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A deep learning model for predicting blastocyst formation from cleavage-stage human embryos using time-lapse images

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Efficient prediction of blastocyst formation from early-stage human embryos is imperative for improving the success rates of assisted reproductive technology (ART). Clinics transfer embryos at the blastocyst stage on Day-5 but Day-3 embryo transfer offers the advantage of a shorter culture duration, which reduces exposure to laboratory conditions, potentially enhancing embryonic development within a more conducive uterine environment and improving the likelihood of successful pregnancies. In this paper, we present a novel ResNet-GRU deep-learning model to predict blastocyst formation at 72 HPI. The model considers the time-lapse images from the incubator from Day 0 to Day 3. The model predicts blastocyst formation with a validation accuracy of 93% from the cleavage stage. The sensitivity and specificity are 0.97 and 0.77 respectively. The deep learning model presented in this paper will assist the embryologist in identifying the best embryo to transfer at Day 3, leading to improved patient outcomes and pregnancy rates in ART.

Infertility affects around 17.5% of the adult population, as per a recent survey conducted by the World Health Organization. The known way to treat infertility is by in-vitro fertilization(IVF). IVF is a widely used assisted reproductive technology where eggs are retrieved from the ovaries, fertilized with sperm in a laboratory, and then implanted into the uterus. It is suitable for various infertility causes, including tubal blockages, male factor infertility, and unexplained infertility.

The success of IVF is multifactorial, involving a combination of biological, medical, and lifestyle components. Two major factors significantly influence the success of IVF (A) Which embryo to transfer and (B) When to transfer the embryo.

The fertility clinics assess the embryo quality on Day −3 which is 70 to 72 hours post insemination(HPI) and is known as the cleavage stage or Day −5 which is 112–120 + HPI and is known as the blastocyst stage. The morphological qualities are assessed on day −3, the grading is based on the number of cells, symmetry, and the degree of fragmentation. At the Blastocyst stage, grading is typically based on three key components: the blastocoel (cavity), the trophectoderm, and the inner cell mass (ICM). The second important factor for a successful IVF is to decide the time of transfer; Most of the clinics prefer to transfer the embryos at the blastocyst stage[1,2] as Blastocyst transfer has several advantages like higher implantation rates, more accurate embryo selection, lower risk of multiple pregnancies, better synchronization with natural conception, greater timing flexibility, and higher pregnancy rates.

Though blastocyst transfer has its advantages, in certain cases where the embryos are few, it may lead to cycle cancellation, as embryos fail to develop into Blastocysts. This situation may lead to mental trauma for the patients. In the study conducted by Xiao et al.[3] and Berkkanoglu et al.[4] transferring the embryo at the cleavage stage is a good option for low-responder patients. Low-responder patients are those who develop fewer follicles using ovarian stimulation.

The cleavage transfers are preferred over blastocyst transfer considering the following:

1. They reduce the risk of culture-related stress on the embryos.
2. It is suitable for patients with recurrent implantation failure or suspected endometrial receptivity issues.
3. In a recent clinical study[5] it was observed that there are no significant changes in the outcome of day 3 or day 5 transfer. Hence, fertility clinics are increasingly opting for cleavage-stage transfers due to lower opera-

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tional costs and reduced resource demands. A clinical trial done by Ahlström et al.[6] supported that embryos transferred at the cleavage stage (Days 2 and 3) strongly correlated with favorable outcomes when embryo selection was based on morphology. Their findings showed that early-stage embryo transfers (Days 2 and 3) can achieve similar live birth outcomes as blastocyst-stage transfers, without the extra cost and complexity involved in extended culture.

Predicting blastocyst formation on Day 3 can reduce costs by saving on incubator space, media, and staff workload, especially in resource-limited settings. Cleavage-stage transfers require fewer consumables and simpler monitoring, lowering operational costs compared to extended Day 5 culture. Additionally, early-stage predictions help avoid unnecessary extended culture for embryos unlikely to reach the blastocyst stage, minimizing the risk of embryo arrest and improving resource efficiency.

The contributions to the paper are summarized as follows:

1. We provide a framework for predicting blastocyst formation at the cleavage stage based on the time-lapse(TL) images captured till 72 HPI that helps reduce time and cost of the process.
2. The accurate prediction of the model helps improve the success rate of IVF by giving the embryo a more conductive uterine environment for development.
3. The proposed prediction model considers a series of embryo images from the time of insemination, making the model more robust than the available models that evaluate the embryo on either day-3 or day-5 images.
4. The proposed model categorizes the embryo image into 11 classes based on 11 cellular events, helping in developing a robust prediction model.
5. The proposed model achieves a commendable accuracy of 93%, outperforming other models by integrating image and series characteristics.

