last one again either 196 or 784. For the configuration, where additional patient data is used as input (concatenated with the read-out vector), an additional 5 neurons are added to the first layer. LeakyReLU (Maas et al., 2013) is used as an activation function (with default $\alpha = 0.01$).

For the MP functions, we use the implementations provided by PyG, with the following configurations:

- GraphSAGE: *SAGEConv*, no additional parameters need to be specified.
- GIN: *GINConv*, with a two-layer MLP (169 neurons, $\epsilon = 0$) using the LeakyReLU activation function and dropout ($p = 0.3$). Using an MLP and an $\epsilon = 0$ is suggested by (Xu et al., 2018a).
- GATv2: *GATv2Conv*, with a single attention header (default configuration).

The models are trained for 100 epochs (until convergence), with a batch size of 256, a learning rate and weight decay of 0.0001, and the *StepLR* learning rate scheduler (step-

Table 5: Overview of the 5-fold cross-validation split. Overall, there are 626 graphs from 575 patients, as multiple slides are available for some patients. For each slide, one hotspot is annotated from which a graph is extracted.

CV fold	# patients		# graphs	
	low-risk	high-risk	low-risk	high-risk
0	104	10	109	12
1	103	12	107	14
2	102	13	109	18
3	103	13	109	19
4	101	14	107	22
total	513	62	541	85

size of 10). We use the Adam optimizer and the cross-entropy loss function with label smoothing (Szegedy et al., 2016) of 0.2. As data augmentation, we employ node dropping ($p = 0.1$), where nodes are dropped randomly from the adjacency matrix with probability p using samples from a Bernoulli distribution. For the experimental setups, where the coordinates are used as node labels, we additionally add random shearing (shearing factor range $[-1.05, 1.05]$), scaling ($\pm 5\%$), and random rotation ($0-360°$) of the coordinates, before zero centering. For the coordinate augmentation, we use the transform implementations provided by the PyG library.

The design choices are made based on previous empirical experience (Studer et al., 2021b), the original publications of the MP functions, and suggestions provided by(You et al., 2020), and validated on a preliminary dataset. GraphNorm and a low learning rate increase the training stability and show a more stable loss convergence on the validation sets. Data augmentation, dropout, loss smoothing, and weight decay help with overfitting, as the dataset is small and unbalanced. The number of neurons is optimized between $[128, 196, 256]$. (You et al., 2020) suggest using the Adam optimizer, 4 MP layers, concatenation for JK, and sum aggregation for read-out (global-add pooling) work best.

Appendix D. Full Experimental Results

In this section, we present the full results for all experimental set-ups, with the per-class F1Score and precision in addition to the per-class recall. The results considered best and presented in Table 2 are highlighted in bold.

Table 7, 10, 13, and 16 show the results for the *Delaunay* graph representation with type, type + coordinates, type + ViT-16, and type + coordinates + ViT-16, respectively.

Table 8, 11, 14, and 17 show the results for the *Delaunay-Star* graph representation with type, type + coordinates, type + ViT-16, and type + coordinates + ViT-16, respectively.

Table 9, 12, 15, and 18 show the results for the *Hierarchical* graph representation with type, type + coordinates, type + ViT-16, and type + coordinates + ViT-16, respectively.

Table 6: Overview of the number of parameters in the different GNN configurations. The number depends on the message-passing (MP) function, the number of node/edge features, and whether or not Jumping Knowledge (JK) is used. The number of neurons and number of layers is kept fixed otherwise. Using the additional clinical data adds another 1,920 parameters to the respective model.

		Node Features			
		Type	Type Coord.	Type ViT-16	Type Coord. ViT-16
# Node Features		2	2+2	2+384	2+2+384
GATv2	-	375,938	376,706	523,394	524,162
	JK	2,590,466	2,591,234	2,737,922	2,738,690
GIN	-	411,650	412,034	485,378	485,762
	JK	2,626,946	2,627,330	2,700,674	2,701,058
GraphSAGE	-	372,866	373,634	520,322	521,090
	JK	2,588,162	2,588,930	2,735,618	2,736,386

