TPM Vol. 32, No. 4, 2025
ISSN: 1972-6325
https://www.tpmap.org/

STEM CELL-DERIVED EXOSOMES FOR SPINAL CORD INJURY REPAIR: AI-DRIVEN ANALYSIS FOR OPTIMIZING THERAPEUTIC EFFICACY

SOOBIA SAEED[1]., MOHSIN QADEER[2], NZ JHANJI[1], SAYAN KUMAR RAY[1], HUMERA ASHRAF[1], HUSHAM M. AHMED[3], ABDUL AZEEM KHAN[4], NAUSHAD ABID[5]

[1] SCHOOL OF COMPUTING, TAYLOR'S UNIVERSITY, MALAYSIA
[2] DEPARTMENT OF NEUROSURGERY, JINNAH MEDICAL AND DENTAL COLLEGE (JMDC)
[3]COLLEGE OF ENGINEERING, UNIVERSITY OF TECHNOLOGY BAHRAIN, KINGDOM OF BAHRAIN
[4]FACULTY OF ISLAMIC TECHNOLOGY, NEGARA BRUNEI DARUSSALAM
[5]COLLEGE OF MEDICINE, KING FAISAL UNIVERSITY, AL-AHSA, SAUDI ARABIA

Abstract This research investigates the application of an advanced AI-driven image analysis solution to assess the therapeutic efficacy of stem cell-derived exosomes in spinal cord injury therapy. This study focuses on analyzing exosomes derived from stem cells, especially from MSCs, due to their regenerative capabilities and immunomodulatory and differentiating properties capable of more amply healing the injured spinal cords within the context of SCI protocols. Traditional techniques of determining the viability of stem cells and readiness for therapy employ varied degrees of invasion and lengthy processes with more or less precision; thus, we here describe a novel image analysis technique for predicting the viability and therapeutic potential of MSC-derived exosomes in SCI models. Phase-contrast microscopy allows our algorithm to analyze exosome preparations in the early proliferation phases associated with SCI-specific therapeutic protocols. With the type of image-analyzing algorithms we describe (the basis of our development is edge detection in which the overlapping of structures among clusters), exosomes are recognized based on their structural features and functional characteristics using an algorithm involving thresholding with morphological operations. We use H-minima transforms and Hidden Markov Models (HMM) for resolving overlapping structures in clusters, relying on marker-controlled watershed approaches to further boost the segmentation result for single exosomes. Machine learning algorithms classify exosome phenotypes based on morphometric and textural features extracted from segmentation. This model driven on a set of 17890 exosomes for month 3, 110,670 for month 6, and 241,010 for month 12 acquired from SCI cultures (Months 3,6, and 12=123,190) for proposed datasets-1 images, 70,293 , and 49,350 exosome acquired from SCI cultures for proposed datasets-3 images developed and with high detection of sensitivity (99%) and specificity (98%) and almost perfect precision (99%) in both detection and segmentation of exosome structures. It yields an AUC of 0.99 (CI9s=0.976-0.988) during the classification of phenotypes of exosomes developing in the early and mid-logarithmic growth stages. Such is a testament to the accuracy and reliability intrinsic to this approach of noninvasively assessing this cell therapy. Thus offering a robust method for the mechanical and informational validation and optimization

Keywords Regenerative, MSC-Derived, Exosomes, SCI, Models, Hidden Markov Models, Machine Learning, Algorithms

I. INTRODUCTION

A stem cell is an undifferentiated cell found in all multicellular organisms with the ability to self-renew and to differentiate into multiple types. Regenerative medicine and tissue engineering have been linked to stem cells in an effort to enhance patients' quality of life and overall health, particularly for those suffering from life-threatening illnesses. Three types of stem cells are known: (1) induced pluripotent stem cells (iPSC); (2) adult stem cells (ASC); and (3) embryonic stem cells (ESC) produced from early-stage embryos. These cells' capacity for regeneration stems from their ability to travel to the damaged area of the body, divide, and create daughter cells

that, given the right circumstances, can differentiate into multiple cell lineages to heal the damaged tissue [1-3]. The culture environment and secretomes secreted can affect stem cells' ability to promote regeneration [4-5]. Numerous clinical diseases have been examined and even treated with stem cell therapy. However, there are risks that require additional assessment (before clinical application). These concerns include immunological rejection, misdirected or misdifferentiated cells, and the main concern, genomic instability or tumor formation [6], [7]. Although the use of stem cells in medicine is growing, the body doesn't have many of them overall. According to standard cell therapy protocols, each treatment needs hundreds of millions of MSC, which means that the cells must expand in vitro for roughly ten weeks prior to implantation [8-12]. This means that extended stem cell growth or modification may lead to cellular senescence or even carcinogenesis in vitro, making the cells unsuitable for therapeutic application. The debilitating disorder known as spinal cord injury (SCI) frequently leaves victims with lifelong neurological abnormalities that severely lower their quality of life as shown in Figure 1. With few alternatives for real regeneration and repair, traditional treatments have mostly been supportive. Since Hippocrates, paraplegia resulting from spinal cord injury (SCI) has alarmed medical professionals and changed the lives of those affected. The primary goals of treatment have been to preserve any intact neural tissue and to lessen the impact of subsequent injuries, such as oedema, bleeding, necrosis, and demyelination. [13-18].

Microglia, fibroblasts, and reactive astrocytes in the spinal cord cause gliosis and scar formation, which restricts neuronal regeneration [19-22] Over the past three decades, stem cell-based therapies have been created and show promise for treating spinal cord injury. Since bone marrow-derived hematopoietic cells from Donald Orlic's lab at the NIH were able to regenerate an infarcted myocardium, stem cells have been frequently used for various organ systems. The three consistent impacts of the many stem cell lines exist despite their biological differences. They are able to replace the damaged necrotic cells through their potential for multi-differentiation, which is their primary strength. Secondly, they can also secrete and produce anti-inflammatory factors to control the inflammatory response in the damaged microenvironment. Finally, they produce a variety of cytokines, growth factors, and cell adhesion factors to aid in tissue regeneration [23-27]. These significant potentials occurred in trial settings and caused the assumption that the neuroregenerative impacts of undifferentiated cells could address treatments that would accomplish promising results in SCI patients. In any case, the uplifting results from labs have so far not converted into genuine outcomes in these patients. Not with standing, late headways in man-made brainpower (man-made intelligence) and foundational cell treatment offer promising roads for additional compelling mediations as mentioned in Figure 1 [28].

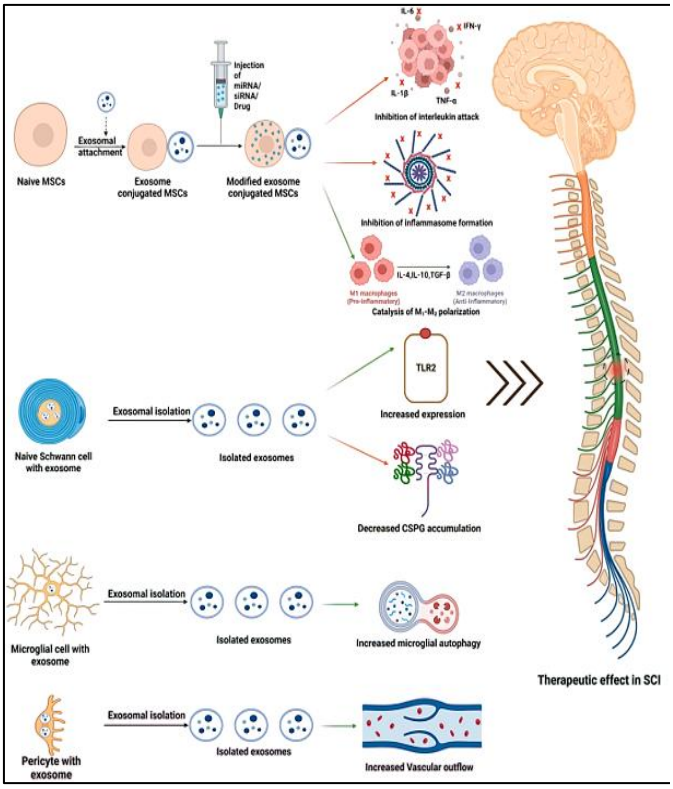

Fig.1. Mechanisms Involving Exosomes from Different Types of Cells in the Treatment of Spinal Cord Injury (SCI) [28].

This Figure 1 depicts the different ways in which exosomes from various cell types exert their therapeutic impact in spinal cord injury (SCI). It focuses on the key aspects of neuroprotection, inflammation suppression, promotion of tissue healing, and modulation of immune response underscoring the importance of exosomes to the treatment of SCI pathology. For exosomes derived from mesenchymal stem cells (MSCs), genetic material is introduced into naïve MSCs, enhancing exosomal attachment for improved bioavailability. These exosomes suppress

interleukin assaults, inhibit the activation of the inflammatory complex, and encourage the transition of microglia from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. However, achieving optimal outcomes using exosome-based treatments is rooted in difficulties related to the complexity of exosomal content and varied responses of patients. The offering of artificial intelligence (AI) is powerful due to its ability to predict the outcomes of therapies and generate understanding. Using AI derivatives, patterns and biomarkers can then be used to finesse exosome composition and therapies, so that maximal repair and functional recovery can be achieved in SCI patients. This study evaluates the provision of AI in analyzing the stem cell-derived exosome for severing spinal cord injury in terms of optimizing efficacy, personalizing therapies, and serving the recovery methodologies from SCI [6-7].

