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Morphological Descriptors as Tool for Characterization of Nuclear Pleomorphism in Breast Cancer

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ABSTRACT

In recent years, the advancement in molecular pathology and genetic analysis of cancerous tissues has significantly remarked an increase in objective and measurable data. However, the traditional approach of morphological analysis in pathology diagnosis remains subjective in comparison, despite the introduction of digital pathology aiding computer-aided diagnosis. Certain pathological grading features, such as nuclear pleomorphism in breast cancer, still depend on a pathologist's expertise and are largely non-quantitative. This study aimed to investigate morphological descriptors as key elements to characterize the qualitative description of nuclear pleomorphism in breast cancer, in line with the Nottingham Histopathology Grading (NHG) system. Four morphological descriptors were extracted from segmented nuclear cells, including area, minimum ferret diameter, minor axis length and perimeter and used to assign scores of 1 to 3 to characterize pleomorphic nuclei. The proposed method was validated using the support vector machine (SVM), achieving promising results with 95.0% and 92.0% in accuracy (*Acc*) and F1 score (*F1*), respectively. This study serves as a pilot investigation for the quantitative measurement of nuclear pleomorphism in breast cancer.

1. Introduction

With the aid of artificial intelligence and concerted improvement in engineering and technology, over the past decades, there has been a successful transition to digital pathology, similar to what

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occurred in radiology in the past [1,2]. This transition has been made possible by advancements in glass slide scanner (also known as whole slide imaging scanner), which are now faster and capable of better image acquisition. Numerous successful transformations of pathology workflows with digital adaptation have been documented (e.g., tubule detection [3,4], tumour region segmentation [5,6], mitotic cells detection [7-9], nuclear pleomorphism [10,11]), each with their own specific challenges and workflows. The implementation of digital pathology offers recognized advantages, such as reduced costs, quicker workflows leading to faster results and easier coordination of multidisciplinary tumour slides.

In breast cancer, to guide the grading process, histopathologists across the globe utilize a standardized grading system, namely NHG system to evaluate breast cancer [12,13]. This grading system comprises of three factors:

i. Degree of nuclear pleomorphism
ii. Extent of tubule formation
iii. Mitotic count

The scoring criteria for tubule formation and mitotic count are determined by quantitative measurements, whereas the scoring for nuclear pleomorphism is based on a qualitative analysis of the tumour's nuclear morphological properties (e.g., size, shape and appearance). This analysis is conducted microscopically, on a scale ranging from 1 to 3, which reflects an increasing deviation in appearance compared to normal epithelium [14]. Table 1 shows the full qualitative definition of nuclear pleomorphism as stipulated by the NHG system.

Table 1
Qualitative definition for nuclear pleomorphism [14]

Feature	Remarks	Scores
Nuclear pleomorphism	Small nuclei with little increase in size respect to normal breast epithelial cells, regular outlines, uniform nuclear chromatin and low degree of variation in size	1
	Increase in cell size with open vesicular nuclei, visible nucleoli and moderate variability in term of shape and size	2
	Vesicular nuclei, often with prominent nucleoli, present significant variation in shape and size, occasionally with very large and eccentric forms	3

In contrast to tubule formation and mitotic count, as aforementioned, nuclear pleomorphism is not defined quantitatively. Consequently, across the three factors, the scoring of nuclear pleomorphism is the least reproducible, which limits its applicability in digital pathology. Due to the qualitative nature of nuclear pleomorphism and the challenges of creating a reference standard, very limited works are found in this field. Thereof, this motivates the investigation of nuclear pleomorphism from the morphological perspective and the use of these features as a tool to characterize the object of interest. This paper attempts to translate and quantify nuclear pleomorphism across different scores in accordance with the definition provided by the NHG system.

2. Related Works

Mercan *et al.,* [11] proposed a two-stages methodology for detection of nuclear pleomorphism. In the first stage, an epithelial cell detection network was proposed to identify tumour and normal cells. This involved training a RetinaNet detection model with 256 × 256-pixel image patches from Hematoxylin and Eosin (H&E)-stained breast cancer whole-slide images. The model predicted fixed-

size bounding boxes for epithelial cells, labelling each as normal or tumour. In the second stage, a deep regression network was proposed to score nuclear pleomorphism. The patch sampling strategy for training the regression network involved identifying areas with high nuclear composition within the selected regions of interests using the epithelial cell RetinaNet model. Thereof, the epithelial cell detection network was used to locate invasive tumour regions, which were then scored for nuclear pleomorphism using the deep regression network.