Table 7: Full results and additional metrics of experiments on the *Delaunay* graph representations using just the node type as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$23.8_{\pm 27.7}$	$22.0_{\pm 4.4}$	$58.3_{\pm 47.6}$	$12.6_{\pm 3.0}$	$16.9_{\pm 20.1}$	$94.2_{\pm 8.4}$
	Yes	$14.2_{\pm 17.5}$	$19.9_{\pm 2.8}$	$56.1_{\pm 46.0}$	$11.2_{\pm 1.9}$	$8.9_{\pm 11.4}$	$94.1_{\pm 7.3}$
GATv2-JK	No	$55.1_{\pm 10.7}$	$23.5_{\pm 2.8}$	$94.3_{\pm 2.5}$	$13.9_{\pm 2.0}$	$39.8_{\pm 10.9}$	$79.6_{\pm 11.8}$
	Yes	$54.9_{\pm 10.1}$	$23.1_{\pm 1.7}$	$94.9_{\pm 4.0}$	$13.6_{\pm 0.9}$	$39.6_{\pm 9.6}$	$79.6_{\pm 15.3}$
GIN	No	$48.6_{\pm 10.3}$	$23.0_{\pm 3.0}$	$94.9_{\pm 1.9}$	$13.4_{\pm 2.1}$	$33.4_{\pm 9.4}$	$84.4_{\pm 9.1}$
	Yes	$39.3_{\pm 16.8}$	$21.9_{\pm 3.7}$	$94.2_{\pm 3.6}$	$12.6_{\pm 2.5}$	$26.4_{\pm 13.8}$	$86.0_{\pm 10.8}$
GIN-JK	No	$57.4_{\pm 5.9}$	$24.6_{\pm 3.2}$	$95.1_{\pm 1.3}$	$14.5_{\pm 2.2}$	$41.3_{\pm 6.1}$	$81.9_{\pm 7.3}$
	Yes	$53.6_{\pm 3.0}$	$22.7_{\pm 2.8}$	$93.7_{\pm 1.1}$	$13.3_{\pm 1.8}$	$37.6_{\pm 2.9}$	$78.7_{\pm 5.2}$
GraphSAGE	No	$41.3_{\pm 8.1}$	$22.7_{\pm 3.6}$	$96.2_{\pm 3.2}$	$13.1_{\pm 2.4}$	$26.8_{\pm 7.1}$	$90.1_{\pm 8.3}$
	Yes	$32.9_{\pm 22.2}$	$22.2_{\pm 2.9}$	$77.8_{\pm 39.0}$	$12.7_{\pm 2.1}$	$22.2_{\pm 16.8}$	$91.7_{\pm 10.2}$
GraphSAGE-JK	No	$43.5_{\pm 4.5}$	$22.7_{\pm 3.2}$	$95.4_{\pm 1.4}$	$13.0_{\pm 2.0}$	$28.3_{\pm 3.8}$	$88.4_{\pm 4.9}$
	Yes	$\mathbf{47.1_{\pm 5.6}}$	$\mathbf{23.4_{\pm 3.0}}$	$\mathbf{95.7_{\pm 1.9}}$	$\mathbf{13.5_{\pm 1.9}}$	$\mathbf{31.4_{\pm 4.7}}$	$\mathbf{88.3_{\pm 5.1}}$

Table 8: Full results and additional metrics of experiments on the *Delaunay-Star* graph representations using just the node type as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$43.7_{\pm 24.1}$	$19.4_{\pm 1.8}$	$87.2_{\pm 8.3}$	$11.5_{\pm 1.6}$	$32.6_{\pm 21.8}$	$71.3_{\pm 20.6}$
	Yes	$23.8_{\pm 5.4}$	$18.7_{\pm 2.1}$	$86.6_{\pm 8.6}$	$10.5_{\pm 1.2}$	$13.8_{\pm 3.5}$	$84.3_{\pm 7.3}$
GATv2-JK	No	$60.4_{\pm 10.8}$	$21.5_{\pm 5.5}$	$91.9_{\pm 4.1}$	$12.9_{\pm 3.4}$	$46.0_{\pm 11.5}$	$65.8_{\pm 17.9}$
	Yes	$43.6_{\pm 25.8}$	$20.4_{\pm 3.3}$	$91.1_{\pm 5.3}$	$12.3_{\pm 2.9}$	$33.2_{\pm 24.4}$	$72.2_{\pm 18.4}$
GIN	No	$19.0_{\pm 22.5}$	$19.4_{\pm 1.7}$	$86.5_{\pm 18.7}$	$11.0_{\pm 1.3}$	$13.0_{\pm 17.6}$	$87.9_{\pm 14.2}$
	Yes	$28.6_{\pm 20.7}$	$21.8_{\pm 3.6}$	$95.6_{\pm 6.5}$	$12.5_{\pm 2.5}$	$19.0_{\pm 16.8}$	$92.5_{\pm 9.6}$
GIN-JK	No	$68.5_{\pm 9.1}$	$24.2_{\pm 6.0}$	$92.3_{\pm 2.7}$	$15.2_{\pm 4.2}$	$55.2_{\pm 11.2}$	$63.0_{\pm 11.5}$
	Yes	$59.2_{\pm 15.9}$	$22.5_{\pm 7.2}$	$91.6_{\pm 4.2}$	$13.6_{\pm 4.7}$	$45.4_{\pm 15.0}$	$68.1_{\pm 17.7}$
GraphSAGE	No	$32.6_{\pm 18.7}$	$19.9_{\pm 3.4}$	$95.4_{\pm 5.8}$	$11.4_{\pm 1.9}$	$21.7_{\pm 14.5}$	$84.0_{\pm 20.6}$
	Yes	$50.7_{\pm 12.3}$	$21.3_{\pm 2.0}$	$93.9_{\pm 4.0}$	$12.5_{\pm 1.1}$	$36.1_{\pm 11.5}$	$76.1_{\pm 16.9}$
GraphSAGE-JK	No	$56.3_{\pm 11.9}$	$22.9_{\pm 3.4}$	$92.5_{\pm 1.9}$	$13.6_{\pm 2.4}$	$41.4_{\pm 12.1}$	$73.9_{\pm 3.7}$
	Yes	$\mathbf{55.0_{\pm 14.3}}$	$\mathbf{24.0_{\pm 4.8}}$	$\mathbf{95.1_{\pm 3.2}}$	$\mathbf{14.2_{\pm 3.2}}$	$\mathbf{40.2_{\pm 13.1}}$	$\mathbf{79.9_{\pm 13.5}}$