In this paper, we present a predictive approach to determine whether or not the embryo selected for transfer at 70–72 HPI will grow into blastocysts. Our 2-stage algorithm first identifies the number of cells in each frame. The extracted features are then given to the GRU model that analyzes the sequential information and predicts blastocyst formation.

The model identifies subtle differences in embryo development, enhancing decision-making and improving outcomes in assisted reproduction. Clinicians and fertility specialists can utilize this tool for more accurate embryo selection, increasing the likelihood of successful implantation and pregnancy.

Related work

Time-lapse imaging has brought a breakthrough in IVF laboratories. It continuously monitors the development of embryos without disturbing them. In the field of in vitro fertilization (IVF), time-lapse imaging provides several benefits, such as enhanced embryo assessment, selection, and developmental outcome prediction, which eventually improve treatment outcomes for couples undergoing IVF.

Now with the advent of Time Lapse Monitoring, the embryos can be monitored in real time. Time-lapse imaging technology has since revolutionized embryo monitoring by allowing continuous, non-invasive observation of embryo development within the controlled environment of the incubator, providing more objective data and potentially improving IVF outcomes.

Traditionally embryos were monitored by periodic removal of embryos from the incubator for manual observation under a microscope. In this method, static images were obtained, and the embryologists could assess only the morphological features. The embryologist selected the embryo by counting the number of cells and the percentage of fragmentation.

Morphological Analysis requires skilled embryologists as the cells are overlapping in nature. Many successful algorithms have been published for counting the number of cells. Deep learning models are used to extract the features, identify the cell boundaries, and segment the blastomeres[7,8]. They used Convolutional Neural Networks (CNNs) for this task. CNNs are deep-learning architectures designed to extract meaningful features from structured data, such as images. They are particularly effective in capturing spatial hierarchies within data by applying convolution operations, which allow the model to detect localized patterns. These patterns can include specific shapes, textures, or structures, making CNNs well-suited for tasks like analyzing cell morphology or developmental stages in medical imaging applications.

The cell counting is implemented by Rad et al.[9] as a regression problem using a residual incremental Atrous pyramid, and progressive up-sampling. In another approach[10]. the author used hand-crafted features based on the shapes and textures to count the number of cells. Object detection also plays an important role in identifying blastomeres. Lio et al.[11] proposed a method to identify the overlapping cells using Faster RCNN.

Time-lapse videos help in the study of morphokinetic features representing the dynamic changes in embryos as they develop. Predicting the viability of embryos and choosing the optimal embryos for transfer depends on these features. Embryologists determine which embryos have the best developmental competence by evaluating characteristics such as embryo shape and cell cleavage patterns.

Time Lapse videos play an important role in studying the pronuclear stage morphology classification and assessement[12,13], predicting the formation of Blastocysts from cleavage stage embryos[13–18], implantation prediction[18–20], predicting ploidy status of the embryo[21], blastocysts stage classification[20,22–26], selecting the embryo for transfer[27–31].

Limited artificial intelligence (AI) based studies have been carried out in predicting the formation of Blastocysts from cleavage-stage embryos. The studies conducted are summarized in Table 1. The models developed are primarily based on CNN. Bortoletto et al.[14] developed a CNN model by analyzing embryos at

Paper	Algorithm	Accuracy	Dataset Size
Pietro Bortoletto et al.(2019)14	CNN	SET: 63.9% DET: 79.4%	748 embryos
Kanakasabapathy et al. (2019)16	CNN combined with a genetic algorithm	71.87%	748 Embryos
Dung P. Nguyen (2021)32	CNN	76.19%	1135 Images
Qiuyue Liao et al. (2021)17	DenseNet201, LSTM	78.2%	1319 embryos

Table 1. Deep Learning models for Predicting blastocyst formation from Day 3 embryo images.

70HPI and categorizing predictions for single embryo transfer (SET) and double embryo transfer (DET) with accuracies of 63.9% and 79.4%.

Dung et al. developed a CNN model with three convolution layers followed by pooling layers, achieving a 76.19% accuracy and an AUC of 0.75 for predicting day 3 embryo blastocyst formation[32].

In 2024[32], Sharma et al. developed a model that predicted the cleavage and blastocyst stages at day 2 and day 4, respectively. They utilized the 145 video frames as transfer and avoid videos. Convolutional LSTM is used for spatio-temporal prediction.

