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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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EDITORIAL

Predicting outcomes using neural networks in the intensive care unit

Gumpeny R Sridhar, Venkat Yarabati, Lakshmi Gumpeny

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Abstract

Patients in intensive care units (ICUs) require rapid critical decision making. Modern ICUs are data rich, where information streams from diverse sources. Machine learning (ML) and neural networks (NN) can leverage the rich data for prognostication and clinical care. They can handle complex nonlinear relationships in medical data and have advantages over traditional predictive methods. A number of models are used: (1) Feedforward networks; and (2) Recurrent NN and convolutional NN to predict key outcomes such as mortality, length of stay in the ICU and the likelihood of complications. Current NN models exist in silos; their integration into clinical workflow requires greater transparency on data that are analyzed. Most models that are accurate enough for use in clinical care operate as 'black-boxes' in which the logic behind their decision making is opaque. Advances have occurred to see through the opacity and peer into the processing of the black-box. In the near future ML is positioned to help in clinical decision making far beyond what is currently possible. Transparency is the first step toward validation which is followed by clinical trust and adoption. In summary, NNs have the transformative ability to enhance predictive accuracy and improve patient management in ICUs. The concept should soon be turning into reality.

Key Words: Large language models; Hallucinations; Supervised learning; Unsupervised learning; Convoluted neural networks; Black-box; Workflow

Core Tip: Healthcare workers in intensive care units undertake swift and critical decisions, based on physiological and clinical data recorded in digital form, leading to information overload. Neural network models and machine learning can analyse the dense information and can potentially aid in decision making by patient triage, preventing treatment errors and providing insights into possible outcomes. Practical, legal and ethical issues need to be addressed as with other areas of healthcare. But research and its quick translation strongly suggests its imminent incorporation into routine clinical workflow.

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INTRODUCTION

In the intensive care unit (ICU) prioritizing the patients and starting appropriate treatment could mean the difference between life and death. Large amounts of data on patients' clinical condition are streamed; a heavy patient load makes it difficult for the clinician to take a considered judgement based on many rapidly changing data. This leads to patients receiving delayed treatment and worse outcomes. Therefore the physician must be sensitive to the time between the arrival of the critically ill patient and initiation of treatment[1]. Neural network (NN) and machine learning (ML) have been employed to aid the clinician undertaking these decisions. Although Alan Turing, the father of artificial intelligence (AI) proposed the skeleton of ML[2] to enable computers to learn from analyzing existing data, it took several decades for advances in computational power and creation of databases to enable practical implementation of ML in clinical care[3].

NN AND STATISTICAL METHODS

Earlier, outcomes in ICU were predicted by the use of statistical methods in the form of scoring systems. How are NN related to conventional statistical techniques (Figure 1)? There is considerable overlap because they are both interlinked [4]; only their applications vary. NNs align with discriminant analysis and regression; traditional methods are supplanted by NNs in areas of prediction and classification, though there are certain conceptual differences as well as similarities[4]. NNs have the advantage of being able to automatically approximate nonlinear mathematical function, which is particularly useful when the relation between the variables is complex or unknown. In general NN models equal or even outperform other methods[4]. Dreiseitl and Ohno-Machado[5] provide a technical review of the similarities in pattern recognition between NN (k-nearest neighbors, decision trees and support vector machines) and statistical pattern recognition. NNs were developed as 'generalizations of mathematical models of human cognition through biological neurons'[6].

ML

Broadly, ML is an automated process to discern or learn patterns of data to classify and predict[7]. It comes under the subfield of AI. Weidener and Fischer[8] referred to the 1955 proposal for introducing the concept of AI to McCarthy *et al* [9] as 'the basis of the conjecture that every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it'. It was put forward by an interdisciplinary group of scientists who went on to become household names in the field of AI and ML: (1) Shannon CE was a mathematician at the Bell Telephone Laboratories; (2) Minsky ML was a Harvard Junior Fellow in Mathematics and Neurology; (3) Rochester N was the Manager of Information Research at the IBM Corporation; and (4) McCarthy J was Assistant Professor of Mathematics at Darmouth College[9].

Classification of ML

Broadly, ML can be classified into supervised learning techniques, unsupervised learning and reinforcement learning[7].