Das *et al.,* [10] proposed a batch mode active learning on the Riemannian manifold to score nuclear pleomorphism. Their active learning approach involves selecting samples for labelling, which is formulated as a constrained submodular optimization task that is solved using a greedy algorithm. To estimate the class labels for histopathological breast cancer images, they employed the TRAnsductive multi-label learning (TRAM) algorithm, which eliminates the need for manual annotation. They conducted sub modularity-based dynamic batch mode active learning on three kernelized Riemannian metric variants (i.e., Stein divergence, Jeffrey divergence and log-Euclidean metric) and compared the results with state-of-the-art algorithms for scoring breast cancer nuclear atypia. The evaluation metrics indicated that all of the algorithm variants demonstrated superior performance when using information from the unlabelled samples, confirming the effectiveness of the Riemannian kernelized distance metric in identifying the most diverse and non-redundant samples for active learning.

Saito *et al.,* [15] proposed a method for measuring pleomorphism and heterogeneity using the cell-level co-occurrence matrix. The proposed method relies on the Gray-level co-occurrence matrix (GLCM), which captures the relationships between neighbouring pixel intensity levels in an image, followed by the application of analysis functions like Haralick features [16]. The ideology is that, in histopathology images, nuclear can be measured and each has distinct features such as size, roundness, contour length and intra-nuclear texture data. Three types of neighbourhoods were defined for each nuclear, create the co-occurrence matrix and apply Haralick feature functions to determine pleomorphism and heterogeneity quantitatively. The proposed method was termed Cell Feature Level Co-occurrence Matrix (CFLCM), where one pixel corresponds to one nuclear feature.

Wei *et al.,* [17] proposed the BiCNN model, a deep convolutional neural network for classifying breast cancer in pathological images. The BiCNN model is structured with an input layer, convolution layer, pooling layer and a SoftMax classifier with loss. To avoid over-fitting, the raw BreakHis database is augmented 14 times by applying rotation, scaling and mirroring. The authors used two training strategies: training the BiCNN model from scratch and using transfer learning. In the transfer learning approach, the model is first unsupervised pre-trained on ImageNet and then fine-tuned on the BreakHis dataset using the BiCNN architecture.

Gandomkar *et al.,* [18] proposed a Deep Residual Network (MUDeRN) to classify breast histopathological images into multiple categories. The malignancy level of the cancer is first determined using a Residual Network (ResNet), followed by classification into specific subtypes and ultimately, the outputs of the ResNets are combined using a meta-decision tree (MDT).

Alom *et al.,* [19] developed an Inception Recurrent Residual CNN (IRRCNN) by combining the strengths of the Residual Network (ResNet), Inception Network (Inception-v4) and Recurrent CNN (RCNN) to improve the performance of breast cancer classification compared to the individual networks.

Wan *et al.,* [20] proposed a method to extract features from breast tumour histopathological images via multi-stages: pixel-, object- and semantic-level. At the pixel-level, the features extracted include textural features such as Kirsch filters, first-order features, Gabor filters and Haralick features, as well as HoG and LBP. Object-based features were also extracted, which represented the spatial interdependency of nuclei using Voronoi Diagram (VD), Minimum Spanning Tree (MST) and

Delaunay Triangulation (DT). The semantic-level features captured heterogeneity of cancer biology using Convolutional Neural Networks (CNN)-derived descriptors. The extracted features were reduced in dimension using graph embedding and then fed into a cascaded ensemble of SVM-based classifiers.

In this work, the goal is to investigate the roles of morphological descriptors in characterizing the nuclear pleomorphism into different scores in accordance with the definition (Table 1) provided by the NHG system. The findings of this work serve as the pilot study/ preliminary investigation, acting as the building block for the quantitative measurement of nuclear pleomorphism in breast cancer.

3. Methodology

The methodology consists of four primary stages:

i. Image pre-processing
ii. Nuclear segmentation
iii. Derivation of morphological features
iv. Classification.

In the first stage, the H-channel was extracted from the input RGB histopathology images and then converted to Hue-channel images. A global thresholding method was applied to the Hue-channel images, with experts intervening to ensure a satisfactory segmentation output. Morphological features that reflect the qualitative descriptions of nuclear pleomorphism, as defined by the NHG system, were derived and identified in this stage. Finally, a Support Vector Machine (SVM) was used to validate the proposed method. Figure 1 displays the block diagram of the overall methodology.