In light of the aforementioned observations, exosomes derived from stem cells are extremely promising for the advancement of regenerative medicine and tissue engineering, especially for conditions such as spinal cord injury wherein treatment options are currently limited. Exosomes hold great promises for cellular therapies as these can migrate and reach damaged areas of damaged tissues, guiding healing by releasing cytokines and growth factors among other mechanisms. However, major challenges still persist for the in-practice translational front concerning immunogenicity, genomic instability, and risk of tumor formation during a prolonged period of in vitro expansion. Artificial intelligence-supported stem cell research does hold the possibility of improving the current therapies, although real-life applications seldom exhibit success on par with preclinical studies. Continuing experimental approaches and clinical trials are vital to ensure that stem cells may deliver their full therapeutic benefit and renew the hope of SCI patients and others in need of innovations in regenerative therapies.

II. LITERATURE REVIEW

Cell communication is vital for many processes occurring physiologically and pathologically. Besides the soluble factors secreted, there exists a membrane-shed extracellular vesicle (EV) communication, collectively referenced to as the secretome. EVs are membrane-bound structures that shuttle bioactive molecules between cells through nanovesicles of a size similar to a spherical nanoparticle, i.e. exosomes (30-150 nm). They contain proteins such as Hsp70, Hsp90, GTPases, annexins, and tetraspanins including CD9, CD63, CD81, and CD82. Exosomes thus efficiently transport both genetic material and bioactive substances from donor to recipient cells. Thus, exosomes have potential applications such as delivery vehicles in regenerative medicine and injury repair, including spinal cord injury [8-9].

Mesenchymal stem cells (MSCs) have been adult stem cells that possess multiple differentiation capabilities and immunomodulatory properties. In recent decades, MSC's have gained attention in regenerative medicine owing largely to their ability to home to damaged tissues coupled with secretion of paracrine factors which inhibit inflammation and modulate immune response. The official WHO recommendation highlights the importance of this issue, prompting increased global engagement in promoting stem-cell research where adult stem cells can be utilized as sources for postnatal regenerative therapies. The issues concerning poor cell survival and genetic alterations which have been common are also attached as challenges faced by cell-based therapies [10-14]. Such challenges have piqued interest in MSC exosome as non-immunogenic, sterilizable, easily storable delivery vehicles. These suggest the candidates for applicability in the off-the-shelf therapy. Recent studies have suggested that MSC-derived exosomes recapitulate many biological functions of MSCs, including induction of angiogenesis, tissue repair, and recognition as viable candidates for regenerative therapies. In the present state of research, some of the sources of MSCs influencing the composition and therapeutic potential are also known. For instance, MSC-derived exosomes from human endometrial (hEnMSCs) demonstrated great prospects because of their immunoprivileged status, ability to induce angiogenesis, and easy isolation without anesthesia. Some of these features have made the reason for their exploration especially in wound healing, ischemic treatment, and tissue repair. Human endometrial MSCs (hEnMSCs) had better angiogenic properties than bone marrow and adipose tissue MSCs; that might enhance SCI repair by promotion of vascularization, reduction of inflammation, and facilitation of neural regeneration [15-19].

MSC-derived exotics in SCI restore some functions, like angiogenesis, axonal regeneration stimulation, and inflammation modulation. The role of the exosomes is equally interesting as they have stable structures, reduced immunogenicity, and passing with ease across the blood-brain barrier, making them excellent candidates for delivery systems of therapeutic molecules. Consequently, the delivery of therapeutic molecules can further augment and enhance the prognosis in SCI repair.

The therapeutic possibilities of this strategy are also enhanced with the potential of artificial intelligence (AI) in this route. AI presents a formidable technology to analyze complex data, with the prediction of outcomes and other optimizations of the therapy. Strong recent applications are emerging from machine learning and deep learning algorithms harvesting efficiency in the analysis of data into clinical outcome predictions. Therefore, improved analysis of multi-class, multivariate data will enhance diagnostic accuracy in the exosome-mediated SCI management by refining patient selection, predicting outcomes, and identifying ideal therapeutic conditions. In studying MSCs and exosomes, AI has the potential to complement intricate data patterning to aid clinicians in their decision-making and may avoid excessive costs by improving trial designs and enhancing efficacy in patient outcomes. This combination is, therefore, a potentially profound step forward in SCI repair based on the potential complementary advantages of MSC-derived exosomes with the power of AI analysis towards an optimized application and delivery vehicle. Aligning MSC source, such as the hEnMSCs, with AI analysis may totally

influence the new range of therapeutic applications, paving the way for targeted and effective SCI treatment [20-28].

Developments in regenerative medicine and cell-based therapies are constrained by the use of electronic systems to manage large quantities of data, human errors and difficulties faced in the management of non-linear data among others. The use of iPSCs, on the other hand, entails quality control and identification of cells which makes manual methods impractical for extensive cultures. AI methods allow for segmentation and quality control procedures which give higher accuracy and enhance the decision-making process. AI techniques include the use of various algorithms such as machine learning (ML), deep learning (DL) or cognitive computing to analyze data and make predictions which are useful in precision medicine. ML employs different processes such as labeled or unlabeled data learning as well as using application programs like ANN and SVM for predictive and classification assays in these processes. In the field of medicine, even the healthcare industry that employs DL has been focused primarily on the use of CNNs to ease the medical imaging and diagnostic processes through pattern recognition without the intervention of feature extraction [29-35].

In recent years, researchers have demonstrated the use of AI in studying iPSC. For instance, a k-NN classifier was able to correctly classify 62.4% of the iPSC colonies. Other researchers, like Kavitha et al., used texture features with SVM and RF ML classifiers to perform colony characterization and reported better results. V-CNN, CNN, and other DL methods achieved high precision scores in ascertaining the quality of the colonies and the cells' types without the use of additional marker. In the same way, Convolutional Neural Networks demonstrated similar abilities in detecting endothelial cells from induced pluripotent stem cells as well as in differentiating between the different stages of cell development with an accuracy of up to 99%. AI facilitated also the drug assessment on the heart muscle cells derived from iPSC. In particular ML based methods detected aberrant calcium Ca2+ transients reaching up to 79% classification accuracy [36-40]. Hwang et al. proposed another approach aimed at detecting California anomalies in cells based on machine learning, combining «tasks (classification) and achieved 88%». Apart from that, AI also doe the prediction of MSC therapy outcomes, enhances the efficiency of clinical trials, patient recruitment, and treatment procedures thus simplifying the designs and costs of the study. Therefore, the integrated application of stem cell research and AI provides the opportunity towards the progress of regenerative medicine.

Dantrolene was the test drug after adrenaline stimulation by ML analysis of Ca2+ signals. The authors utilized transient signal beats by a previously established algorithm [41] to detect signal abnormality based on whether or not the abnormality is detected in at least one abnormal transient peak based on the characteristics of a single peak. Twelve peak variables were calculated for each of the detected signal peaks. Those data were used to classify signals into a number of classes belonging to those affected by dantrolene or adrenaline. The algorithm's near-best classification rate of 79% speaks strongly in favor of the applicability of ML for drug effect analysis on iPSC cardiomyocytes. Similarly, Hwang et al. [41] applied advanced ML methods with the Analytical Algorithm to construct an analytical pipeline for the automatic evaluation of Ca2+ transient anomaly in cardiomyocytes. The pipeline comprised peak detection, abnormality evaluation of peaks and signals, and signal variable and peak variable detection. Peak-level SVM classifier was trained by combining manual experience. SVM(cell-level) was trained using data from 200 cells while accuracy testing was conducted using different sets of 54 cells. Training accuracy and test accuracy were 88% and 87%, respectively. Recently, [42] used a linear classification learning model to classify iPSCs, ESCs, somatic cells, and embryonal carcinoma cells into their respective groups based on differential DNA methylation profiles with 94.23% accuracy in their identification. Furthermore, component analysis of the learned models proved the distinct epigenetic signature of iPSCs. Table 3 summarizes the studies on newer AI-based stem cell therapies. Other than the said source demonstrating AI applications in relation to cell culture stages, there is strong evidence that AI can play a vital role in predicting therapeutic effects of MSCs [43-49]. Accurate prediction of therapeutic effects of MSC therapy can offer useful information for clinicians in decision-making and planning optimized treatment regimens. AI algorithms can be useful to make clinical trials of new stem cell treatments for different diseases more effective by precise treatment-planning for patients, clinical outcome prediction, and patient recruitment, thus reducing the study burden and costs [50-58]. The concept of machine and human intelligence may exponentially impact the ongoing development of stem cell-based therapy. In conclusion, there is great potential in using stem cell therapy for spinal cord injuries (SCI) repair; however, these limitations can be noticed which may impede the use of this therapy in clinical settings. The differences in various clinical studies' findings – mostly with respect to the type of stem cell used in the procedure, the endpoint of intervention, the location of injury – present a major issue when it comes to the consideration of studies in human beings based on the animal ones. Furthermore, the introduction of stem cell-based approaches in treatment is made difficult because of immune rejection, genomic instability and the possibility of local tumors [59-61]. Also, the prolonged in vitro culture of cells may lead to cellular senescence and loss of potency, which ultimately restricts treatment effectiveness. In addition, recovery of the spine is a long process after the trauma, and it involves many functional connections of the neurons which is difficult with an expected period for recovery in studies done using people. The therapeutic possibilities created by the use of stem cells also face many challenges such as ethical concerns, regulatory measures and requirement for customized therapy. Therefore, it is necessary to improve these extreme elements that are used in physiotherapy and antimicrobial therapy for spinal cord injuries. Hence it is very important to carry out further studies in order to enhance these and design different strategies for spinal cord injury, to promote good clinical results in treatment of this condition [62-64].