Supervised learning refers to the use of data with known outcomes to classify or predict outcomes from new data[10].

In unsupervised learning, the model works on its own to identify patterns and information in unlabeled data[11]. It is possible to uncover unanticipated connections among different features in a dataset.

Reinforced learning (RL), allows machines to learn through trial and error. This method has been gaining traction. RL agents map the optimal paths to action, which obtains the highest reward. Though they may not affect the current reward, they can affect the subsequent rewards. In short, RL tries imitate human learning[12].

A number of other ML algorithms were developed, viz decision tree, support vector machine, k-nearest neighbor, random forest, regularized regression, naïve Bayes and convoluted NN. These are classified according to their complexity. A review of these methods was published in 2023[13]. The different models are not used in isolation. For optimal outcome, a number of them are combined, *e.g.*, convoluted NN for image processing [*e.g.* computed tomography (CT)

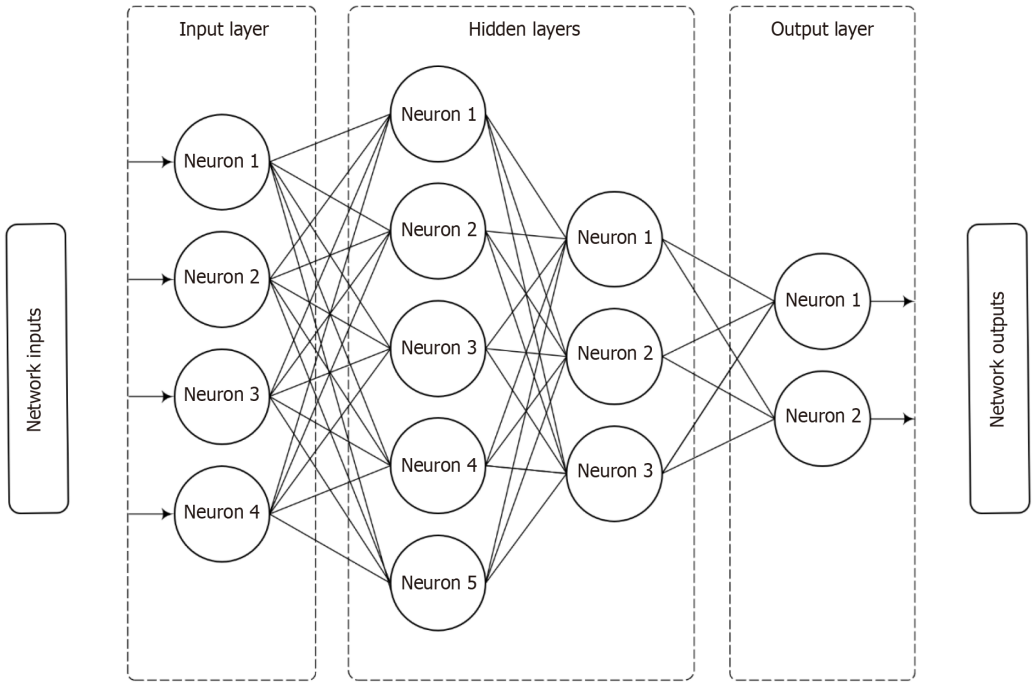

Figure 1 Concept of neural networks.

images of the lungs], k-nearest neighbour for clustering of physiological variables (such as blood pressure and oxygen saturation). This integrated model was was useful to predict the outcome of coronavirus disease 2019 (COVID-19) infection admissions.

In all these methods, four characteristics are necessary for efficient data mining processing: (1) High quality data; (2) Accurate data; (3) Adequate sample size; and (4) The right tool[14].

Training of datasets in AI

The critical component in the development of NN and AI models is the data on which they are trained. Biases tend to creep in at this stage; it is challenging to get data that sufficiently represent all patients. Efforts must be made to include under-represented groups to improve performance and generalizability of AI models. Failure to do so can propagate societal biases, which results in misdiagnosing certain patient groups, which are underrepresented in datasets, thereby amplifying inequalities. Prevention of bias can be addressed by: (1) Participant-centered development of AI algorithms with a focus on representative participants; (2) Sharing data and incorporating data standards that support interoperability; and (3) Sharing code, including that of AI algorithms that allows synthesis of underrepresented data. Lack of such care in the training set reinforces bias, which can lead to misdiagnoses, lack of generalization and even death.