In this paper, we develop a prediction model for blastocyst formation at the cleavage stage using a combination of ResNet architecture and GRU cells. The ResNet-GRU model, integrates Residual Neural Networks (ResNet) with Gated Recurrent Units (GRU). ResNet - GRU model was developed in 2023 by[34] to detect Glaucoma disease which affects the vision of the people. The retina cropping is done by Unet++technique. High accuracy was achieved using ResNet - GRU model. The ResNet- BIGRU model[35] developed in 2023 is used to diagnose epilepsy using electroencephalogram (EEG) signals. Convolutional neural networks (CNNs) were utilized in this study to extract the high-dimensional features. Then prior and next sequence information was combined using gate recurrent units (GRUs) to fully integrate the adjacent EEG signal information and enhance model detection accuracy.
[35]

Proposed model

The proposed model is designed as a 2-stage prediction model. This prediction task involves TL Videos, the frames are extracted from the videos and given to the model. To obtain accurate results our model comprises of the stages (1) Preprocessing the images (2) Feature Extraction (3) Time Series Analysis.

Dataset

The public dataset Human embryo time-lapse video dataset[36] is used in this study. The dataset consists of embryos from 716 infertile couples who underwent Intracytoplasmic Sperm Injection (ICSI) cycles. To address potential biases, videos with fewer than six annotated phases were excluded by the authors, retaining only those with comprehensive annotations. From the remaining videos, the authors then randomly selected 10% to create a dataset of 704 videos. High-resolution images are provided to ensure that subtle morphological changes can be observed and analyzed. The dataset contains videos of 522 Blastocyst embryos chosen for the transfer and 182 embryos did not reach the blastocyst stage. As the dataset is unbalanced data augmentation is used for balancing the classes, this step is necessary to avoid the machine learning model becoming biased.

Cropping of the images

The frames extracted from TL videos require cropping as it is an important preprocessing step in embryology that helps in standardization, focusing on relevant features. The cropped images contribute to an accurate and reliable assessment of embryo quality and developmental potential.

The Raw images were cropped using the following approach:

- Step 1: The largest circle was detected using a hough circle. The pixels outside the circle were marked as black pixels.
- Step 2: The boundaries were extracted using a unique method where a block of 4 pixels was considered, if all the pixels are white then all the pixels in the image are made zero.
- Step 3: The image was then divided into 16 sub-parts.
  - Each block was checked for the density of pixels.
  - The 4 neighboring blocks with high pixel density were considered.
  - The 5th and 6th high-density neighboring blocks were considered for the allotment of 100 pixels.

Figure 1 illustrates the cropping process. Figure 1A displays the original image. Figure 1B demonstrates the unique boundary extraction method, which is significantly faster and more efficient than other methods. Figure 1C depicts the division of the image into 16 parts to identify the high-density block. Figure 1D presents the final cropped image.

Feature extraction

Cell counting plays a critical role in embryo prediction by providing valuable information about the developmental stage and quality of embryos. Convolution Neural Networks play a vital role in image classification. We implemented the CNN, VGG16, ResNet, and DenseNet models in this work. The models were fine-tuned on

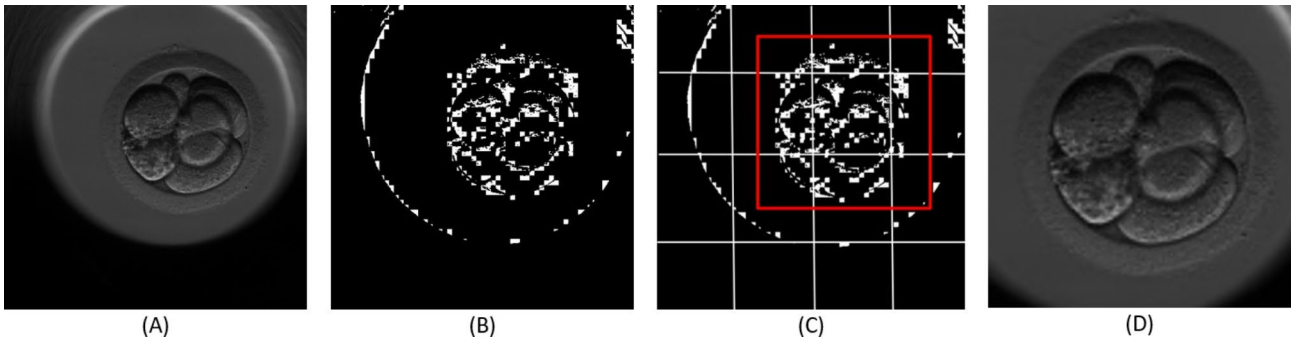

Fig. 1. Cropping the embryo image **A**. Original image **B**. unique boundary extraction method **C**. Division of image **D**. cropped image.