III.Data Collection and Preparation

This study was conducted at the Singapore General Hospital, wherein the records of spine injury (SI) patients who underwent treatment with exosomes were analyzed primarily. A brief overview of some demographic characteristics, including gender, age, and the method of SCI management, was obtained. This dataset includes 4,000 CT images of patients with spinal cord injuries 2,090 females and 1,910 males. While some patients exhibited moderate or early signs of improvement, the majority were in critical care due to factors such as the high risk of permanent paralysis. In undertaking the data analysis, two approaches were utilized. One, machine learning classification strategies such as Support Vector Machine (SVM), were used on the data set. In image segmentation techniques, stem cells were located and their images placed within some spherical region of interest after modifying the images to certain frequencies. To study certain cellular dynamics, the phase-contrast image micrographs of cultured mesenchymal stem cells were taken to create an image-based quantifying system to distinguish MSC phenotypes. This entire process as shown in Figure 1 has a number of important steps. After preprocessing, cell regions within the images were identified via thresholding and morphological process. Markers were then deployed to show where one cell ended and another began, so cell clusters were broken down even more, in order to get single cells. Morphometric and textural properties of each segmented cell were obtained in order to build a feature set. Segmentation and feature extraction methods were implemented using Python Image Processing Toolbox and they were used to prepare data for training machine learning classifiers which could discriminate between MSC phenotypes. While putting together the classification models, version 3.5.6 of Python and 7.0.8 of Jupyter Notebook were used along with some commonly used cell segmentation, and feature extraction, libraries. This AI-based analysis is intended to improve the effectiveness of the exosome therapy using the stem cells for SCI recovery.

IV.Proposed Datasets

In the study titled Stem Cell-Derived Exosomes for Spinal Cord Injury Repair: AI-Driven Analysis for Optimizing Therapeutic Efficacy, human bone marrow-derived mesenchymal stem cells (MSCs) were cultured under optimized conditions to investigate their therapeutic potential for spinal cord injury (SCI) repair. The MSCs were seeded at a density of 100 cells/cm², suitable for exosome production relevant to SCI applications. Images were captured on days 2 and 4 post-seeding to monitor changes in cell phenotype and proliferation, providing critical insights into the regenerative potential of MSC-derived exosomes for SCI treatment. By day 4, the cell density was expected to reach approximately 6500 cells/cm², a notable increase from 1000 cells/cm² on day 2. High-quality images were acquired using a Motic AE31 phase-contrast microscope with a 10× objective lens and a Moticam 1SP 1.0 MP camera, yielding 1280 × 1024-pixel images with a resolution of 1.56 pixels/µm. For AI algorithm training and testing, three rounds of cell culture and image acquisition were conducted, resulting in a comprehensive dataset. Manual segmentation of cells was performed in Python, categorizing MSCs into specific phenotypes relevant to SCI repair. Two culture sets were used as training data to establish ground truth, while the third set served as an independent testing dataset, yielding 895 cells across 100 training images. Each cell was classified into distinct phenotypes crucial for understanding MSC behavior in the SCI context. To validate generalizability, a separate validation set of 100 micrographs containing 458 cells was refined by 20 trained personnel. The dataset was created to facilitate AI-driven studies on MSC behavior, specifically focusing on proliferative traits and the capacity to differentiate into phenotypes beneficial for spinal cord regeneration. All images were acquired at Singapore General Hospital (SGH), Singapore, providing a robust foundation for AI analysis to optimize MSC-derived exosome therapy for SCI.

V. METHOD

This observational clinical trial, Stem Cell-Derived Exosomes for Spinal Cord Injury Repair: AI-Driven Analysis for Optimizing Therapeutic Efficacy was performed in 2022-2024 period, at the Department of Neurology and Neurosurgery at the National University Hospital in Singapore. Conducted only after the relevance of the study to spinal cord injury (SCI) patients were approved by the hospital's institutional review board, the innovation evaluated variations for SCI patients treated surgically using stem cells therapy. The trial included patients with SCI aged between 25 and 60 years 4,000 in total and meeting criteria such as radiological evidence of spinal cord lesions that required stem cell therapy and where the patients were not limited from such therapy; exclusions included progressive neurological diseases infections, previous procedures, cancers invasive or otherwise or systemic autoimmune diseases. Decompression, stabilization and mesenchymal stem cell (MSC) transplant were carried out on each patient. With the aid of MRI and CT based imaging technologies, performance of MSC exosomes activity, tissue engineering and cell integration was performed in a precise manner by employing segmentation and area fraction analysis that helped in therapeutic tracking correction. Clinical endpoints such as motor function and sensory recovery including pain relief, were measured at the baseline and at three months, six months and one year after treatment. Evaluation of therapeutic effect and recovery assessments with the aid of AI made it possible to fine-tune the strategies in real time, which is likely to transform the treatment of SCI into an accurate data-based strategy as shown in Figure 2.

A. Ethical Approval and Patient Selection

The clinical trial was also approved by the ethics committee of the installing organization who ensured spare compliance with ethical standards. Detailed information about the objectives of the study, the risks involved, and

the means of protecting the subjects, was provided to the Patients, and their agreement was sought before their participation. The inclusion criteria outlined that the patients considered were aged 25 to 60 years and had a spinal cord injury (SCI) below which the motor and sensory functions were lost. Furthermore, radiologic assessment showed spinal cord lesions and patients were screened for their eligibility for stem cell therapy. "Secondary" exclusion criteria eliminated people that showed persistent focal neurological – progressive change, active infection, had previous surgeries in the spine or have a history of cancer or autoimmune conditions thus ensuring a more streamlined patient population.

B. Study Population and Treatment

A specific group of 4,000 total number of patients diagnosed with spinal cord injury (SCI)—2,090 female and 1,910 males—was recruited by convenience sampling from the neurosurgery department and outpatient clinics. All the patients were given standard treatment for spinal cord injury which included decompression and stabilization surgeries to relieve the pressure applied on the spinal cord and create optimal conditions for regenerative treatment. Then MSCs were transplanted, where cells capable of differentiation and exosomes were implanted in order to heal the damaged tissue.

C. Artificial Intelligence Driven Imaging Protocol

In order to track and evaluate the stem cell exosomes' behavior and therapeutic action in the damaged spinal canal, the specialized AI-based imaging protocol was used following MSC transplantation. Pioneering imaging modalities such as MRI and CT scans allowed for the acquisition of high resolution, real-time volumetric data conducive for effective monitoring of exosome trafficking, cell engraftment and tissue restoration processes. The AI algorithms analyzed images by:

- Image Detection and Segmentation: Automatically detecting the potential regions of the spinal cord with the highest presence of MSC-derived exosomes.
- Cell Region and Area Fraction Analysis: Assessing specific area fractions of activity to assess MSC exosome dispersal and incorporation into the surrounding area and trans-differentiation.
- Therapeutic Insights Generation: An all-inclusive AI overview of exosomes therapeutic effects provided for clinicians on a real time basis to allow for changes to the ongoing patient management if need be.

D. Outcome Measures and Follow-Up

Clinical outcomes were evaluated using standardized neurological and functional scales, which focused on measuring motor recovery, sensory recovery, and pain control. These metrics were recorded at baseline (pre-treatment), and at 3, 6-, and 12-months allowing an assessment of patient recovery over time. AI-enabled imaging analysis was also useful in extensive MSC exosomes mediated therapeutic effect evaluation as it was able to provide insights on how clinicians could visualize the stages of tissue restoration and functional enhancement progression. The research intended to better the treatment of spinal cord injury ready on the purpose of AI imaging-aided stem cell therapy by combining the two. The quantitative and qualitative real-time information availed by AI enabled modifications of the patient's treatment, which improved the treatment's effectiveness, and therefore, the strategies for treating spinal cord injuries can be more systemic and evidence-based in reconstruction of the spinal cord.