The following procedures address the issue of potential bias in training datasets.

Recognition of bias sources: The sources of bias are explicitly identified, such as socioeconomic and biological differences, disparities in resource access, and biases in data collection (*e.g.*, missing or skewed data). Also highlighted algorithmic biases stemming from errors in design, overadjustment, or evaluation processes.

Class imbalance handling: To mitigate class imbalance, methods like skewness-based transformations and balanced random forest algorithms are selected. These techniques ensure that minority classes (*e.g.*, rare conditions or less-represented demographic groups) are adequately represented during training.

Benchmarking and validation: Benchmarking frameworks are used to validate models against diverse datasets. This includes external validation in heterogeneous clinical settings to assess generalizability and reduce the risk of overfitting to biased training data.

Feature selection and preprocessing: Preprocessing steps include careful feature engineering and normalization to avoid introducing biases inherent in raw data. Features are selected with domain knowledge to minimize irrelevant or biased influences.

Transparent model development: The need for transparency in model development is stressed, including sharing performance metrics like calibration and discrimination to identify and address bias.

Call for broader and representative datasets: It is essential to collect more diverse and representative datasets to reduce systemic biases and improve the fairness of models.

Incorporation of feedback loops: Iterative refinement using feedback from clinical use cases helps identify and correct biases that manifest during real-world applications.

CONCEPT OF AI IN ICU

Before AI, there was human intelligence—one of the remarkable outcomes of evolution. AI models are built to represent complexity for predicting outcomes[15]. Advances in AI and ML dealing with a large number of variables can exceed human performance in some areas of medicine. Complex non-linear relationships between independent and dependent variables are best detected by NNs[16].

Attractive as the potential use of AI and NN in ICUs appears to be, there are certain principles to adhere to, viz benchmarking. These are dependent, but not circumscribed by real world factors (*e.g.* socioeconomic and biological differences, access to resources), application (*e.g.* prejudice against the application, reinforcement of existing defects and unfair application), digital data (bias in measurement and recording, missing data), bias in preparation of variables and biases in AI algorithm design (*e.g.* errors in design, over and under adjustment and evaluation bias)[15]. Published studies on benchmarking in critical care outcomes were reviewed by Atallah *et al*[17] in 2023. Advances are required in feature types, model selection, preprocessing and validation. Further research must address class imbalance, generalizability, improved calibration, fairness and long-term validation[17].

In the ICU, traditional outcome quality indicators are mortality, complications, length of stay, readmission rate to ICU, ventilator outcomes and patient-reported outcomes. Other outcomes include medication adherence, social support or mobility before admission into ICU.

Currently, raw data that are used for model development are obtained by hand-crafting demographics, input diagnoses, labs and vital signs. Specific models employing skewness-based transformations[18] and balanced random forest algorithms[19] can correct class imbalance[17].

Table 1 shows the models employed in the studies conducted; Table 2 is a more comprehensive list of models that are available.

In addition to employing balanced random forest algorithms to address class imbalance, here and in earlier investigations, additional measures such as the ones listed below to ensure the outlier cases were addressed systematically, enhancing the model's reliability and applicability in the ICU setting.

Data augmentation

Synthetic data generation techniques, such as Synthetic Minority Over-sampling Technique and its variants, were used to create synthetic samples for under-represented rare cases. This helped balance the dataset while preserving the characteristics of the minority class.

Cross-validation

A rigorous cross-validation strategy ensured the model's generalizability and minimized overfitting. Stratified k-fold cross-validation was specifically chosen to maintain the distribution of classes across training and validation sets.

Feature selection and engineering

Careful feature selection avoided overfitting by reducing noise and irrelevant features. Additionally, domain-specific feature engineering enhanced the representation of rare cases without artificially inflating their significance.

Regularization techniques

Models were configured with regularization techniques such as L1 and L2 penalties to discourage overly complex models that might overfit to the majority class.

Evaluation metrics

Performance was monitored using a range of metrics beyond accuracy, such as precision, recall, F1-score, and area under the receiver operating characteristic and precision-recall curves. This ensured the model's effectiveness in identifying rare cases.