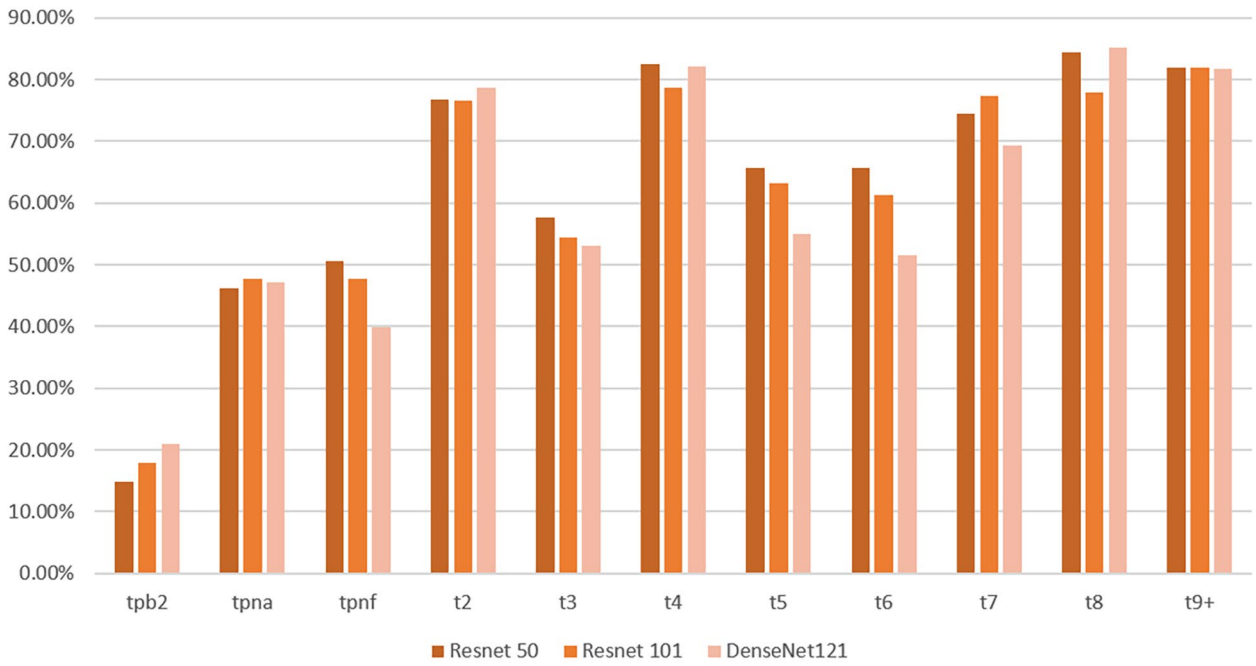

Fig. 2. Accuracy of cellular stages of ResNet50, ResNet101 and DenseNet121 models.

embryo images of eleven cellular events. ResNet and DenseNet Models performed better than the conventional CNN and VGG models.

The confusion matrix study demonstrated that the ResNet50 and ResNet101 architectures performed significantly better in identifying cellular events than the DenseNet model. Figure 2 shows the accuracy of different models. Since ResNet50 architecture correctly identified most cellular events, its features were utilized for subsequent processing.

ResNet50 model parameters

Residual networks or ResNet is a CNN architecture introduced by Kaiming He et al. and belongs to the ResNet family[37]. They introduced a paradigm shift in deep learning architectures by addressing the vanishing gradient problem associated with deep neural networks. The advantage of the residual model lies in its use of residual connections, or skip connections, which enable the network to learn residual functions. By allowing information to bypass one or more layers, these connections facilitate the training of extremely deep networks by mitigating the degradation problem.

The model was initialized with the Imagenet weights. Embryo images were used to fine-tune the model to effectively classify the embryo cellular event. The top layers of ResNet50 are discarded instead, a global average pool layer was used, with a Dense Layer of 11 neurons and softmax activation function.

The Loss function used was categorical cross-entropy. A stochastic Gradient Descent (SGD) optimizer with a learning rate of 0.0005 and a momentum of 0.7 was used for training.

200 random cases are selected for training and validation of cellular events. The model is then trained for 20 epochs. The validation accuracy achieved is 75.96%. This model helps to extract the morphological features, where it can extract the features and classify the cellular event. The model trained exhibits difficulty in accurately classifying the cellular events tpb2 (time to polar body appearance), tpna (time to pronuclei appearance), and tpnf (time to pronuclear fading) compared to other cellular events that are blastomere division from 2-cell stage to 9 (and more) cells-stage (t2,t3,t4,t5,t6,t8 and t9 +).

Figure 3 depicts a t-SNE (t-distributed Stochastic Neighbor Embedding) plot that visualizes the PCA (Principal Component Analysis) features extracted from ResNet (Residual Network) features. This plot was created to assess whether the extracted cellular event features could effectively classify embryos based on their likelihood of developing into a blastocyst.

t-SNE is a technique used for dimensionality reduction, particularly well-suited for the visualization of high-dimensional datasets. PCA is another dimensionality reduction technique that transforms the data into a set of linearly uncorrelated components. In this study, features were first extracted using ResNet, a deep convolutional neural network known for its ability to capture intricate patterns in image data. These high-dimensional ResNet features were then reduced using PCA before being visualized in two dimensions with t-SNE.