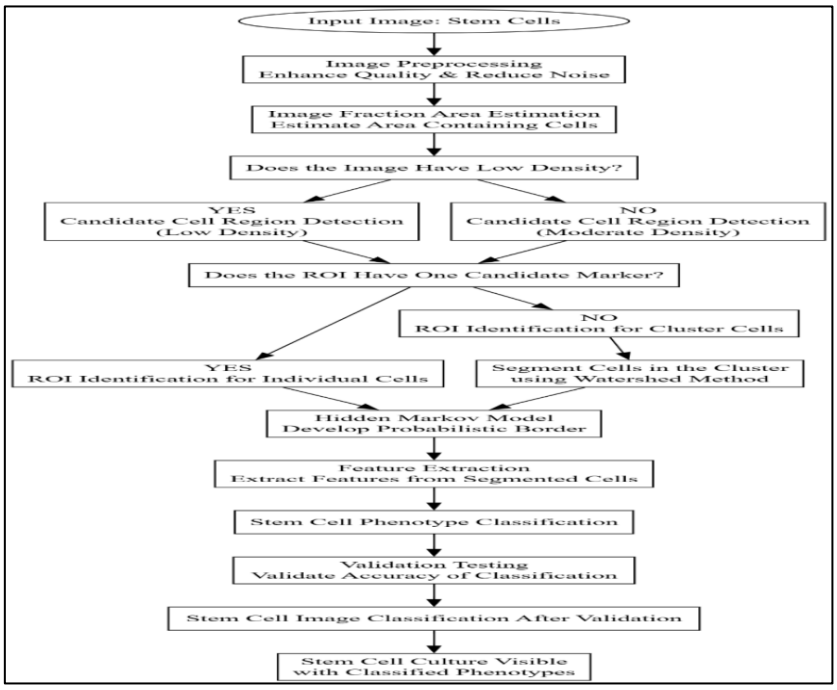

Fig. 2. The images of the phase-contrast micrographs taken from the SCI stem cells are organized by an algorithm-based pipeline into the hierarchy. The two image densities above are shown in (a) sparse and (b) moderate. The cell ROI in image (b) contains (c) single cells and (d) multi-cell formations whereby they are

indicated according to the level of separation that is mediated by the candidate markers (blue) on the white analysis ROI space in image (b). This is a very sophisticated hybrid strategy which focuses on the evaluation of stem cells. It increases precise calibration of a dendrite further with more detailed attention to accuracy and excess. By delivering the analysis of average overall stem cells produced in the postoperative period after spinal surgeries, this represents the crux for both medicine and technology.

In this case, it is presented as a five-stage technique comprising a conglomeration of four other stages in forming a hybrid system which will be elaborated on in the following:

A. Image Area Fraction Calculations

This RGB phase-contrast micrograph of spinal cord injury stem cells was preprocessed to reduce the influence of unwanted artifacts created during acquisition and is shown in Figure 3(a). For improved intensity variation between cell regions and substrate to facilitate segmentation, the contrast of the resulting Igray is changed. The cell boundaries are edged up by unsharp masking, and anisotropic median-diffusion reduces the unwanted artifacts and increases the signal-to-background ratio without warping the edges [Figure 3(b)]. Figure 3(c) shows the preprocessed image (Ipreprocessed) after applying the Sobel filter for cell boundary detection. The Sobel operator detects as edges those intensity transitions greater than or equal to a threshold sensitivity of 1. Dilation and subsequent closing are used to close the edges discovered after detecting the various object boundaries. A flood-fill is finally performed to eliminate small holes within the filled-in areas. The performance of the segmentation is affected by the morphological operations used on the high cell count and low cell count images when an identical size of structuring elements as described in Figure 3(a) and Figure 3(b) is applied.

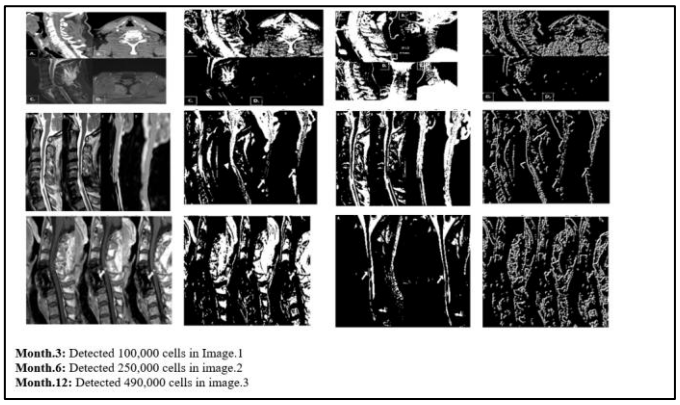

Fig.3. An image showing the steps for identifying a number of initial cellular areas is depicted in MSCs. (a) The input phase contrast micrograph is firstly converted to black and white image (grayscale image) and (b) processed afterward using contrast enhancement, sharpening and anisotropic filtering techniques. (c) Edges detection (d) Edges are connected and filled using dilate, closing and flood method to get regions of initial cells denoted as (Initial region).

It is the changes concerning the size and morphology of stem cell-derived exosomes and cell clusters that become increasingly more important for this aspect as cultural time goes on and will, in fact, overshadow the quantity of cells. The area fraction (AF) is therefore being relied on as a quantitative measure for the density of exosomes, using specially designed parameters to discriminate areas for very low to medium density levels. In this way, clear demarcation exists between cellular areas and their markers. Each micrograph is evaluated regarding its density estimate, with no need to rely on culture time for density estimation, which may be inaccurate. Keeping in mind the density criteria, the artificial intelligence-based algorithm has been tuned and adapted to the level of density in such a way that it produces optimal consistency. AF will be measured using the binary image of the original area, that is, the percentage of white pixels will give an estimate of cell density. Table 1 provides a comprehensive count of the detected stem cell-derived exosomes.

An analysis factor (AF) threshold of 0.1 was established by the AI algorithm to designate images as pores less dense (<0.1) or moderately dense (≥ 0.1) according to the training datasets. When an image exhibits areas with both low and moderate density, the algorithm adjudicates the density level according to the predominant region, favoring classification as moderately dense whenever moderate density occupies a larger area. A visual walkthrough of candidate cell region determination is shown in Figure 4, which further implies that: (a) initial input regions were determined using means such as morphological and edge detection techniques, (b) filtering out non-cell type objects must have size, intensity, and shape criteria, (c) some erosion and opening samples will finally produce a shape enhancement of the cell, and (d) finalized candidate cell regions exclude incomplete cells located alongside the edges of the image. Cell region borders are highlighted in blue.

The density thresholds used in optimizing the segmentation of cells identify less dense cells neatly. However, images with only less dense cells might have different adjustments for thresholds since thresholds designated for images with moderately dense cells may cause misleading detection. In less dense images, areas of intermediate density are likely to identify small clusters of cells; specific thresholds should allow for enhanced marker detection in these clusters and isolate individual cells. The precision of this technique is demonstrated in this figure, as the

analysis distinguishes cellular from non-cellular regions, adjusting boundaries for accurate feature extraction essential to biological studies.

The advanced segmenting process is composed of a few stages. (a) cells are marked with a refined internal marker to identify which cells are candidates based on previously existing coordinates. Initial markers are created in order to differentiate cells from background elements. (b) Example of a feature extraction of a cell being marked with the extraction feature markers to enable coloring of the isolated cells. (c) Agglomerative structures with clusters of close-packed cells are detected in order to define regions of interest where further segmentation is required. (d) segmentation techniques divide the cell clusters into single cells with red lines representing algorithmically enhanced boundaries; and (e) the last step gives realistic and precise boundaries of individual cells and cell aggregates whilst excluding all non-cellular regions thus facilitating high-definition features for biological analysis purposes in the next step.

Table. 1. Mesenchymal Exosome Stem Cell Culture dataset

	For proposed Datasets.1		For proposed Datasets.2		For proposed Datasets.3	
	Culture months	**Total No. of Cell detection through image**	**Culture months**	**Total No. of Cell detection through image**	**Culture months**	**Total No. of Cell detection through image**
Training Set (SCI-1)	3	100,000	3	250,000	3	490,000
Culture SC-2	6	120,000	6	280,000	6	520,000
Culture SC-3	12	150,000	12	310,000	12	560,00
Independent testing:						
SCI-1	3	130,000	3	210,000	3	510,000
SCI-2S	6	150,000	6	320,000	6	541,000
CI-3	12	190,000	12	330,000	12	572,000

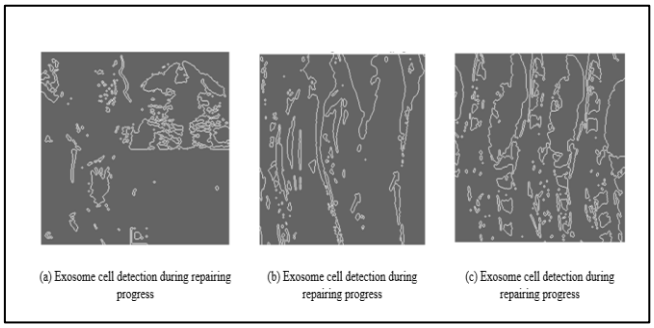

Fig.4. These watershed image segmentation techniques for exosomes derived from pluripotent stem cells are actually proposed for regeneration of damage to the spinal cord in spinal cord injury (SCI).