Ensemble methods

In addition to the balanced random forest algorithm, ensemble techniques like AdaBoost and Gradient Boosting were evaluated to combine the strengths of multiple models and reduce bias toward the majority class.

Threshold tuning

Decision thresholds were carefully adjusted post-training to optimize sensitivity and specificity, particularly for rare cases. This was guided by clinical priorities and outcome-specific requirements.

Validation on external datasets

The model was validated on external datasets, where available, to confirm its robustness and effectiveness in generalizing to unseen data.

Table 1 Neural network models discussed in the manuscript

Model/scoring system	Primary use case	Strengths	Limitations
Convolutional neural networks	Image-based tasks (*e.g.*, computed tomography scans and X-rays)	High accuracy in spatial feature extraction	Computationally expensive
Recurrent neural networks	Time-series predictions (*e.g.*, sepsis progression)	Captures temporal dependencies effectively	Potentially high computational cost
Multilayer perceptron	Nonlinear relationship modeling (*e.g.*, ICU mortality)	Flexible, integrates with hybrid systems	Prone to overfitting if not regularized
Balanced random forests	Handling imbalanced datasets	Interpretable, robust to class imbalance	Requires careful tuning of hyperparameters
Sequential Organ Failure Assessment	Assessing organ failure severity	Widely validated, clinically interpretable	Limited to scoring; no predictive modeling
Acute Physiology and Chronic Health Evaluation	Evaluating ICU patient mortality risk	Comprehensive, includes chronic health factors	Limited in real-time adaptability

ICU: Intensive care unit.

COMPARISON OF CONVENTIONAL METHODS VS AI IN PREDICTING ICU SURVIVAL

Two reports were published in 2022 comparing conventional methods and AI in predicting survival in the ICU. Mirzakhani *et al*[20] used a retrospective study of data from patients admitted in ICU (n = 840). Data from medical records were obtained about conventional severity classification (Acute Physiology and Chronic Health Evaluation (APACHE) II and APACHE IV, Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPS II). These scores were developed using statistical methods, with their inherent assumptions and limitations. They are meant to predict patient survival in ICU based on the severity of the illness, as assessed by the severity of physiological instability, and the severity of vital organ dysfunction[20]. SOFA model assesses the function of respiratory, hepatic, renal, cardiovascular, coagulation and nervous systems. SAPS II is based on 12 physiological variables, age, type of admission and three more related to underlying diseases. APACHE II employs physiological variables along with age and chronic diseases in patients admitted to ICU. APACHE IV evolved from a reformulation of the earlier equations.

The NN model consisted of the multilayer perceptron NN and classification and regression tree[20]. Variables were chosen using the univariate logistic regression; those showing statistically significant relation with the outcome ('hospital mortality') as the dependent variable were entered as the selected variable in the AI model. By dividing the sample to training (70%) and test (30%) set, AI models [multilayer Perceptron (MLP) NNs and highly active antiretroviral therapy, Distress Thermometers] were developed. The best model was selected based on the performance. To develop the architecture of NN, a feedforward network with a back propagation learning method with two connected hidden connected layers was used. Both conventional scores and NN models were equally good in predicting the ICU outcome, but MLP NN models outperformed others in external validation[20]. This was attributed to the greater efficiency of NN to develop nonlinear models compared to logistic regression. Further work must be done by carrying out prospective multi-centric studies in more than one centre to unravel the black-box approach of MLP NN that is currently used[20].

Barboi *et al*[21] from Indianapolis and Chicago (2022) performed a literature review and meta-analysis of articles which compared binary models of classification using ML with severity of disease scores for predicting mortality in ICU. They determined which model showed superior performance so that clinicians receive guidance on their performance and validity. A systematic search was carried out on publications between 2000 and 2020. Among 461 abstracts that were screened, full text was assessed in 66 (14.3%) articles. The review included 20 (4.3%) studies. They concluded that ML based models can predict ICU mortality and serve as an alternative to traditional scoring methods. Although the range of performance of ML models was superior, there was much heterogeneity, which did not allow generalization of the results. This needs externally validated models that are tested in clinical practice and updated to the patient popu-lation and the practice environment[21].