However, as observed in Fig. 3, the morphological features alone, which include characteristics derived from the cellular events captured in the embryo time-lapse videos, do not form distinct clusters that could clearly differentiate between embryos that will develop into blastocysts and those that will not. This suggests that while ResNet can extract rich and detailed features from the images, these features, when used alone, are insufficient for reliable classification based on morphology alone.

Recognizing the limitations of using only morphological features, the study proceeded to incorporate a more temporal aspect of the data by passing these features to a GRU (Gated Recurrent Unit) model.

GRU model

The GRU is a special type of recurrent neural network (RNN) that addresses the vanishing gradient problem and can capture long-term dependencies in sequential data. GRU works on selectively updating the network's hidden state at each time step by applying gating mechanisms. Controlling the flow of information into and out

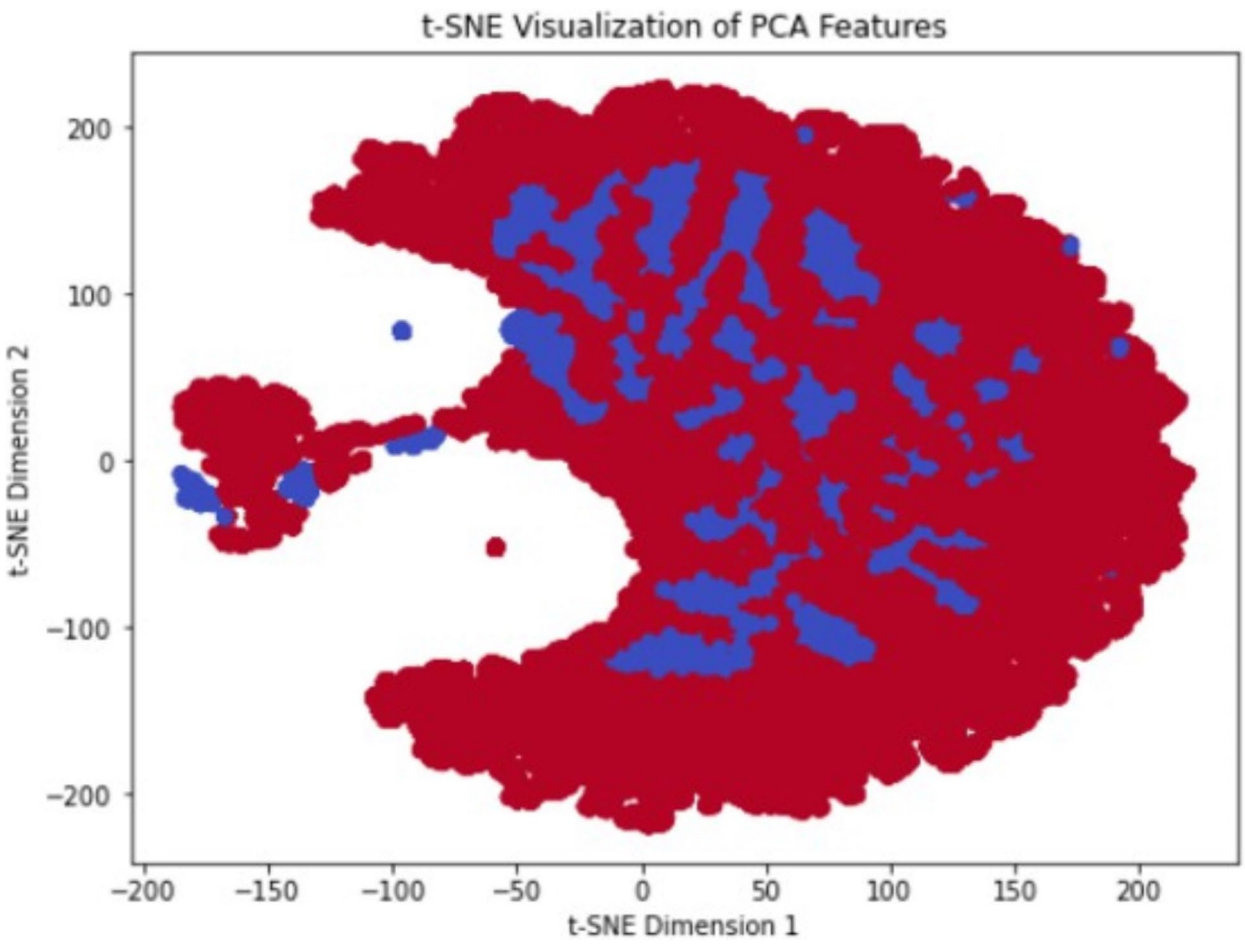

Fig. 3. t-SNE visulization of blastocyst and non blastocyst classification after training ResNet model on 11 cellular stages.

of the network is done by gating mechanisms. The reset gate and the update gate are the two gating mechanisms of the GRU.