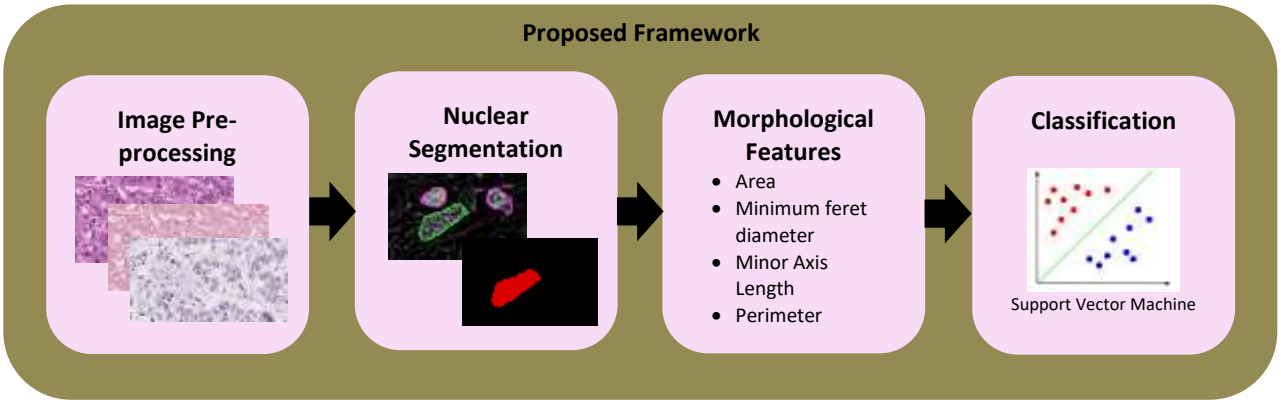

Fig. 1. Block diagram of the overall methodology

3.1 Image Pre-Processing

In histopathology images, particularly in H&E-stained sections, a common challenge is the presence of colour inconsistencies or variations in appearance. This problem arises from various factors such as the heterogeneity of the disease, variations in staining protocol, differences in manufacturers, timing of stain absorption, reagent concentration and thickness of biopsy sections. To address this issue, a colour unmixing method [21] was developed to separate H&E-stained images into H-channel and E-channel. Since H-dye predominantly stains the nuclear cells, the H-channel was used for subsequent analysis. The method involved calculating the optical vectors of the RGB input

image, converting the RGB input images to optical density and removing pixels with an optical density value of 0.20 as they are considered background. Singular value decomposition was then calculated on the optical density tuples and the two largest singular values were determined. These optical density-transformed pixels were projected onto this plane and normalized to unit length and the angle with respect to the first singular value decomposition direction was calculated for each point. This mapping of directions in the plane to a scalar provided a detailed approach to the method [21]. In this work, brief modification done on the threshold value (i.e., threshold value of 0.20) in removing the background pixels.

3.2 Nuclear Cells Segmentation

A previous study by Jian *et al.,* [22] discovered that the Hue-channel can better highlight the nuclear cells in RGB histopathology images. Thus, prior to nuclear segmentation, the H-channel image was first obtained as part of the image pre-processing stage to assure minimal artifacts in the subsequent segmentation pipeline. Next, CellProfiler [23] was implemented to threshold the nuclear cells from the H-channel image background. Here, a global thresholding method [24] was applied. Cell Profiler is an open-source software, developed using Python programming language, intended to perform automated detection, analysis and measurement of a wide range of biological objects in images. The focus of this study was to investigate the morphological features that define nuclear pleomorphism in accordance with the NHG system. Thus, solving known challenges in nuclear segmentation such as overlapping and clumped nuclear cells were not the main focus of this study. Nonetheless, to assure the morphological features were extracted from the correct object of interest. Experts' intervention was involved here to select nuclear cells that were deemed as good segmentation.