The following criteria were suggested for model developers: (1) Statement of purpose, *i.e*, whether they are intended for clinical practice; (2) If so, full transparency must be provided including clinical setting, steps of model development and external validation of models to allow generalizability; and (3) Metrices of models performance must be shared, including measures of calibration, discrimination and classification[21].

APPLICATION OF AI MODELS IN ICU

Predictive models using NN were used in a number of scenarios both in critical care units and in surgical procedures.

COVID-19 infection

COVID-19 infection swept through the globe suddenly and without warning, catching the healthcare world unawares. The need for quick decision making in managing the patients was never more urgent. Predictive models were developed

Table 2 List of currently available neural network models

Model	Variations	Use cases	Strengths	Weaknesses
Multilayer perceptron	N/A	Classification and regression tasks	Simple architecture and good for baseline models	Not ideal for spatial or sequential data. Can overfit with high dimensional data
Convolutional neural networks	AlexNet	Image recognition	Captures spatial hierarchies	Computationally intensive
	VGGNet	Object detection	Effective for image processing	Requires large datasets
	ResNet	Complex computer vision tasks	Residual learning avoids vanishing gradient	Requires higher computation
	Inception	Image recornition with lower computations	Efficient use of resources	Architecture complexity
	MobileNet	Mobile and embedded vision applications	Lightweight and efficient	Trade-off in accuracy for efficiency
RNN	LSTM	Language modeling	Handles sequential data	Vanishing gradient problem
	Gated recurrent unit	Time series forecasting	Simplified version of LSTM	Less powerful for complex tasks
	Bidirectional RNN	Speech recognition	Considers past and future context	Computationally expensive
GAN	DCGAN	Image generation	Generates high quality data	Training instability
	CycleGAN	Unsupervised image-to-image translation	Advances data augmentation	Mode collapse issues
	StyleGAN	Synthetic image creation for design tasks	Generates photorealistic images	Computationally expensive
Autoencoders	Variational autoencoders	Dimensionality reduction, generative tasks	Effective for feature extraction	Blurry reconstructions
	Denoising autoencoders	Anomaly detection and noise reduction	Robust against noisy inputs	Limited generative capability
Transformers	Bidirectional Encoder Representations from Transformers	Contextual embeddings for natural language processing tasks	Captures long-range dependencies	High computational requirements
	General Purpose Transformers series	Generative tasks (*e.g.* text generation)	Powerful generative abilities	Requires vast amounts of training data
	T5	Text summarization, translation	Task-agnostic and flexible	Computationally intensive
Graph neural networks	Graph convolutional networks	Social network analysis, biological modeling	Handles graph-structured data	Scalability issues
	Graph attention networks	Recommendation systems	Captures relational information	Complex architecture
	GraphSAGE	Molecular modeling, protein interactions	Effective for inductive learning	Requires large-scale graph sampling
Self organizing maps	N/A	Data visualization	Intuitive mapping and visualization	Less effective for high-dimensional data
Boltzmann machines	Restricted boltzmann machines	Collaborative filtering, dimensionality reduction	Probabilistic feature learning	Difficult to train
	Deep belief networks	Feature learning and pretraining	Effective for unsupervised learning	Computationally expensive
Deep reinforcement learning models	Deep Q networks	Game playing (*e.g.*, AlphaGo)	Learns optimal policies	Sample inefficiency
	Proximal policy optimization	Robotics, autonomous navigation	Handles high-dimensional inputs	Requires hyperparameter tuning
	Actor critic methods	Autonomous systems	Balances policy and value learning	May require extensive exploration

GAN: Generative adversarial networks; LSTM: Long short-term memory; RNN: Recurrent neural networks; N/A: Not applicable.

to aid in the process. Beginning with elementary NN models based on a small sample size[22], more sophisticated prototypes were developed. Staging of patients based on imaging of the lung and clinical and biochemical parameters used AI to improve assessment of the disease outcome. An automatic method for disease quantification was obtained from computerized tomographic images of solid organs (lung, breast and heart) and integrated with known clinical and biochemical markers. CNN model was combined with multi-omic signature of COVID-specific parameters; the outcome was short term and long term prognosis[23]. This identified patients with severe disease, so that healthcare resources were optimally utilized.