In the model as depicted in Fig. 4 we used the two GRU layers with the first layer having 512 neurons and 2nd layer having 256 neurons. Dropout Layer of 0.4 is used to improve the performance of neural networks by preventing overfitting. Dense layers are used for the final binary classification. The loss function used is sparse categorical. The optimizer used is Adam (Adaptive Moment Estimation), a widely-used optimization algorithm. Adam adapts the learning rate during training for each parameter, making it effective for complex models and ensuring faster convergence by balancing speed and stability. The 2048 features extracted by ResNet50 are then given to this GRU Model. The dataset was divided into a 70:30 ratio, with 70% allocated for training and 30% for validation. The model was evaluated on the validation data, achieving an AUC of 0.93, a specificity of 77%, and a sensitivity 97%.

Discussions

This study introduces a two-stage model to predict blastocyst formation from the cleavage stage by integrating both spatial and temporal information. In the first stage, the ResNet50 architecture is employed to extract essential features from time-lapse images, achieving an accuracy of 75.96%. However, since blastocyst development is a dynamic process requiring sequential analysis, a Gated Recurrent Unit (GRU) model is incorporated in the second stage to capture temporal dependencies. GRUs streamline model architecture by combining the forget and input gates into a unified update gate, improving the efficiency of learning and enhancing the model's performance. The proposed model demonstrates strong predictive ability, with an AUC of 0.93, sensitivity of 97%, and specificity of 77%, emphasizing the importance of incorporating temporal information for accurate prediction.

Previous studies employed various architectures to address embryo classification challenges. For instance, Kanakasabapathy et al. used a combination of CNNs and genetic algorithms by classifying embryos into five categories. Classes 1 and 2 represented no-blastocyst formation, while Classes 3, 4, and 5 indicated high-quality blastocyst formation. However, the model's AUC values ranged between 0.51 and 0.77, suggesting limited predictive power without time-lapse imaging. Similarly, Lio et al. applied the DenseNet201 architecture with