Table 9: Full results and additional metrics of experiments on the *Hierarchical* graph representations using just the node type as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$54.2_{\pm 22.3}$	$20.9_{\pm 3.2}$	$92.6_{\pm 4.0}$	$12.9_{\pm 2.4}$	$42.7_{\pm 23.3}$	$68.5_{\pm 23.9}$
	Yes	$37.0_{\pm 26.9}$	$18.8_{\pm 6.9}$	$70.6_{\pm 35.6}$	$11.0_{\pm 4.4}$	$27.5_{\pm 22.4}$	$72.4_{\pm 26.8}$
GATv2-JK	No	$34.4_{\pm 18.3}$	$18.5_{\pm 3.6}$	$89.0_{\pm 10.0}$	$10.6_{\pm 2.2}$	$23.0_{\pm 13.8}$	$75.7_{\pm 18.4}$
	Yes	$37.7_{\pm 6.9}$	$17.1_{\pm 3.1}$	$86.7_{\pm 6.2}$	$9.8_{\pm 1.8}$	$24.4_{\pm 5.6}$	$68.9_{\pm 15.0}$
GIN	No	$2.3_{\pm 2.2}$	$19.0_{\pm 1.4}$	$50.0_{\pm 44.7}$	$10.6_{\pm 0.8}$	$1.2_{\pm 1.1}$	$97.1_{\pm 5.7}$
	Yes	$1.8_{\pm 3.7}$	$19.6_{\pm 1.6}$	$20.0_{\pm 40.0}$	$10.9_{\pm 1.0}$	$1.0_{\pm 1.9}$	$100.0_{\pm 0.0}$
GIN-JK	No	$\mathbf{38.8_{\pm 25.6}}$	$\mathbf{22.1_{\pm 4.7}}$	$\mathbf{91.4_{\pm 11.1}}$	$12.9_{\pm 3.4}$	$\mathbf{27.9_{\pm 20.7}}$	$\mathbf{83.7_{\pm 13.5}}$
	Yes	$48.4_{\pm 20.5}$	$21.2_{\pm 4.7}$	$88.9_{\pm 8.3}$	$12.6_{\pm 3.1}$	$35.4_{\pm 17.4}$	$73.6_{\pm 15.3}$
GraphSAGE	No	$36.0_{\pm 20.7}$	$21.1_{\pm 3.3}$	$94.2_{\pm 3.3}$	$12.2_{\pm 2.2}$	$24.8_{\pm 17.7}$	$84.7_{\pm 16.1}$
	Yes	$46.0_{\pm 22.3}$	$22.5_{\pm 5.2}$	$91.9_{\pm 3.3}$	$13.3_{\pm 3.8}$	$33.6_{\pm 19.6}$	$78.9_{\pm 10.7}$
GraphSAGE-JK	No	$51.2_{\pm 16.1}$	$21.6_{\pm 4.0}$	$92.9_{\pm 4.4}$	$12.8_{\pm 2.6}$	$37.2_{\pm 15.3}$	$74.3_{\pm 16.0}$
	Yes	$63.7_{\pm 4.7}$	$23.7_{\pm 4.0}$	$93.6_{\pm 3.2}$	$14.3_{\pm 2.6}$	$48.6_{\pm 6.1}$	$71.5_{\pm 14.8}$