3.3 Derivation of Morphological Descriptors

According to the definition of nuclear pleomorphism provided by the NHG system (Table 1), the key element to characterize nuclear pleomorphism into scores 1 to 3 was found to focus on the morphological features (e.g., area and shape) of the nuclear cells. Thus, an empirical analysis was conducted on the nuclear cells, constituted of 50 independent cells aiming to select morphological descriptors that could significantly reflect the key element aforementioned. The selected features were area, minimum ferret diameter, minor axis length and perimeter. The data pertaining to the area was extracted via the pixel count on the segmented nuclear cells; the minimum ferret diameter was the minimum diameter measured in pixels between two boundaries of a segmented nuclear cell; the minor axis length was measured in pixel across the minimum line segment between the boundaries of nuclear cells after ellipse fitting, whereas; perimeter was the measure of the total length of nuclear cell's boundary.

3.4 Classification

To validate the proposed method, an SVM was utilized. SVM [25] is a well-established technique widely used in numerous studies and has been demonstrated to be superior in addressing statistical classification problems, including the classification of nuclear cells. SVM was selected to classify the nuclear pleomorphism into different scores/ classes, with the Radial-based function (RBF) chosen as the core function. The RBF kernel enables the SVM to gain flexibility in selecting the form of a threshold that separates the classes. The selection of SVM with RBF kernel is strongly supported by

recent literature [25-28]. In this study, the inputs of SVM were the four morphological descriptors (Section 3.3) extracted from Section 3.2.

3.5 Dataset

Seven breast cancer histopathology slides were acquired from the Pathology Department at Hospital Tuanku Fauziah in Kangar, Perlis, Malaysia. The slides were subjected to a standard H&E staining procedure and then scanned using an Aperio CS2 Whole Slide Imaging scanner to generate digital images. Five images were captured from each slide, with each image corresponding to a different dominant area on the slide. These images were saved in TIFF file format and are 8-bit RGB colour images with dimensions of 614x1264 pixels, with a pixel size of 0.2521 mm per pixel. In this work, the focus lies within the nuclear cell level such that a predetermined number of nuclear cells were used in different analyses for research purposes. Table 2 summarises the dataset used in this work.

Table 2
Dataset used in this work

Analyses		Number of nuclear cells		
		Score 1	Score 2	Score 3
Nuclear segmentation		20	20	20
Morphological descriptors analysis		20	20	20
Validation	Training	10	10	10
	Testing	10	10	10

3.6 Evaluation Metrics

Several evaluation metrics were utilized to examine the outcomes of the study, including a measurement depicted in the confusion matrix. The confusion matrix is a commonly used error matrix term to visualize the classification's performance. This investigation computed Accuracy (*Acc*) and F1 score (*F1*) by utilizing true positive (*TP*), false positive (*FP*), true negative (*TN*) and false negative (*FN*). *TP* represents cases in which the method predicts "yes," and they are genuinely "yes," whereas *FP* represents cases in which the method predicts "yes," but they are actually "no." *TN* represents instances in which the method predicts "no," and they are genuinely "no," while *FN* represents instances in which the method predicts "no," but they are actually "yes." The equations for *Acc* and *F1* are provided in Eq. (1) and Eq. (2), respectively.

$$Acc = \frac{TP+TN}{TP+FP+TN+FN} \quad (1)$$

$$F1 = \frac{2*Recall*Precision}{Recall+Precision} \quad (2)$$

4. Results and Discussions

To gain a better understanding of the proposed method, as mentioned in Section 3.5, breast histopathology images were collected and utilized for validation purposes. This section provides a detailed description of the experimental results and a discussion of the study output. The core of the experimental results and discussions lie within the segmentation of nuclear cells, analysis of morphological descriptors and validation of the proposed method.

4.1 Results for Nuclear Segmentation

Prior to the study, a comparison was done using common software such as MATLAB and Ilastick [29] pertaining to nuclear segmentation. Analysis was done on the segmentation of 20 independent nuclear cells using a modified K-Mean method [30] (performed using MATLAB), Ilastick [29] and CellProfiler [23]. The analysis found that the CellProfiler performed better than the other software with promising segmentation capability and equipped with algorithms to segregate clumped and overlapping cells. The justification for superiority in cell segmentation was done by expert intervention via manual inspection of the segmentation outputs from each software. Also, the finding herein was found aligned with an established work in selecting the software for nuclear cell segmentation [15]. Figure 2 shows the samples of segmentation output for nuclear cells in scores 1 to 3. Figure 2(a)- 2(f) shows the samples of segmentation output, such that the green colour shows the cell's boundaries, where Figure 2(g)- 2(l) shows the samples of filled region for the respective cells. From the figure, it is evident that the CellProfiler was capable to segment the nuclear cells accurately which then serve as the building block for the subsequent steps.