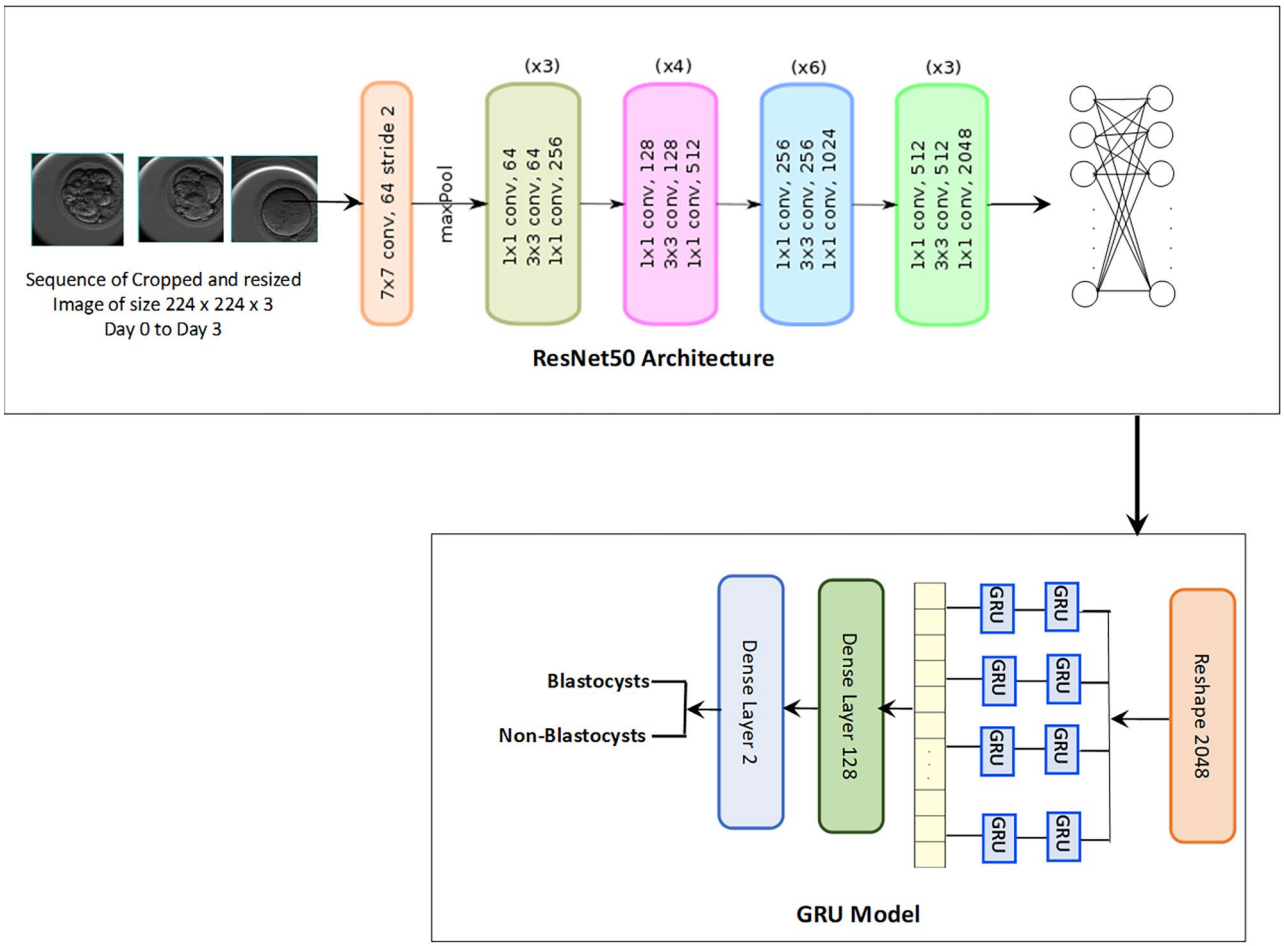

Fig. 4. ResNet50 architecture trained on day-0 to day-3 images. GRU model comprises two GRU layers with 512 units and 256 units, the dense layer predicts the final label.

Model	Morphological Features	Morphokinetic Features	Classification Type	Accuracy
CNN	6–10 cell image at 70HPI	Not Considered	Binary	63.9%
CNN with GA	6–10 cell image at 70HPI	Not Considered	Binary Multiclass	71.8% 35.56
DenseNet201-LSTM	Cell Counting Algorithm based on 5- classes	LSTM Cells are used	Binary	76.9%,
ResNet50 – LSTM (ours)	Feature extraction based on 11 classes	LSTM Cells are used	Binary	84.9%
ResNet50 – GRU (ours)	Feature extraction based on 11 classes	GRU Cells are used	Binary	93.05%

Table 2. Comparison of deep learning models based on morphological and morphokinetic features for embryo evaluation.

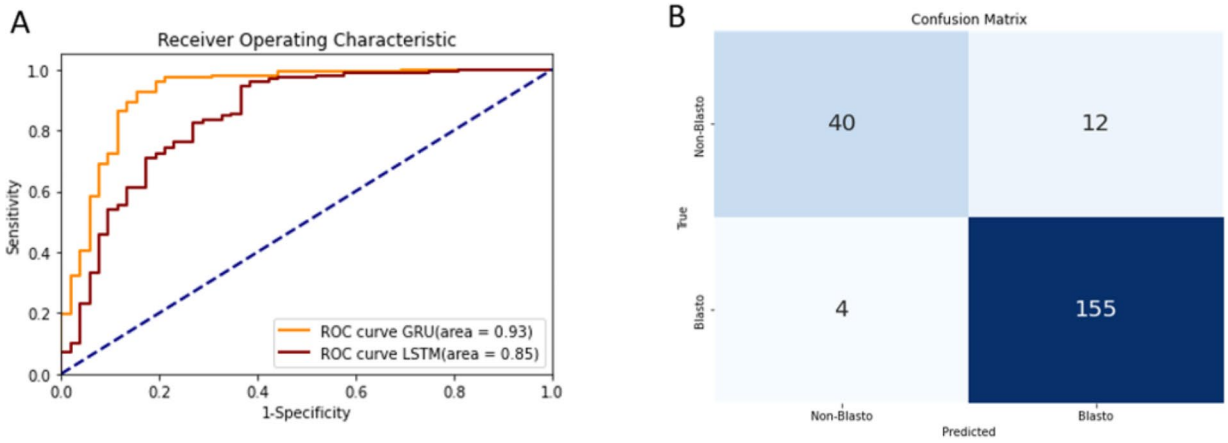

Fig. 5. **A**: Receiver operator characteristic (ROC) curves and area under the receiver operating characteristic of the ResNet-GRU and ResNet-LSTM Model **B**. Confusion matrix for predicting the blastocyst formation at day 3.

LSTM cells, achieving 78.2% accuracy, an AUC of 0.82, a sensitivity of 85.9%, and a specificity of 66.3%. The model comparison, along with the technique used for blastocysts classification, is summarized in Table 2.