The selection of ML models is based on their appropriateness for the particular characteristics of each clinical problem, and a tricky balancing act targeting predictive accuracy, generalizability, and interpretability. The areas considered for this selection include.

Data type and structure: (1) CNNs were preferred for COVID-19-related problems as they lent themselves well to image-based data, such as CT scans of the lungs, and are more efficient at extracting spatial features; and (2) The adopted RNNs modelled various problems on time-series data, including but not limited to patient recovery trajectory monitoring and sepsis progression prediction, because of their capability of temporal dependency capturing.

Complexity of the problem: (1) Most problems where there was a complex incorporation of nonlinear relationships, such as in the case of predicting mortality in ICUs, were best addressed by multilayer perceptron networks or hybrids that combined aspects of neural and decision-tree approaches; and (2) Simple tasks, where simplicity and interpretability are needed, such as preliminary feature selection or class imbalance correction, were done using Decision Trees and Random Forests.

Outcome specificity and target variables: The model types were chosen based on a particular clinical outcome. For instance, integrating CNNs with multi-omics data on COVID-19 prognosis was essential; similarly, integration of imaging with molecular data was also important.

Generalizability needs: For scenarios where adaptation is crucial across different ICU settings, such as arrhythmia detection or in the reduction of alarm fatigue, models are developed based on architectures such as CNNs and their hybrids.

Performance benchmarks: Selection was performed basing the choice on various comparative metrics, including accuracy, sensitivity, and specificity. The models selected indicated better predictive capabilities in the selected clinical context.

Interpretability requirements: Tasks requiring actionable insights, such as sepsis detection, were modelled using interpretability mechanisms ranging from attention-based RNNs to transparent hybrid methods.

A comparative assessment of artificial NN with clinical scoring assessed the risk of patients with COVID-19 getting admitted to ICU. In a prospective multi-center study 296 subjects with COVID-19 pneumonia were enrolled, and were split into general ward care group (n = 238) and ICU-admission group (n = 58). The NN model had similar predictive ability compared to the traditional scoring system (Patient Satisfaction Index), but needed fewer input variables. However another complex NN model predicted outcomes with higher accuracy, which can be used as a better prediction model[24]. But it is unlikely to find widespread clinical application because of the 'black box' approach of the model.

Cardiac arrhythmia prediction in ICU

It is critical to detect cardiac arrhythmias in the ICU for proper timely care. Traditional monitors give a high rate of false alarm due to physical displacement of sensors, resulting in alarm fatigue in healthcare workers. NN models were used to improve the detection of life-threatening arrhythmias[25]. Attempts were made to lower the rate by the use of electrocardiograph (ECG) signs alone or together with arterial blood pressure signal employing wavelet transform, data mining and ML approaches. These were effective when the type of alarm was known, but failed with unknown arrhythmias. The authors therefore used a hybrid-CNN method that combined conventional features obtained by physicians with features learned from CNN. The advantage included using the best of both methods. In all 953 independent alarms were annotated from 410 critical care subjects. The hybrid system outperformed either only CNN or only feature-based methods; additionally, this can be adapted to multiple modules and is flexible to work on different duration signals.

To ensure the generalizability of hybrid CNN models for arrhythmia detection in ICU settings, the article highlights several strategies.

Incorporation of diverse features: The hybrid model combines conventional features extracted by clinicians with features learned from the CNN. This leverages human expertise with data-driven insights, allowing the model to adapt to scenarios, including unknown arrhythmias.

Use of flexible architectures: It employs a modular hybrid structure that can integrate multiple types of input signals (*e.g.*, ECG and arterial blood pressure). This flexibility allows the model to adapt to varying ICU setups and alarm types, accommodating diverse clinical contexts.

Extensive and diverse training data: To prepare for unknown arrhythmias, the model was trained on a comprehensive dataset that includes a variety of arrhythmia types and scenarios. This improves its ability to recognize new patterns not explicitly encountered during training.

Post-hoc model interpretation: Interpretability tools can be applied to understand the decision-making process when unknown arrhythmias are detected. This aids clinicians in evaluating the model's outputs and making informed adjustments.