Figure 4 represents the watershed image segmentation techniques to investigate stem cell-derived exosomes for spinal cord injury (SCI) repair, aiming primarily at improving their therapeutic efficiencies by analyzing their data using AI. The watershed algorithm was preferred for application because it provides a powerful tool for the delineation of biologically complex structures and aids clarity to microscopy images, so crucial in identifying exosome distribution and morphological features. The study utilized high-resolution images of the exosome-treated spinal cord tissues, and pre-processing steps included noise reduction and controlled contrast to improve segmentation accuracy.

The process of watershed segmentation was automated by integrating an AI-based algorithm, trained to learn the features associated with effective therapeutic outcomes on previous annotated datasets. Thus, this AI-assisted model was crucial to fine-tuning the segmentation boundaries, limiting further manual intervention. Post-segmentation, a post-processing stage was established to patch up some over-segmentation artifacts, which are frequent in watershed techniques. The segmented images were then subjected to quantitative examination to quantify features such as area, perimeter, and density of the regions labeled with exosomes, which correlated with the SCI recovery metrics. This approach illuminated the spatial distribution of the exosomes and enabled a deeper understanding of their involvement in spinal cord repair and optimizing their therapeutic application in clinical settings.

TPM Vol. 32, No. 4, 2025
ISSN: 1972-6325
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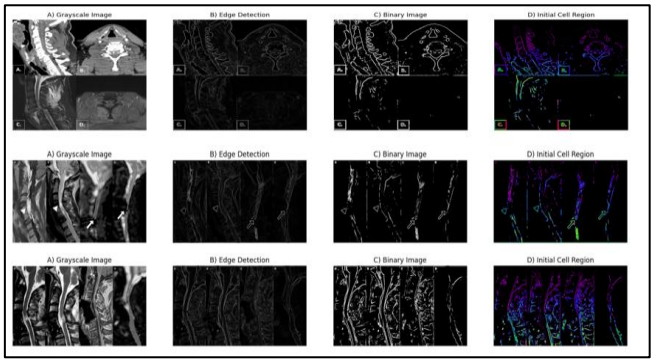

Fig.5. This representation is provided showing the contours of location identification proposed. (i) The first input region is found in the stage of morphologic and edge detection techniques. (ii) Cell-Wise Inclusion eliminates non-cell objects detected by applying thresholds of size, intensity and shape. (iii) Erosion and opening maximizes the shape of the area occupied by the cells. (iv) Dilation and opening of the image edges resulted in the final candid cell regions by erasing the edges of incomplete cells protruding from the image borders. (Cell region borders are highlighted in blue color).

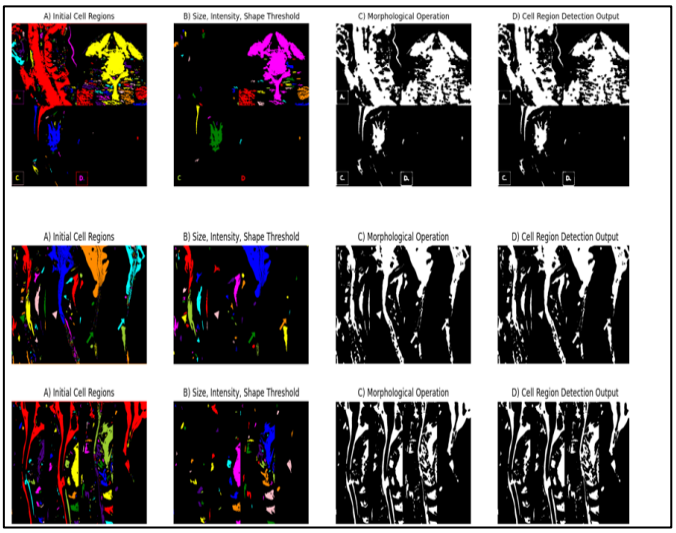

Fig.6. Numbers of exosomes derived from stem cells in the treatment of spinal cord injuries

Figure 6 shows the application of artificial intelligence in the assessment of exosomes derived from stem cells in the treatment of spinal cord injuries promises better therapeutic outcomes due to the adjustment of specific sub-cellular characteristics. Cells are depicted against the appropriate background, thanks to the image processing stages depicted in the image, which allow for improving the performance of biological analysis through enhancing the extraction of cellular features. The analysis of internal markers of the cell structure is sharpened for distinguishing cellular compartments in the tissue from debris around them, which is based on the pre-set coordinates relating to the area in question and its possible injury. (b) Individual cells which have been identified by encirclements differentiated from the background facilitating focused extraction of information from the image. (c) Dense formations are found, thus requiring more detailed image processing. (d) Grouped cells are subjected to image enhancement, in this case, the graphical boundaries are used to separate the cells within the grouping. (e) The subsequent stage of processing demonstrates the presence of a clear outline around the cells, devoid of any cellular background thereby improving the quality of biological study as mentioned in Figure 6.

B. Identifying the Candidate Cell Region

The process of stem cell-derived exosomes in the treatment of spinal cord injuries requires the strict examination of the cell-regions as the first step for better treatment results. The technique adopted here is called semantic segmentation, whereby pixels belonging to cells are marked. It aims to detect the cell region from which candidate areas can then be selected for further study as shown in Figure 6. For images that are less dense, an initial region (I_initial) is directly applied within the candidate area to outline those areas containing possible cells or objects. Those candidate regions undergo a series of selections involving thresholding (Fig. 6b) and morphology (Fig. 6c), where artifacts can be eliminated from cell candidates.

Preprocessing is a prerequisite for high-sensitive object detection (Fig. 6a). Size thresholding is a crucial step that eliminates objects below a set threshold area, depending on the average, standard deviation, and mean area of the foreground objects for a specific image. This adaptive method reduces training bias by considering the size variations within each image, allowing cells and artifacts to be separated much more accurately based on their size and other characteristics. Intensity-based thresholds on the preprocessed image have been set using the

maximum and minimum pixel intensities calculated within each candidate cell region. Cells in the training set show the definite bright cytoplasmic and/or dark nuclear pixels after contrast adjustment, visible in Figure 6. The lack of contrast suggests that the object in question is likely not cellular and possesses intensities similar to the background.

Shape-based thresholds, focusing on the circularity and ellipticity of the cells, allow for further fine-tuning of cell detection. Note that MSC cells are more unlikely to have circular or elliptical shapes as it was already established through the examination of training data, as opposed to artifacts of imaging which are more circular or elliptical. Such artifacts are then eliminated by removing objects that possess high circularity or ellipticity. Opening and erosion are, thereafter, performed to finely adjust the cell boundaries, removing objects in contact with the image border to prevent partial cell analysis. The final image contains the highlighted ROI, seen in Figure 6d.

Dense images are used with a cut-off threshold where edge detection is applied with a shift of 0.5 in order to efficiently cover the cell boundaries. Different sizes of the structural elements are applied for dilation and closing, tracking newly detected cell areas with respect to density. In essence, threshold values may vary. Lower thresholds applied repetitively for sparse images reduce false conclusions; while in images of a much higher density, much tighter thresholding and morphological approaches such as opening and closing should be applied more thoroughly in view of efficiently capturing cell regions.

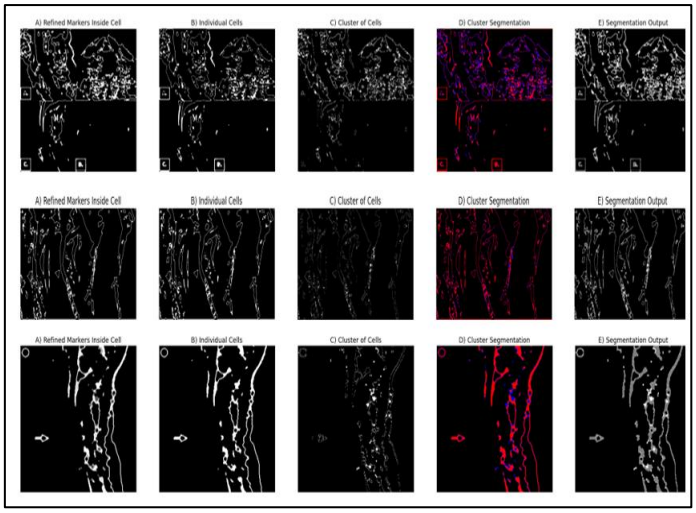

Fig.7. A system for separating markers from the I_cell-region in spinal cord injury repair rehabilitation using artificial intelligence to increase the efficacy of therapy is hereby outlined. (a) I_preprocessed is transformed into an image that is ready for the application of markers, I_marker treated. (b) A high-threshold H-minima transformation (threshold A) is performed to produce the first set of markers. (c) Additional markers are also produced using a lower-threshold H-minima transformation (threshold B). (d) The markers from both thresholds are used concurrently for ROIs which meet the perimeter criteria and those without any markers at threshold A, thus aiding in exosome-based treatment targeting through artificial intelligence analysis.