We conducted an additional study to evaluate the performance of LSTM cells combined with the ResNet50 model and the classification of 11 cellular stages. The comparative results are presented in Fig. 5A, where the performance of both models is analyzed. As demonstrated, the GRU cells outperform the LSTM-based approach, achieving a higher AUC and a more balanced trade-off between sensitivity and specificity.

A key advantage of the proposed model is its ability to classify 11 cellular events, compared to the 5 events used in Lio et al.'s study. Research by Coticcho et al.[38] has shown that the timing of polar body appearance and pronuclear appearance is associated with the potential of embryos to develop into high-quality blastocysts. Furthermore, a study by Kenji Ezoe et al.[39] indicated that the timing of pronuclear fading significantly impacts pregnancy outcomes. The inclusion of these critical timing factors enhances the model's evaluation and predictive accuracy regarding blastocyst formation. The key developmental patterns that this model captures such as cleavage rate and morphology, are not inherently age-dependent. Hence the model works across all age groups.

Additionally, cropping the images to focus solely on the embryo ensures that the ResNet model analyzes only the critical embryonic structures and morphokinetic changes. By eliminating external elements such as residual culture media, reflections, or incubator artifacts, the model can better concentrate on features relevant to development. This approach enhances the accuracy and reliability of predictions.

Reducing the culture period from five to three days lowers costs by minimizing incubator time, media usage, and labor demands. Extending to Day 5 increases operational challenges, including the need for skilled embryologists, specialized equipment, and additional resources. It also risks embryo arrest, reducing the number of viable embryos for transfer or cryopreservation, making blastocyst-stage transfers more resource-intensive and expensive than cleavage-stage transfers, especially in low-resource settings.

However, the model has some limitations. This deep learning model is a classification model hence it classifies the embryo as blastocyst or non-blastocyst at Day 3. The grade is definitely a crucial factor in the success of IVF but considering the study by Zou et al.[40], low-grade blastocysts also result in successful pregnancies. According to this study the transfer of single low-grade blastocysts resulted in a reduced live birth rate of around 30% compared to 44% for single good-grade blastocysts. Another challenge arises from the nature of Time-Lapse Microscopy (TLM), which captures three-dimensional embryos as two-dimensional images at a single focal

depth. This limitation can impair the model's ability to detect deformed or overlapping cells accurately, affecting its predictions. Furthermore, the dataset used for training and testing is relatively small, limiting the model's generalizability. Expanding the dataset would likely improve the model's robustness and predictive accuracy.

In summary, the proposed two-stage model offers significant advancements over prior approaches, particularly in predicting blastocyst formation at 72HPI. Its predictive capability holds promise for personalized treatment, especially for low-responder patients, by providing insights that guide embryo selection and improve the chances of successful outcomes in assisted reproduction.

Conclusion

Our paper presents a novel framework for predicting blastocyst formation at the cleavage stage using time-lapse images, offering a more efficient and cost-effective approach. Considering a series of embryo images from insemination, our model demonstrates increased robustness compared to existing models. Furthermore, the categorization of embryo images into 11 classes based on cellular events enhances the predictive capability of our model. The GRU model captures the temporal dependencies and progression of cellular events over time, potentially providing a more holistic understanding of the developmental trajectory of each embryo. The combination of ResNet for feature extraction and GRU for handling temporal sequences represents a hybrid approach that aims to utilize both spatial and temporal information. With an impressive accuracy of 93%, our model represents a significant advancement in the field, highlighting the importance of integrating image and series characteristics for improved outcomes in assisted reproduction.

Overall, our work creates a deep learning system that can precisely predict blastocyst development at the cleavage stage. It will be an assist to the medical team. By developing this prediction model, we take a significant step toward leveraging deep learning for the analysis of medical images. This advancement supports embryologists and fertility clinics, leading to improved outcomes. The retrospective clinical trials serve as a validation of the effectiveness of the deep learning models developed. Integrating this model into clinical practice alongside ongoing trials can greatly assist in identifying suitable embryos for extended culture and high-potential blastocyst for transfer, hence enhancing the success rate of IVF.

Data availability

The datasets analysed during the current study are available in the Human embryo time-lapse video dataset repository, https://doi.org/10.5281/zenodo.7912264.

Received: 26 June 2024; Accepted: 6 November 2024
Published online: 14 November 2024

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Author contributions

K.K. Conceived the experiment(s), designed the study, conducted the experiments, analyzed the data, wrote the manuscript, reviewed, and edited the manuscript.P. D. supervised the study, and reviewed, and edited the manuscript.

Funding

The authors declare that they have not received funding for the current study.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Additional information

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