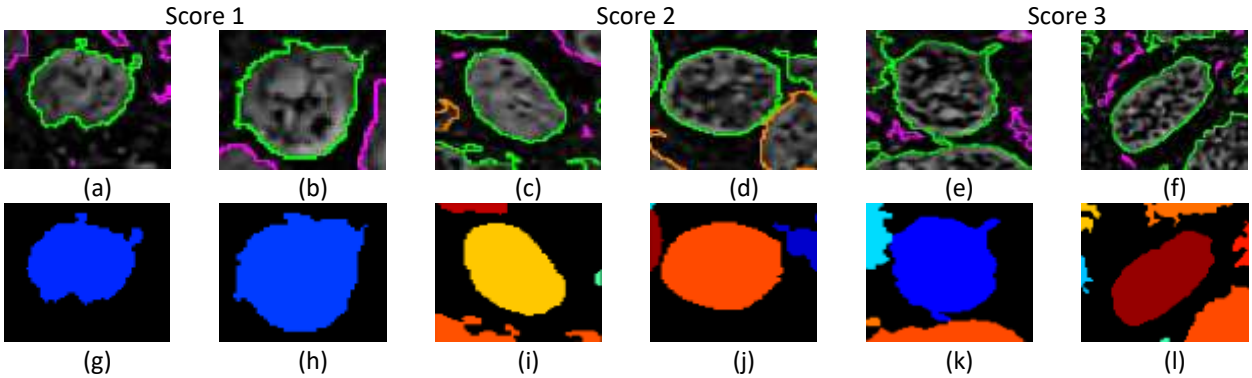

Fig. 2. Samples of segmentation output for nuclear cells in scores 1 to 3. (a)-(f): samples of segmentation output; (g)-(l): samples of the respective filled region

4.2 Result for Morphological Descriptors Selection

As aforementioned, the selection of morphological descriptors was in accordance with the definition of nuclear pleomorphism provided by the NHG system. Here, four morphological descriptors, namely area, minimum ferret diameter, minor axis length and perimeter were selected. Figure 3(a) - 3(d) shows the box plots for the mentioned descriptors, respectively, tabulating data across scores 1 to 3, such that 20 nuclear cells (in each score) were extracted and used in the analysis. Based on Figure 3(a) - 3(d), the box plots for scores 1 and 2 are well segregated (or with minimal overlapping values) reflecting properties as a discriminative feature. Referring to the same figure, though values of score 3 (lower boundaries) are found to overlap with score 2 (upper boundaries), both the scores have distinct median values showing the concentration of data across scores 2 and 3 are in distinct regions. For example, in Figure 3(a) - 3(d), the median value of scores 2 and 3 are 1298.6 and 1786.0; 35.2 and 39.5; 34.4 and 38.6; 175.7 and 223.8, respectively.

4.3 Validation

To validate the applicability of the selected morphological descriptors, 10 and 10 segmented nuclear cells were respectively used as the training data and testing data. The validation process was performed using SVM with RBF kernel, a commonly used classifier in multiclass classification [31-33].

The experiment was repeated five times and the mean value of *Acc* and *F1* were extracted. Based on the classification outputs, the obtained *Acc* and *F1* are 95.0% and 92.0%, respectively. The promising result in *Recall* (i.e., 100.0%) shows the superior sensitivity of the selected morphological descriptors in reflecting the nuclear pleomorphism across different scores.