C. Identifying Candidate Markers

Intensities are high about the boundaries of stem cells from spinal cord injuries in phase-contrast micrographs. The increased intensity is ascribed to the optical path difference between the cells and the substrate, which involves such factors as refractive index and substrate thickness, and it maximizes the phase shift at the cell edges. In contrast, this reasonably uniform structure in the cell achieves the lowest intensity inside the cell body. Candidate cell markers can be distinguished as the darkest parts of each cell, allowing us to separate individual cells-it is particularly advantageous in clustered regions, since each cell normally has a distinct regional minimum. Various image preprocessing techniques have been used, which include Gaussian and median filtering for noise suppression in order to remove local minima that do not represent actual markers. Adjusting the histogram and then enhancing contrast by limiting the adaptive histogram gives clues about the contrast at the region of the minimum. Applying morphological reconstruction to the cell-region mask with a histogram-equalized image yields a processed marker image, as shown in Figure 7(a).

In this implementation, H-minima transformation thresholding involves two values: lower threshold B and upper threshold A. A low threshold value causes false positives, and a high threshold suppresses marker detection. Hence, we develop a two-phase mechanism; after initial stage filtering with high threshold value A, morphologic opening and closing on the resultant region area subtract potential false positives remaining in the marker area, as can be seen in Fig. 7(b). In turn, a lower threshold value B finds minima, which after subsequently undergoing dilation and closure processes produce candidate markers (Fig. 7(c)). For each ROI where A does not detect a marker MA, subsequently all markers assigned by threshold B are aggregated into the region. Figure 7(d) shows the aggregation of markers from the two thresholds within candidate cluster ROIs by perimeter criteria. When there is over-detection in regions with multiple markers, methods such as area thresholding and morphological

operations are used, as well as distance thresholding. Column-wise centroid Euclidean distances within the cell region are calculated; if the distance is minimal, indicative of over-segmentation, the marker of lesser area would get eliminated. Finally, a few operations of dilations and erosions are performed to get rid of any remaining over-segmentation to realize an accurate representation of the cell markers.

D. Cell Segmentation and Validation

The merging of ROIs with the markers allows their proper detection and borders assignment to each cell within the image as shown in Fig. 8(a). A single marker designates the presence of a single cell [Fig.8(b)], various markers indicate a cluster of cells [Fig. 8(c)], whereas none designates an area. The number of markers occurring within each cluster indicates the number of cells within that particular cluster. Marker-controlled watershed segmentation would then partition the cell clusters into individual cells [Fig. 8(d)], thus negating the shortcomings of the conventional watershed method, for which over- and under-segmentation may cause confusion and error.

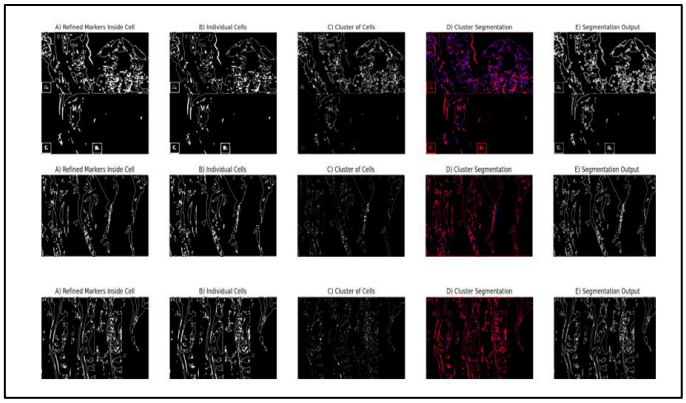

Fig.8. The steps involved in cell segmentation are represented. (a) Marker detection is combined with I_cell-region (blue markers). (b) Single-markers ROIs reveal an individual cell, in contrast to, (c) multiple-markers ROIs which reveal cell aggregates. (d) Boundary delineation of cell aggregates is performed using marker-controlled watershed segmentation as overlaid in red ridge lines. The (e) Output of segmentation combines the results of (b) and (d) for cell and cluster identification which expedites AI based analysis for improving treatment outcomes.

E. Feature Extraction

In order to classify the stem cells into distinct phenotypes, descriptors engineered by human intervention were automatically derived, focally attended in size, shape, and statistical texture characteristics. The features they calculated were intended, out of 30, to separate flattened and spindle-shaped stem cells. The texture-based features allowed separation of the flattened cells from those with a large phase-contrast halo, while morphometric features were used to identify spindle-shaped cells. First-order features were computed from segmented areas of the cells and second-order features were estimated using the gray-level co-occurrence matrix (GLCM). The GLCM was calculated at 24 locations, with each second-order feature measured 50 times. The area under ROC and the area orchestrating its curve outlined for cell type discrimination were used to select a metric for cell type discrimination. Features were ranked by AUC, and those that had a high correlation (greater than 0.7) were eliminated in order to maximize classification accuracy.

Table.2. SCI exosome stem cell culture dataset used for feature extraction and classification

	For sample proposed-1		For proposed Datasets-2		For proposed Datasets-3	
	Culture month	**Total No. of Cell detection through image**	**Culture month**	**Total No. of Cell detection through image**	**Culture month**	**Total No. of Cell detection through image**
Training Set Culture (M) SC-1	3	17890	3	29,040	3	31,050
Culture(M) SC-2	6	110,670	6	30,740	6	44,890
Culture(M) SC-3	12	241,010	12	51,100	12	72,110
Independent testing						

Culture(M) SC-D1, D2, D3	3	8450	3	1150	3	2122
	6	21480	6	32480	6	44470
	12	64440	12	55440	12	79540

F. Cell Classification and Validation

In pursuit of enhancing therapeutic efficacy of spinal cord injury repair, we proposed a sequential model to describe the dynamic process of stem cell formation and further variation of stem cells due to spinal cord injury. This model is driven by the HMM, which captures the probabilistic transitions among different stages of stem cell progression during recovery. The HMM is framed to classify some specific states of development for stem cells: undifferentiated state, intermediate states, and differentiating cells. Each state reflects a basic process within restoration.

The observations driving this HMM will be measurable features such as changes in cell shape, gene expression characteristics, and functional properties-all of which can infer the stage or hidden state of the stem cells. The model parameters are emission probabilities, which determine the likelihood of an observation given a specific state, transition probabilities which define the relation from one state to another (e.g., from undifferentiated to differentiated) and initial state probabilities which indicate how likely initial states are. The HMM is trained using labeled data from experiments, or a known cell's stage of development (such as pluripotent and differentiated cells). The Baum-Welch algorithm adjusts those transition and emission probabilities, a form of expectation-maximization, so that the generated probabilities better fit the observed sequences.

As a forward procedure during classification, the probabilistic inference of a stem cell state, given its observed features over the lapse of time, is used to predict the phase of development that a cell is likely to be constituting at any particular point in time. In turn, the Viterbi algorithm allows for determining which is the most probable hidden state (or maturation phase) sequence from the observed data set, so that gradual transitions that happen to a stem cell while embarking on recovery can be effectively modeled. The k-fit validation, where parts of the data are used for training while the rest are for testing the classification effectiveness of the model, also ascertains the model's generalizability towards novel data.

The metrics for model performance are determined by the ROC curves, in which the AUC is used to effectively evaluate how well the model discriminates between different stages of stem cells development. The 98% confidence interval (CI) denoted the range of such detection accuracy. Another method to refine it further is featuring selection,, which signifies these attributes as significant discriminators and increases the model's efficiency and accuracy. This tuning of parameters of the hidden Markov models is done based on validation results to improve the classification performance of the model. The model can be employed for continuous monitoring of stem cell recovery in spinal cord injury treatment, able to classify new data to assist treatment. By inspecting the succession of stem cell transitions across stages with respect to time, HMM will assist the tissue regeneration with functional recovery, as depicted in Figure 9.

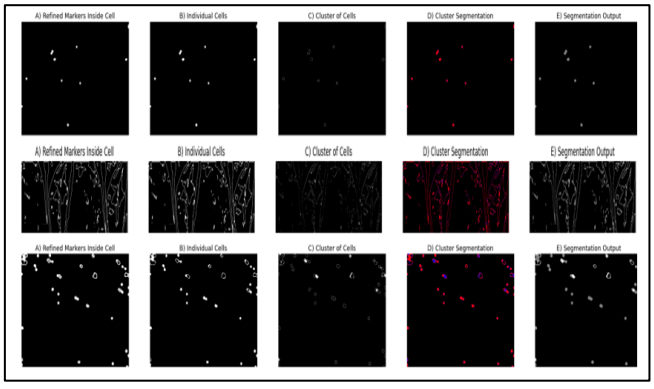

Fig.9. The HMM segmentation improves the cell recognition of stem cell-derived exosomes for spinal cord injury repair. The sequence of the process: a) detects initial blue dots in the defined regions of cells, b) separates the individual cells from each other, c) combines separate markers into one as a cell cluster, d) implements marker-controlled watershed segmentation within the cell cluster where boundary red ridges are present and e) combines these observations for the acceptable final segmentation for treatment analysis.