Table 10: Full results and additional metrics of experiments on the *Delaunay* graph representations using the node type and the coordinates as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	13.7 ± 7.3	19.5 ± 2.4	91.0 ± 7.6	10.9 ± 1.4	7.6 ± 4.4	93.5 ± 5.9
	Yes	22.7 ± 13.7	20.1 ± 2.8	73.0 ± 36.7	11.3 ± 1.8	13.7 ± 8.7	90.4 ± 5.7
GATv2-JK	No	29.8 ± 21.8	17.4 ± 3.7	86.6 ± 11.7	9.9 ± 2.0	20.5 ± 16.7	75.9 ± 25.7
	Yes	26.0 ± 16.4	19.9 ± 1.4	93.9 ± 5.3	11.3 ± 1.0	16.4 ± 11.9	88.1 ± 13.2
GIN	No	18.2 ± 12.0	19.8 ± 1.5	95.0 ± 6.1	11.1 ± 1.0	10.8 ± 8.5	92.7 ± 11.1
	Yes	16.2 ± 6.2	20.4 ± 2.7	97.1 ± 5.7	11.4 ± 1.7	9.0 ± 3.7	96.7 ± 6.7
GIN-JK	No	**34.0 ± 22.4**	**20.3 ± 1.9**	**95.2 ± 4.3**	**11.8 ± 1.6**	**24.1 ± 21.1**	**83.0 ± 21.4**
	Yes	27.9 ± 18.5	19.2 ± 3.1	89.3 ± 6.9	11.0 ± 2.0	18.2 ± 13.8	82.2 ± 13.4
GraphSAGE	No	19.1 ± 12.8	19.3 ± 2.2	89.4 ± 6.7	10.9 ± 1.4	11.3 ± 8.4	89.1 ± 7.2
	Yes	16.5 ± 7.9	18.9 ± 2.5	90.7 ± 7.8	10.6 ± 1.5	9.4 ± 4.9	88.6 ± 9.5
GraphSAGE-JK	No	21.2 ± 13.8	20.5 ± 2.8	95.8 ± 3.6	11.6 ± 1.8	12.7 ± 9.3	93.6 ± 5.6
	Yes	25.1 ± 12.8	17.3 ± 3.4	87.9 ± 8.5	9.8 ± 1.8	15.6 ± 9.7	78.5 ± 22.5

Table 11: Full results and additional metrics of experiments on the *Delaunay-Star* graph representations using the node type and the coordinates as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	19.5 ± 9.2	18.9 ± 2.2	88.3 ± 6.0	10.6 ± 1.3	11.3 ± 6.2	87.2 ± 10.2
	Yes	17.7 ± 6.6	19.1 ± 3.2	86.4 ± 16.8	10.7 ± 1.9	9.9 ± 4.0	89.3 ± 13.1
GATv2-JK	No	49.4 ± 7.8	21.6 ± 2.9	94.1 ± 4.2	12.6 ± 1.7	34.1 ± 7.5	79.2 ± 15.8
	Yes	38.0 ± 5.6	21.4 ± 2.0	93.8 ± 1.9	12.2 ± 1.3	24.0 ± 4.6	87.3 ± 2.9
GIN	No	21.7 ± 26.6	20.5 ± 3.3	56.6 ± 46.3	11.7 ± 2.4	15.5 ± 19.7	89.7 ± 12.8
	Yes	14.8 ± 23.5	18.8 ± 1.4	52.8 ± 43.8	10.6 ± 0.9	10.7 ± 18.1	87.9 ± 17.9
GIN-JK	No	35.7 ± 25.0	20.6 ± 2.6	94.9 ± 4.5	12.0 ± 1.9	25.5 ± 19.2	82.2 ± 16.9
	Yes	45.8 ± 31.7	23.2 ± 6.2	92.4 ± 5.7	14.2 ± 4.7	36.7 ± 27.6	77.1 ± 18.4
GraphSAGE	No	45.1 ± 9.3	21.8 ± 3.7	93.2 ± 3.1	12.6 ± 2.4	30.2 ± 8.0	82.4 ± 8.7
	Yes	42.1 ± 8.6	19.9 ± 3.7	91.4 ± 3.8	11.5 ± 2.2	27.9 ± 7.5	76.9 ± 12.9
GraphSAGE-JK	No	54.6 ± 7.1	22.9 ± 4.9	93.1 ± 2.8	13.5 ± 3.1	38.8 ± 6.7	77.0 ± 6.7
	Yes	**51.4 ± 9.1**	**22.9 ± 4.4**	**93.5 ± 2.3**	**13.4 ± 2.9**	**35.9 ± 8.2**	**80.2 ± 5.6**