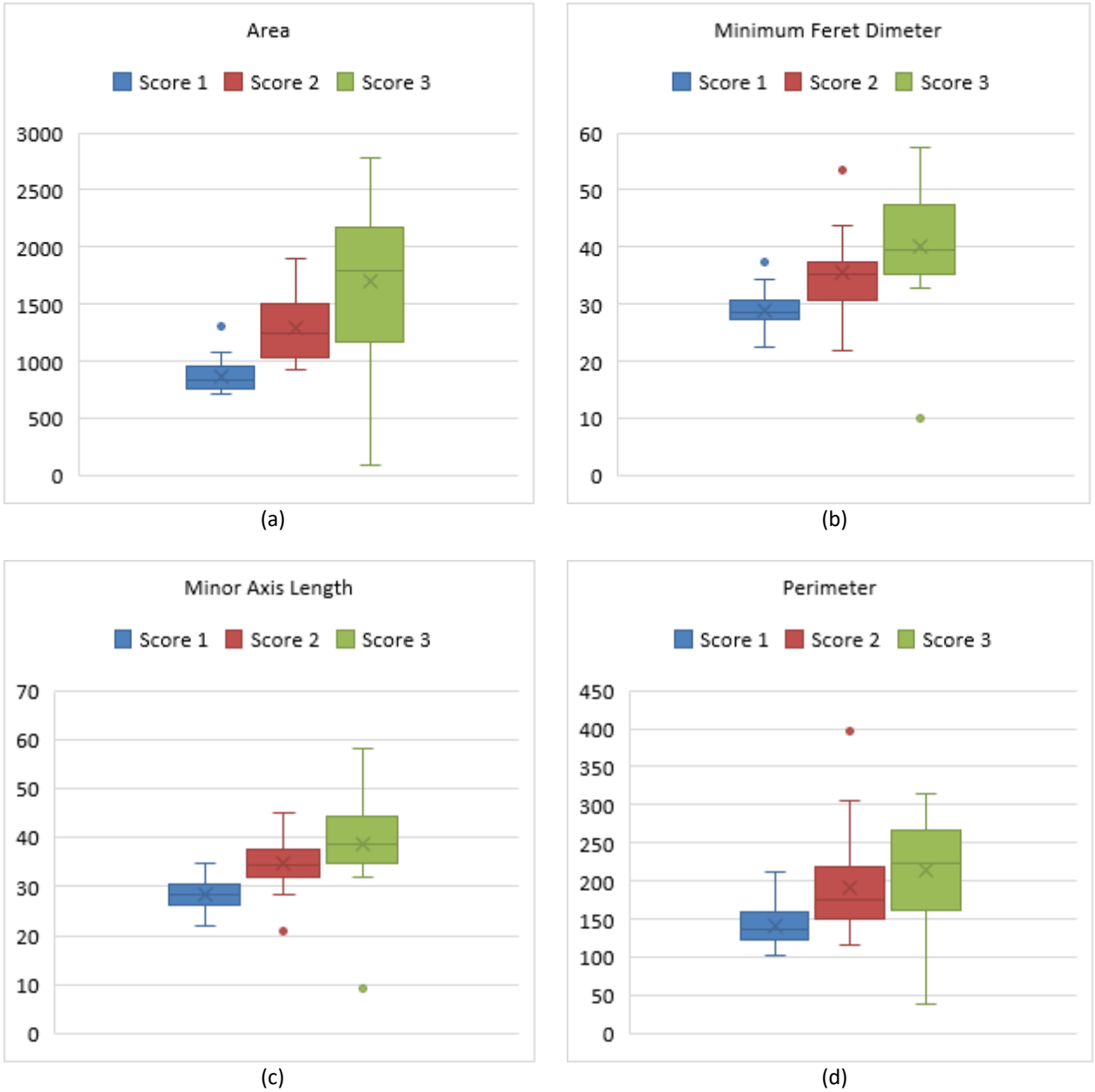

Fig. 3. Box plots for four selected features reflecting the morphological properties of nuclear cells in scores 1 to 3. (a) Area (b) Minimum ferret diameter (c) Minor axis length (d) Perimeter

5. Conclusion

This work aimed to investigate morphological descriptors as key elements to characterize the qualitative description of nuclear pleomorphism in breast cancer into different scores in accordance with the NHG system. Here, four morphological descriptors, namely area, minimum ferret diameter, minor axis length and perimeter, were extracted from the segmented nuclear cells. These morphological descriptors were then used to characterize the segmented nuclear cells into scores

of 1 to 3 based on the pleomorphic features. In the segmentation stage, CellProfiler was used as the segmentation medium whereas in the validation process, the SVM with RBF kernel was implemented. The classification output shows encouraging results such that the obtained *Acc* and *F1* are 95.0% and 92.0%, respectively with a high percentage in *Recall* (i.e., 100.0%). It is important to note that this study is meant to serve as a pilot investigation/ preliminary study for the quantification of nuclear pleomorphism in breast cancer. In future work, a comprehensive dataset would be used to further validate the applicability of the morphological descriptors as a medium for quantification towards the goal of digital pathology. Also, mathematical modelling would be performed to effectively combine the selected morphological descriptors into one unique equation reflecting the nuclear pleomorphism across different scores. The study hypothesizes that the mathematical equation can be used to measure nuclear pleomorphism in breast cancer in accordance with the NHG system.

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