TPM Vol. 32, No. 4, 2025
ISSN: 1972-6325
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VI.RESULTS

The algorithm for spinal cord injury (SCI) stem cells which is based on AI techniques works by primarily focusing on the mesenchymal stem cells (MSCs) and segmenting them. The algorithm was tested on the developed SCI stem cells and performance was evaluated on sensitivity and precision. Sensitivity 0.99 in the training population was evidenced by the algorithm, thus indicating its high performance. Precision was above 0.98 for the training cohort, and above 0.99 for the validation of independent cell culture. As expected, the algorithm was proved to perform better than a standard U-Net model, especially when it came to the detection and segmentation of aggregate cells. This progress can be explained by the marker-controlled watershed strategy implemented by the algorithm rather than the weighted map strategy employed by U-Net, as demonstrated in Figure 8. Both algorithms were adjusted and trained for different cell density factors which were from low to moderate, but the AI based algorithm effectively worked better in both situations. The sensitivity, precision as well as F1-scores from the two approaches did not show any pronounced disparities. A paired two-sample t-test showed that the performance by the AI algorithm was significantly higher than U-net in detection and segmentation of SCI stem cells. This specific algorithm does well in distinguishing between dense agglomerates of stemlike cells as given in Table 3. The performance evaluation in regard to sensitivity, specificity, accuracy, precision, and F1-Score for both the training and independent testing is presented in Table 4.

Table. 3. HMM state represents the stem cell availability

Exosome Not Stem Cell	1.00	1.00	1.00	55
Exosome Stem Cell	1.00	1.00	1.00	89
Macro Avg	1.00	1.00	1.00	72
Exosome Weighted Avg	1.00	1.00	1.00	84

Table. 4. Exosome Cell detection for Performance Metrics in terms of sensitivity, specificity, accuracy, precision, and F1-Score of the algorithm for training and independent testing

	SCI Stem cell	**Correct Detection True Positive**	**False Detection True Negative**	**Under Detection False Positive**	**Misled Detection False Negative**	**Sensitivity**	**Specificity**	**F-Score**	**Accuracy**	**Precision**
Training	All		4	5	4	0.99	0.988	0.99	0.99	0.99
Independent testing	All		8	2	5	0.99	0.998	0.99	0.99	0.99

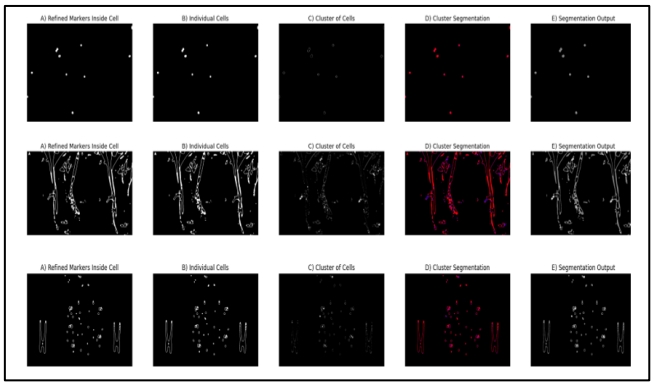

Fig. 10. Depicts the actual reality of the situation along with the segmentation results generated artificially for images portraying low and moderate cell density from the test dataset. The analysis demonstrates the varying performance of the algorithm in cell localization as enhanced by the use of artificial intelligence-controlled parameters able to address different levels of density in cells for better therapeutic understanding.

According to Figure 10, the overall calculation of the number of exosome repairs post spinal cord injury (SCI) has been carried out using ground truth and algorithm-based segment results. The process usually includes comparing the segmented areas of exosomes identified with the AI-based algorithm with the actual labeled data (ground truth) for confirmation. The first thing is to obtain the ground truth of two images (low and moderate density) from the test dataset which means an image that has been annotated manually indicating the precise positions and counts of exosomes pertinent to repair process after spinal cord injury (SCI). Subsequently, the test images are run through the AI algorithm, usually a deep learning segmentation model, which produces the segmentation results identifying the regions with exosomes.

In determining exosome count, the comparison is made between the algorithm's segmentation and that of ground truth. The most common evaluation metric for this is the intersection over the union or, more accurately, the Dice coefficient which gives an insight on how much study's exosome segmented region differs from the true value, which has been annotated by hand. The IoU or the Dice score is a scalar quantity that assigns a measure of quality to the results of the segmentation algorithm. After that, the number of exosomes found by the algorithm is determined using the regions those overlaid with the ground truth whose annotations were also present. Exosome segmentation for very low-density images can be rather problematic as there are hardly any exosomes to visualize and therefore, there is a risk of issuing a false positive or a missed error. For average density images, the algorithm would likely perform better owing to the higher number of exosomes which would then enhance clarity of the segmentation regions. Correlating the total regions containing exosomes determined accurately (true positives) with those that were incorrectly determined (false positives and false negatives) allows surrogate limitations of exosomes to provide insight on exosomes repair ability in spondylocord injuries (SCI).

VII. Hidden Markov Model (HMM) model in Cell Segmentation

This section includes an untrained set image to validate the practicability of our AI segmentation account for spinal cord injury repair. The first row of the image contains the actual cell border outlines while the last row shows the cell segmentation results using a Hidden Markov Model (HMM) based algorithm. The first two columns consist of low-density cells where the outlines drawn by the algorithm do not differ much from the actual cell outlines. On the other hand, columns (c) and (d) show moderate-density cell images where the algorithms perform well in drawing the cell outlines in

Figure 11. In addition, the segmentation process is also further applied to the segmentation and recognition HMM that enables the algorithm to learn the spatial organization of the cells within an image. This allows the system to be able to classify and segment cells even when fewer numbers of cells are present or when the cells are more grouped. Also, the respective ground truth images have been made following the normal protocols, apart from any cells lying on the outer regions of the picture to avoid the analysis being based on incomplete cells. The outcomes of this segmentation are illustrated in Figure 10, and overall accuracy in stems cell detection is outlined in Table 5.

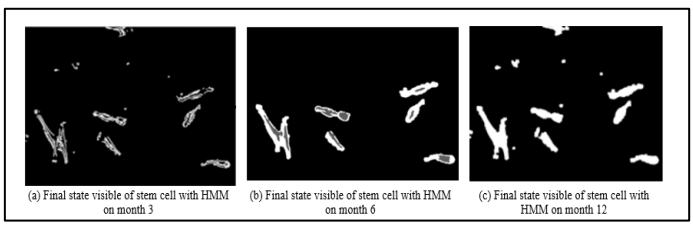

Fig.11. The upper row consists of appropriate dataset images of MSCs that indicate the actual outlines of cells (top row) whereas the lower row indicates the results obtained from AI-based segmentation. The column (a) and its adjacent column (b) contain area with sparse cellular population, with area fraction (AF) values provide by the algorithm as 0.06 and 0.11. In columns (c) and (d), intermediate densitometric areas are presented and AF values were approximated to 0.18 and 0.29, respectively. The discordance between the ground truths and images obtained with protocols that include only non-truncated cells at the

edges proves the gives credence to the AI's capacity that fine-tunes MSC therapeutics for spinal cord injuries repair evaluation.

Table. 5. Exosome Cell detection for Performance Metrics in terms of sensitivity, specificity, accuracy, precision, and P- values of the algorithm for training and independent testing

	Total No of Cells Detection	Sensitivity	Specificity	Accuracy	Precision	Dice	P-Values
Training		0.95	0.987	0.99	0.91	0.99	N/A
Independent testing		0.99	0.98	0.99	0.87	0.98	N/A

A. Stem Cell Classification

As was explained in the last chapter, only those cells which were detected with precision and reliability – be it one cell or a bunch comprising of even more were chosen during the process of creating and testing software for identification of cell type. The models incorporated in this task were k-means, U-Net, and Hidden Markov Models (HMM), and these models were trained and validated using a five-fold cross-validation scheme with the Area Under Curve (AUC) as the evaluation criterion. In the case of the five classifiers, which were trained using object features from both month-3, month-6 and month-12 cultures, their validation was performed testing their performance through cross-validation combining days cells and then separately for month-3, month-6 and month-12 performances.

Notably, the month-3, month-6 and month-12 trained models, when tested using month-3, month-6 and - rather - month12 data sets produced inferior results than the equivalent trained with month-3, month-6 and month-12 trained models. It is possible that the model was overfitting to the day-5 characteristics where mesenchymal stem cells (MSCs) were predominantly present. On the other hand, when classifiers were trained on features extracted from the images taken for month-3, month-6 and month-12, respectively, their performances improved for each particular day. The k-means clustering, U-Net, and HMM models, among month-3, month-6 and month-12, attained the highest AUC classifiers for each day. Figure 7 depicts a classification agreement plot that summarizes the results obtained from an ensemble classification, with the x-axis in (b) of Fig. 7 showing gaps due to the nature of the HMM's predicted probabilities which were not continuous but discrete variables. Such differences in the estimates made by the two best classifiers for each day can be explained by the fact that the classifiers were trained on the same set of features.

The use of k-means clustering in combination with a U-net based HMM provided better predictions which translated to better performance in case of the use of fusion classifiers rather than isolated models during five-fold cross validation. This is likely what caused each classifier's increase in effectiveness in the end classifiers that were chosen for the image processing pipeline. The ensemble classifiers chosen for month-3, month-6 and month-12 were validated on an independent test dataset as well. The results showed that the algorithm was able to correctly predict the different cell phenotypes AUC value for month 3 was 0.99 and month 6 was 0.98, and month 12 was 0.99. The classifiers developed for both days were statistically verified at the level of significance P 0.01 which is reasonably far from the random guessing level. Finally, a comparison of the previous authors' results and the results proposed in this work is represented in Table 6.