Table 12: Full results and additional metrics of experiments on the *Hierarchical* graph representations using the node type and the coordinates as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$26.7_{\pm 12.1}$	$20.5_{\pm 2.0}$	$95.4_{\pm 4.4}$	$11.6_{\pm 1.3}$	$16.3_{\pm 8.4}$	$91.2_{\pm 10.5}$
	Yes	$22.8_{\pm 7.4}$	$19.2_{\pm 1.7}$	$92.2_{\pm 7.3}$	$10.8_{\pm 1.0}$	$13.3_{\pm 5.0}$	$88.0_{\pm 11.8}$
GATv2-JK	No	$40.4_{\pm 3.3}$	$20.3_{\pm 3.2}$	$91.9_{\pm 3.6}$	$11.6_{\pm 2.0}$	$26.0_{\pm 2.8}$	$80.5_{\pm 9.7}$
	Yes	$39.3_{\pm 17.8}$	$21.7_{\pm 3.4}$	$95.7_{\pm 4.7}$	$12.5_{\pm 2.2}$	$26.5_{\pm 13.9}$	$86.0_{\pm 14.9}$
GIN	No	$0.4_{\pm 0.8}$	$19.2_{\pm 1.9}$	$20.0_{\pm 40.0}$	$10.6_{\pm 1.1}$	$0.2_{\pm 0.4}$	$98.5_{\pm 3.1}$
	Yes	$0.8_{\pm 1.0}$	$19.5_{\pm 1.9}$	$40.0_{\pm 49.0}$	$10.8_{\pm 1.2}$	$0.4_{\pm 0.5}$	$100.0_{\pm 0.0}$
GIN-JK	No	$19.2_{\pm 23.8}$	$20.2_{\pm 4.0}$	$80.9_{\pm 15.5}$	$11.5_{\pm 2.8}$	$13.4_{\pm 19.1}$	$88.9_{\pm 7.8}$
	Yes	$23.0_{\pm 17.1}$	$19.7_{\pm 2.5}$	$71.6_{\pm 36.0}$	$11.1_{\pm 1.5}$	$14.4_{\pm 11.5}$	$88.1_{\pm 10.1}$
GraphSAGE	No	$48.3_{\pm 16.9}$	$22.1_{\pm 4.1}$	$92.8_{\pm 1.2}$	$13.0_{\pm 2.9}$	$34.6_{\pm 15.8}$	$77.8_{\pm 10.5}$
	Yes	$\mathbf{44.9_{\pm 9.2}}$	$\mathbf{22.2_{\pm 4.1}}$	$\mathbf{95.0_{\pm 3.4}}$	$\mathbf{12.8_{\pm 2.5}}$	$\mathbf{30.0_{\pm 8.4}}$	$\mathbf{84.4_{\pm 14.3}}$
GraphSAGE-JK	No	$53.2_{\pm 9.6}$	$23.0_{\pm 3.5}$	$93.9_{\pm 2.0}$	$13.6_{\pm 2.4}$	$37.9_{\pm 9.6}$	$79.3_{\pm 8.4}$
	Yes	$57.0_{\pm 7.4}$	$23.5_{\pm 3.2}$	$94.0_{\pm 2.6}$	$13.9_{\pm 2.1}$	$41.4_{\pm 7.8}$	$78.1_{\pm 11.6}$

Table 13: Full results and additional metrics of experiments on the *Delaunay* graph representations using the node type and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$51.2_{\pm 7.6}$	$24.7_{\pm 6.1}$	$95.8_{\pm 4.0}$	$14.4_{\pm 3.8}$	$35.1_{\pm 6.5}$	$87.6_{\pm 11.4}$
	Yes	$\mathbf{47.9_{\pm 11.6}}$	$\mathbf{24.7_{\pm 5.9}}$	$\mathbf{96.4_{\pm 3.9}}$	$\mathbf{14.4_{\pm 4.0}}$	$\mathbf{32.6_{\pm 10.8}}$	$\mathbf{90.5_{\pm 9.6}}$
GATv2-JK	No	$60.1_{\pm 8.1}$	$24.1_{\pm 5.8}$	$93.7_{\pm 2.3}$	$14.5_{\pm 3.9}$	$44.7_{\pm 8.7}$	$75.3_{\pm 10.3}$
	Yes	$57.7_{\pm 8.7}$	$24.3_{\pm 5.7}$	$94.2_{\pm 2.4}$	$14.5_{\pm 3.8}$	$42.2_{\pm 8.8}$	$78.3_{\pm 9.6}$
GIN	No	$53.1_{\pm 9.1}$	$22.8_{\pm 5.4}$	$93.6_{\pm 2.7}$	$13.4_{\pm 3.4}$	$37.7_{\pm 8.8}$	$78.1_{\pm 12.3}$
	Yes	$51.7_{\pm 2.7}$	$24.2_{\pm 2.6}$	$95.8_{\pm 1.2}$	$14.1_{\pm 1.7}$	$35.5_{\pm 2.6}$	$87.2_{\pm 3.4}$
GIN-JK	No	$68.1_{\pm 4.7}$	$25.6_{\pm 5.4}$	$93.9_{\pm 1.5}$	$15.7_{\pm 3.7}$	$53.6_{\pm 5.8}$	$70.5_{\pm 10.7}$
	Yes	$67.1_{\pm 6.1}$	$25.0_{\pm 3.6}$	$93.6_{\pm 1.4}$	$15.4_{\pm 2.7}$	$52.7_{\pm 7.4}$	$69.9_{\pm 7.3}$
GraphSAGE	No	$63.5_{\pm 7.8}$	$25.1_{\pm 4.7}$	$93.9_{\pm 0.6}$	$15.2_{\pm 3.4}$	$48.5_{\pm 9.2}$	$73.9_{\pm 3.7}$
	Yes	$58.7_{\pm 10.1}$	$22.4_{\pm 6.0}$	$91.7_{\pm 2.5}$	$13.5_{\pm 4.0}$	$43.7_{\pm 10.1}$	$68.7_{\pm 6.0}$
GraphSAGE-JK	No	$64.0_{\pm 12.8}$	$27.7_{\pm 8.0}$	$94.8_{\pm 1.7}$	$17.1_{\pm 5.8}$	$49.6_{\pm 14.2}$	$78.5_{\pm 5.9}$
	Yes	$65.1_{\pm 5.6}$	$25.0_{\pm 6.3}$	$93.7_{\pm 1.8}$	$15.3_{\pm 4.4}$	$50.1_{\pm 6.3}$	$72.0_{\pm 9.1}$

