World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:17, No:01, 2023

Artificial Intelligence Based Method in Identifying Tumour Infiltrating Lymphocytes of Triple Negative Breast Cancer

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Abstract : Tumor microenvironment (TME) in breast cancer is mainly composed of cancer cells, immune cells, and stromal cells. The interaction between cancer cells and their microenvironment plays an important role in tumor development, progression, and treatment response. The TME in breast cancer includes tumor-infiltrating lymphocytes (TILs) that are implicated in killing tumor cells. TILs can be found in tumor stroma (sTILs) and within the tumor (iTILs). TILs in triple negative breast cancer (TNBC) have been demonstrated to have prognostic and potentially predictive value. The international Immune-Oncology Biomarker Working Group (TIL-WG) had developed a guideline focus on the assessment of sTILs using hematoxylin and eosin (H&E)-stained slides. According to the guideline, the pathologists use “eye balling” method on the H&E stained- slide for sTILs assessment. This method has low precision, poor interobserver reproducibility, and is time-consuming for a comprehensive evaluation, besides only counted sTILs in their assessment. The TIL-WG has therefore recommended that any algorithm for computational assessment of TILs utilizing the guidelines provided to overcome the limitations of manual assessment, thus providing highly accurate and reliable TILs detection and classification for reproducible and quantitative measurement. This study is carried out to develop a TNBC digital whole slide image (WSI) dataset from H&E-stained slides and IHC (CD4+ and CD8+) stained slides. TNBC cases were retrieved from the database of the Department of Pathology, Hospital Canselor Tuanku Muhriz (HCTM). TNBC cases diagnosed between the year 2010 and 2021 with no history of other cancer and available block tissue were included in the study (n=58). Tissue blocks were sectioned approximately 4 µm for H&E and IHC stain. The H&E staining was performed according to a well-established protocol. Indirect IHC stain was also performed on the tissue sections using protocol from Diagnostic BioSystems PolyVue™ Plus Kit, USA. The slides were stained with rabbit monoclonal, CD8 antibody (SP16) and Rabbit monoclonal, CD4 antibody (EP204). The selected and quality-checked slides were then scanned using a high-resolution whole slide scanner (Pannoramic DESK II DW- slide scanner) to digitalize the tissue image with a pixel resolution of 20x magnification. A manual TILs (sTILs and iTILs) assessment was then carried out by the appointed pathologist (2 pathologists) for manual TILs scoring from the digital WSIs following the guideline developed by TIL-WG 2014, and the result displayed as the percentage of sTILs and iTILs per mm^2 stromal and tumour area on the tissue. Following this, we aimed to develop an automated digital image scoring framework that incorporates key elements of manual guidelines (including both sTILs and iTILs) using manually annotated data for robust and objective quantification of TILs in TNBC. From the study, we have developed a digital dataset of TNBC H&E and IHC (CD4+ and CD8+) stained slides. We hope that an automated based scoring method can provide quantitative and interpretable TILs scoring, which correlates with the manual pathologist-derived sTILs and iTILs scoring and thus has potential prognostic implications.

Keywords : automated quantification, digital pathology, triple negative breast cancer, tumour infiltrating lymphocytes
Conference Title : ICDPFD 2023 : International Conference on Digital Pathology and Future Directions
Conference Location : Singapore, Singapore
Conference Dates : January 09-10, 2023