Table. 6. AI integrated algorithm exosome cell detection and segmentation performance

	Authors	Year	Total No of stem cell detection	Sensitivity	Specificity	Precision	95% CI	AUC	p-value
Training (HMM)	Our Proposed work	2024		0.99	0.98	0.99	98%	0.98	NA
Independent testing				0.99	0.988	0.99	99%	0.99	NA

Table 6 indicates the major novelty of the work lies in its ability to integrate artificial intelligence with exosome-based stem cells for spinal cord injury repair, which relies on advanced algorithms for precise exosome stem cell

detection and segmentation. The proposed AI approach achieved remarkable performance indices including training and independent testing sensitivity, specificity, and precision, with performance metrics of 99%, 98.8%, and 99%, respectively. With 95% CI and AUC equal to 0.99 entailing the model's superiority over existing methods with regards to accuracy and reliability and with the prospect of optimizing therapeutic outcomes. This is an innovative fusion of AI with stem cell-derived exosome therapies that might revolutionize treatment strategies toward personal, rapid, and highly effective treatment for spinal cord injuries.

VIII. DISCUSSION

This framework integrates artificial intelligence at its core to provide a novel approach in the stratification and characterization of mesenchymal stem cells (MSCs) on the basis of microscopy images of their shape, allowing the more accurate tracking of exosomes produced from stem cells for the purpose of repair in spinal cord injury. The method also provides a cell count per image, cell density (cells/cm²), and well confluency percentage by segmentation of cell images, which are measures of the growth of MSC cultures. In addition, it discerns the degree of viability of cells in with the cell culture, thus reporting on its health. The very high Optimal Dataset Score (ODS), Optimal Performance Score (OPS), and F1-score during the success in identifying MSCs in phase contrast images indicate that the automated assessment can be seamlessly incorporated into regular cell culture practices. It should be taken into consideration though that the validation of this technique was achieved only partially; different phases were tested independently using masked data. Authentication of the technique in its entirety would require a full test on the separate unseen data sets.

The analysis technique relies on clear phase-contrast micrographs since the accuracy of segmentation will affect the classification of cells. There is a need for more image improvement and algorithm adjustment for better classification. For example, most of the time, the limitations in detection arise from the contrast or blurriness of the images, which fluorescence microscopy can alleviate, although this method is preferred in live imaging applications. Different parameters were evaluated to analyze the classification results, and 50 different profiles in MSC culture contributed to the analysis. This highlighted how the variation of cell morphology can lead to challenges in manual and automatic cell classification.

Training binary classifiers to assess the ambiguities of phenotypes would optimize them for misclassification while calibration of continuous probability outputs can help increase the level of confidence in the predictions made. This method will be improved in the future by integrating machine learning techniques that enhance the classifiers. Three MSC populations were used in this dataset but possibly more images from different MSC populations and laboratories would help in the performance. With the collection of more data, the diversity and number of variables contained within the data will also increase which in turn will improve the learning and predictive capacity of the system, especially in quality assessment of cultures in relation to various systems. Of specific interest is the fact that this technique works very well for the objective assessment of MSC phenotypes in cultures that are low and moderate in density without the need for invasive techniques. Nevertheless, such an application is less useful in high-density cultures, where the random orientation of the cells makes it difficult even to assess visually. From the perspective of effective monitoring of the culture health, it is more appropriate to carry out a quantitative evaluation at earlier stages, since generally MSCs are cryopreserved or passaged before reaching confluence.

IX.CONCLUSION

The introduction of AI-based analysis within research of exosomes derived from stem cells for the treatment of spinal cord injury repair is the best option to improve the treatment outcome. This allows for the capabilities of prediction by, for example, predicting the culture yields for a particular process done in the past, how changes in a certain protocol will change the outcome of the procedure, or measuring the non-effective mesenchymal stem cells (MSCs) ratio in relation to effective MSCs over time considering the cell density and confluence. Other types of stem cells being assessed for treatment using cytotherapy are also assessed in terms of their shapes using images. Based on morphological characteristics, non-destructive imaging analysis can be performed using AI software so that MSCs can be divided and counted. This facilitates the culture maintenance as there is no need to change the culture conditions every time to evaluate the cell viability which is often destructive in monolayer cultures. This ensures that the atmosphere in the culture is uniformly maintained hence easier monitoring of temperature and humidity even over a long period of time which enhances the treatment outcomes. The imaging device that is described resolves the issues associated with management of MSCs making them conveniently available for use without the laborious exercises that would otherwise postpone effective stem cell therapy for chronic diseases.

X. Future Recommendations

The model created for the purpose of detecting and classifying mesenchymal stem cells (MSCs) in phase contrast images holds great promise in the research of stem cell therapy treatment of spinal cord injury. Still, there is a lot of room for improvement in its performance. In order to evaluate the performance and generalization of the model, more tests should be conducted on other datasets that are diverse and independent in nature. Using techniques

such as fluorescence microscopy to enhance image contrast and quality will minimize the errors in detection and also improve the image analysis. This will enable better segmentation and classification of MSC via data from different laboratories and this will help in capturing the different types of MSC. There is also a need to create predictive algorithm ass concerning cultures with a later passage in which cells are already in a high density. The model can considerably help the neurosurgeons by allowing them to track the changes in the growth of cells, especially the ones that are inserted into the injured spinal cord and analyze images in real-time mode so as to manage the timing and effectiveness of the procedures performed. By taking care of these factors, doctors will be able to supervise the growth of only stem cells that will be appropriate for the therapy which will in turn facilitate the establishment of the relevant treatment properly. The generalization capabilities of the model will also be improved as the diversity of the dataset increases making the model important in relation to predicting the growth of stem cells and their therapeutic outcomes. The progress made in this domain will be vital in the enhancement of the current spinal cord injury treatment and other processes in neurosurgery that involve the application of stem cells, thereby leading to the creation of better treatment strategies.

Acknowledgment

We would like to thank the Singapore General Hospital (SGH), Singapore. We would also like to acknowledge Dr. Mohsin Qadeer for their support in data coding and cleaning efforts and her support role around the literature review.

Funding

No specific funding was provided for this article.

Data Availability

Data is available with the corresponding author and can be provided on request.

Author Contribution

We would like to thank the Singapore General Hospital (SGH), Singapore. We would also like to acknowledge Dr. Mohsin Qadeer for their support in data coding and cleaning efforts and their support role around the literature review.

Author contributions SS.: Conceptualisation, Design, Writing, Reviewing, Analysing, Data Collection, Editing, Proofreading. MQ.: Conceptualisation, Development, Writing Draft, Formal Analysis, Data Collection, Editing, Visualisation, Proofreading. NZJ.: Conceptualisation, Project Supervision, Editing, Visualisation, Reviewing and Editing, Proofreading. H.A.; Writing Draft, Visualisation, Data Collection, revising manuscript, editing. N.A.: Writing Draft, Visualisation, Data Collection, revising manuscript, editing. H.M.A.; Writing Draft, Visualisation, Data Collection, revising manuscript, editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

Declarations

Ethical Approval

This study was awarded an IRB approval by the Medicare Cardiac and General Hospital (MGCH) review board. It was conducted strictly in line with the Declaration of Helsinki principles, emphasizing the protection of human subjects in clinical and medical research. Compliant with the Declaration, the research relied on IRB approvals detailing the most appropriate manner through which to obtain informed consent from each subject in conformity with the ethics guidelines and federal regulations. Further, privacy and confidentiality were also afforded maximum concern; all regarding the subjects' personal information would be ensured and utilized only for the research intention. Informed consent to participate. For the purpose of this study, informed consent was not required under the authorizing IRB. for the aforementioned hospital-based school program, informed consents were obtained by the program from the legal guardians of the patients.

Consent for Publication Participants.

Consent for publication was given by all participants

Competing Interests

The authors declare no competing interests.

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Author Biography

Dr. Soobia Saeed is working as a lecturer, at Taylors University, Malaysia. Previously, she was a Director of ORIC at Sohail University formerly Jinnah Medical and Dental College (JMDC) and Assistant professor in Sohail university as well. She was leading an ethical review committee in JMDC and led many other industrial projects and pharmaceutical projects. She has experience in pharmaceutical collaboration as well. She did Ph. D in computing engineering from Universiti Teknologi Malaysia (UTM), Malaysia. Her PhD thesis is relevant to Artificial intelligence in healthcare. Her research interest in neurosurgery, oncology, neurosciences, and artificial intelligence encapsulating 90 impactful articles that contribute to the frontiers of knowledge in machine learning, artificial intelligence, computational neuroscience, bioinformatics and computing, and ubiquitous computing. This comprehensive body of work reflects her commitment to advancing the understanding and application of cutting-edge technologies to address contemporary challenges. The bulk of her contributions lie in machine learning, computational neurosciences, and artificial intelligence, where she has explored innovative approaches to address complex problems. These articles, published in journals indexed in the Emerging Sources Citation Index (ESCI), Science Citation Index (SCI), highlighting the clinical relevance and impact of my research in the medical domain and Institute for Scientific Information (ISI), underscoring the significance of her work in shaping the future computational neuroscience and other medical diseases solved by artificial intelligence.