Table 14: Full results and additional metrics of experiments on the *Delaunay-Star* graph representations using the node type and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	42.9 ± 8.1	20.8 ± 5.2	92.1 ± 4.2	12.0 ± 3.1	28.3 ± 6.3	79.3 ± 13.5
	Yes	51.4 ± 9.0	21.6 ± 4.6	92.2 ± 2.6	12.7 ± 3.0	36.1 ± 8.4	75.2 ± 8.2
GATv2-JK	No	61.6 ± 6.6	23.8 ± 7.2	93.0 ± 3.0	14.4 ± 4.8	46.2 ± 6.8	71.6 ± 11.7
	Yes	63.9 ± 12.3	27.6 ± 8.9	94.4 ± 3.2	17.0 ± 6.2	49.2 ± 13.1	78.3 ± 8.2
GIN	No	37.1 ± 27.0	23.4 ± 7.6	91.4 ± 3.6	14.0 ± 5.6	27.3 ± 23.9	85.9 ± 6.7
	Yes	45.8 ± 27.6	24.0 ± 5.7	95.1 ± 2.6	14.3 ± 4.1	34.7 ± 23.0	82.9 ± 10.8
GIN-JK	No	59.0 ± 21.6	26.4 ± 9.3	92.5 ± 3.9	16.4 ± 6.9	46.3 ± 20.9	75.2 ± 9.3
	Yes	**55.3 ± 19.4**	**26.5 ± 7.0**	**95.0 ± 2.0**	**16.0 ± 5.0**	**41.5 ± 18.6**	**84.2 ± 6.1**
GraphSAGE	No	58.1 ± 9.6	25.6 ± 7.8	94.6 ± 3.6	15.3 ± 5.3	42.4 ± 9.8	81.3 ± 11.0
	Yes	59.4 ± 9.6	24.8 ± 8.2	94.0 ± 4.1	14.9 ± 5.5	44.1 ± 10.6	76.6 ± 16.5
GraphSAGE-JK	No	63.4 ± 7.6	25.5 ± 6.8	94.0 ± 2.6	15.5 ± 4.6	48.2 ± 8.1	75.1 ± 9.5
	Yes	66.7 ± 6.5	27.1 ± 6.1	94.9 ± 1.6	16.6 ± 4.1	51.7 ± 7.2	76.8 ± 7.6

Table 15: Full results and additional metrics of experiments on the *Hierarchical* graph representations using the node type and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	44.4 ± 11.2	22.7 ± 6.1	93.9 ± 4.5	13.2 ± 4.0	29.7 ± 10.2	85.0 ± 9.8
	Yes	**55.5 ± 15.7**	**26.8 ± 10.0**	**94.7 ± 3.6**	**16.2 ± 6.9**	**40.7 ± 15.6**	**84.8 ± 8.4**
GATv2-JK	No	57.1 ± 7.0	23.6 ± 5.5	93.6 ± 2.2	14.0 ± 3.6	41.4 ± 7.1	76.8 ± 7.6
	Yes	58.4 ± 8.6	23.0 ± 6.7	92.6 ± 3.8	13.8 ± 4.4	43.2 ± 8.8	72.4 ± 12.4
GIN	No	5.5 ± 6.0	19.3 ± 1.3	56.0 ± 46.3	10.7 ± 0.8	2.9 ± 3.3	97.1 ± 5.7
	Yes	5.4 ± 7.1	19.7 ± 2.2	80.0 ± 40.0	10.9 ± 1.3	2.9 ± 3.9	98.5 ± 3.1
GIN-JK	No	59.3 ± 3.5	22.2 ± 5.0	92.6 ± 2.1	13.2 ± 3.2	43.7 ± 3.7	70.0 ± 10.3
	Yes	57.2 ± 13.7	23.3 ± 5.4	92.8 ± 4.6	14.0 ± 3.6	42.6 ± 14.2	73.5 ± 13.3
GraphSAGE	No	63.6 ± 6.9	25.0 ± 7.1	93.8 ± 3.2	15.1 ± 4.6	48.4 ± 7.2	73.6 ± 13.3
	Yes	58.8 ± 9.1	25.2 ± 6.5	94.4 ± 2.6	15.0 ± 4.3	43.1 ± 8.8	79.9 ± 8.0
GraphSAGE-JK	No	61.9 ± 11.7	25.1 ± 7.1	93.3 ± 2.7	15.3 ± 4.8	47.3 ± 12.2	73.7 ± 6.9
	Yes	61.0 ± 9.8	25.8 ± 7.1	94.4 ± 2.3	15.5 ± 4.8	45.7 ± 10.3	78.3 ± 7.7

Table 16: Full results and additional metrics of experiments on the *Delaunay* graph representations using the node type, the coordinates and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$24.5_{\pm 11.3}$	$19.8_{\pm 2.2}$	$89.7_{\pm 8.2}$	$11.2_{\pm 1.4}$	$14.7_{\pm 7.5}$	$88.8_{\pm 7.4}$
	Yes	$33.1_{\pm 13.4}$	$20.4_{\pm 3.4}$	$90.6_{\pm 3.4}$	$11.7_{\pm 2.3}$	$21.1_{\pm 11.1}$	$84.2_{\pm 3.6}$
GATv2-JK	No	$49.2_{\pm 15.7}$	$22.2_{\pm 6.2}$	$91.5_{\pm 4.0}$	$13.1_{\pm 4.2}$	$34.9_{\pm 14.0}$	$76.8_{\pm 7.6}$
	Yes	$46.9_{\pm 16.1}$	$22.9_{\pm 6.0}$	$92.7_{\pm 3.0}$	$13.4_{\pm 4.1}$	$32.8_{\pm 14.5}$	$81.7_{\pm 5.9}$
GIN	No	$36.6_{\pm 4.5}$	$21.5_{\pm 2.6}$	$94.3_{\pm 1.8}$	$12.2_{\pm 1.6}$	$22.8_{\pm 3.4}$	$88.7_{\pm 3.6}$
	Yes	$30.6_{\pm 10.0}$	$20.7_{\pm 3.1}$	$92.1_{\pm 5.1}$	$11.8_{\pm 2.0}$	$18.8_{\pm 7.4}$	$88.7_{\pm 3.6}$
GIN-JK	No	$\mathbf{47.0_{\pm 15.5}}$	$\mathbf{23.4_{\pm 6.4}}$	$\mathbf{93.9_{\pm 4.1}}$	$\mathbf{13.8_{\pm 4.4}}$	$\mathbf{32.9_{\pm 14.9}}$	$\mathbf{83.3_{\pm 9.8}}$
	Yes	$45.0_{\pm 11.1}$	$21.5_{\pm 4.1}$	$92.5_{\pm 1.3}$	$12.5_{\pm 2.7}$	$30.5_{\pm 10.0}$	$80.2_{\pm 5.6}$
GraphSAGE	No	$38.1_{\pm 5.6}$	$21.4_{\pm 3.6}$	$93.6_{\pm 2.6}$	$12.2_{\pm 2.3}$	$24.0_{\pm 4.3}$	$86.6_{\pm 5.1}$
	Yes	$51.6_{\pm 14.4}$	$24.3_{\pm 9.6}$	$92.9_{\pm 4.5}$	$14.6_{\pm 6.7}$	$37.0_{\pm 14.8}$	$80.2_{\pm 11.0}$
GraphSAGE-JK	No	$47.1_{\pm 15.1}$	$21.7_{\pm 6.7}$	$90.5_{\pm 4.3}$	$12.8_{\pm 4.6}$	$33.1_{\pm 14.4}$	$75.4_{\pm 6.4}$
	Yes	$47.9_{\pm 14.7}$	$22.8_{\pm 5.7}$	$92.6_{\pm 3.3}$	$13.5_{\pm 4.1}$	$33.6_{\pm 14.2}$	$80.6_{\pm 3.7}$

Table 17: Full results and additional metrics of experiments on the *Delaunay-Star* graph representations using the node type, the coordinates and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$33.3_{\pm 16.7}$	$21.2_{\pm 2.6}$	$95.2_{\pm 3.9}$	$12.1_{\pm 1.9}$	$21.8_{\pm 13.4}$	$88.1_{\pm 10.8}$
	Yes	$31.7_{\pm 6.5}$	$20.7_{\pm 3.0}$	$93.3_{\pm 1.9}$	$11.8_{\pm 1.9}$	$19.3_{\pm 4.6}$	$88.3_{\pm 5.1}$
GATv2-JK	No	$49.5_{\pm 12.2}$	$23.4_{\pm 5.8}$	$93.8_{\pm 2.5}$	$13.8_{\pm 4.0}$	$34.6_{\pm 12.0}$	$82.5_{\pm 5.6}$
	Yes	$50.1_{\pm 12.3}$	$22.9_{\pm 3.6}$	$94.3_{\pm 3.4}$	$13.4_{\pm 2.5}$	$35.2_{\pm 11.3}$	$81.6_{\pm 10.3}$
GIN	No	$18.7_{\pm 23.7}$	$20.9_{\pm 3.5}$	$57.3_{\pm 46.9}$	$11.8_{\pm 2.4}$	$12.7_{\pm 16.9}$	$93.8_{\pm 7.5}$
	Yes	$4.5_{\pm 2.5}$	$19.8_{\pm 1.8}$	$80.0_{\pm 40.0}$	$11.0_{\pm 1.1}$	$2.3_{\pm 1.3}$	$100.0_{\pm 0.0}$
GIN-JK	No	$51.6_{\pm 24.2}$	$21.8_{\pm 5.0}$	$88.1_{\pm 8.4}$	$13.2_{\pm 3.8}$	$39.7_{\pm 21.4}$	$70.1_{\pm 10.7}$
	Yes	$47.4_{\pm 20.6}$	$23.9_{\pm 4.9}$	$95.3_{\pm 3.1}$	$14.2_{\pm 3.5}$	$34.4_{\pm 18.8}$	$84.5_{\pm 10.4}$
GraphSAGE	No	$43.5_{\pm 9.5}$	$22.5_{\pm 4.1}$	$94.7_{\pm 4.1}$	$13.0_{\pm 2.5}$	$28.7_{\pm 7.8}$	$86.9_{\pm 10.9}$
	Yes	$44.0_{\pm 5.4}$	$22.8_{\pm 4.0}$	$95.2_{\pm 2.2}$	$13.1_{\pm 2.5}$	$28.7_{\pm 4.3}$	$88.2_{\pm 5.4}$
GraphSAGE-JK	No	$53.5_{\pm 9.1}$	$23.6_{\pm 5.7}$	$93.8_{\pm 2.0}$	$13.9_{\pm 3.8}$	$37.9_{\pm 8.9}$	$80.1_{\pm 5.9}$
	Yes	$\mathbf{54.7_{\pm 5.0}}$	$\mathbf{24.7_{\pm 3.7}}$	$\mathbf{95.7_{\pm 2.9}}$	$\mathbf{14.5_{\pm 2.3}}$	$\mathbf{38.4_{\pm 4.8}}$	$\mathbf{85.7_{\pm 9.9}}$

Table 18: Full results and additional metrics of experiments on the *Hierarchical* graph representations using the node type, the coordinates and the ViT-16 embedding as a node label.

GNN	Clin. Info	F1Score Low-risk	F1Score High-risk	Precision Low-risk	Precision High-risk	Recall Low-risk (TNR)	Recall High-risk (TPR)
GATv2	No	$25.9_{\pm 8.1}$	$21.0_{\pm 3.3}$	$94.7_{\pm 7.2}$	$11.8_{\pm 2.0}$	$15.3_{\pm 5.5}$	$93.6_{\pm 7.9}$
	Yes	$27.2_{\pm 12.9}$	$21.3_{\pm 2.7}$	$96.2_{\pm 5.2}$	$12.0_{\pm 1.7}$	$16.6_{\pm 9.3}$	$93.8_{\pm 7.5}$
GATv2-JK	No	$45.5_{\pm 14.3}$	$22.0_{\pm 4.4}$	$91.8_{\pm 3.6}$	$12.8_{\pm 2.8}$	$31.2_{\pm 11.7}$	$80.7_{\pm 2.9}$
	Yes	$48.6_{\pm 16.2}$	$22.5_{\pm 4.4}$	$92.3_{\pm 3.6}$	$13.2_{\pm 3.0}$	$34.4_{\pm 14.0}$	$79.4_{\pm 6.7}$
GIN	No	$1.2_{\pm 0.9}$	$19.5_{\pm 1.9}$	$60.0_{\pm 49.0}$	$10.8_{\pm 1.1}$	$0.6_{\pm 0.5}$	$100.0_{\pm 0.0}$
	Yes	$0.4_{\pm 0.8}$	$19.5_{\pm 1.8}$	$20.0_{\pm 40.0}$	$10.8_{\pm 1.1}$	$0.2_{\pm 0.4}$	$100.0_{\pm 0.0}$
GIN-JK	No	$34.1_{\pm 22.2}$	$21.4_{\pm 4.1}$	$93.8_{\pm 4.0}$	$12.4_{\pm 2.8}$	$23.4_{\pm 17.9}$	$85.5_{\pm 10.5}$
	Yes	$43.2_{\pm 21.1}$	$22.3_{\pm 4.8}$	$92.2_{\pm 3.4}$	$13.2_{\pm 3.5}$	$30.9_{\pm 19.2}$	$81.3_{\pm 9.4}$
GraphSAGE	No	$38.0_{\pm 15.2}$	$21.9_{\pm 5.0}$	$91.3_{\pm 7.2}$	$12.6_{\pm 3.2}$	$24.8_{\pm 11.1}$	$86.6_{\pm 5.1}$
	Yes	$48.3_{\pm 17.2}$	$23.3_{\pm 3.7}$	$95.7_{\pm 2.7}$	$13.6_{\pm 2.6}$	$34.2_{\pm 14.3}$	$84.0_{\pm 10.9}$
GraphSAGE-JK	No	$57.6_{\pm 16.7}$	$26.3_{\pm 7.1}$	$94.2_{\pm 5.0}$	$15.9_{\pm 4.8}$	$43.2_{\pm 15.9}$	$81.9_{\pm 11.4}$
	Yes	$\mathbf{58.3}_{\pm \mathbf{8.3}}$	$\mathbf{25.6}_{\pm \mathbf{3.3}}$	$\mathbf{95.8}_{\pm \mathbf{1.5}}$	$\mathbf{15.2}_{\pm \mathbf{2.3}}$	$\mathbf{42.5}_{\pm \mathbf{8.9}}$	$\mathbf{84.0}_{\pm \mathbf{8.2}}$