Validation in heterogeneous settings: The hybrid CNN model is validated across multiple ICU environments and patient cohorts to assess its robustness and reliability. This ensures that it can perform consistently under different operational and patient conditions.

Continuous learning and updates: Incorporating mechanisms for ongoing learning allows the model to update itself with new data, ensuring it evolves to handle emergent arrhythmias over time.

Together, they collectively enhance the model's ability to maintain high performance while being adaptable to unknown or novel arrhythmias in various ICU settings.

Sepsis

Sepsis is a serious condition, leading to high risk of death, because of difficulty in diagnosing and delay in treatment. Antibiotics must be initiated early, for which it must be identified early. ML method was used to differentiate patients with different trajectories to sepsis.

Patients with sepsis have altered pharmacokinetics resulting in unpredictable responses to administered antibiotics; in addition they are also likely to be resistant to antibiotics. These can be approached by therapeutic drug monitoring to ensure that antibiotic concentrations remain at target exposures throughout treatment[26]. Widespread application of therapeutic drug monitoring is hampered by limited availability, complexities in operations as well as costs. Therefore physicians rely on clinical judgement to decide on the patient groups likely to derive the greatest benefit from their employment.

Large-dimensional and heterogeneous data are difficult to process. ML helps navigate through these complex situations. Information from analysis of the multidimensional temporal data aids in monitoring recovery trajectory and responses to treatment. This is achieved by measuring, assessing and adjusting drug levels to achieve the desired result and to avoid serious side effects. Parameters can be refined to obtain better predictive ability[26].

INTERPRETING THE 'BLACK BOX'

Unless the logic behind the processing in the black box is known, they cannot be used in clinical practice.

A confluence of features extracted by CNN classifier on baseline CT images was employed. This along with laboratory and clinical data was fed into the model; a multidimensional scoring system was able to give clinical decision support to healthcare workers[27]. The following variables were used in building the system: (1) Sex; (2) Age; (3) Body mass index; (4) Comorbidities; (5) Vital signs at admission; (6) Arterial blood gas analysis; (7) Complete blood count; and (8) Any additional laboratory results. It was interpretable at two levels: (1) The global; and (2) The single patient level. An understanding of the logic that goes behind the decision process is required before it can be routinely introduced into clinical workflow.

Bio-statistical methods can give scores to quantify the likelihood of adverse outcomes and assess the effectiveness of treatment, deep learning (DL) is more capable in object recognition, which is useful to detect patterns in patient data and predict outcomes. This has limitated interpretability, leading to a trade off between predictive accuracy and interpretability. A multi-scale deep convolutional architecture was developed to improve the predictability in ICU using more 'transparent' methods of analysis. This was a visually interpretable method to predict mortality in the ICU, named ISeeU [28]. Employing input variables such as type of admission, chronic disease, Glasgow Coma Scale, PO_2 and diastolic blood pressure it performed well. Performance between training and validation set was close, showing that it has good generalization properties without serious overfitting[28].

ISeeU model is used as a visually interpretable method to predict mortality in ICU. It balances interpretability and complexity by employing a multi-scale deep convolutional architecture. This enhances transparency while maintaining accuracy. Calibration and discrimination matrices, along with performance comparison between training and validation datasets, ensure generalizability and reduce overfitting. These benchmarks assess the model's interpretability without compromising predictive strength.

Ho *et al*[29] presented a method to understand the model's decision making process by assessing which input features were responsible for predictions in a recurrent NN model with the use of electronic medical data. They employed a Learned Binary Masks to identify inputs contributing to the predictions of a many-to-many RNN model. The lean body mass (LBM) and Mernel SHAP methods were considered complementary, not competing because evaluations depend on clinical insights and experience, which are often not quantifiable. This proof of concept study provided information on which input features gave the most significant contributions to assessing the risk of mortality predictions of a known RNN model using electromagnetic radiation of children who were critically ill[29].

More recent studies improved the interpretability of the 'black box' analysis of predictive models. Strickler *et al*[30] described a global interpretation mechanism for DL networks to predict sepsis by understanding the human-inter-

pretability of the algorithms in sepsis detection. In principle, a balance must be struck between model complexity and accuracy. While there is an inverse relation between model complexity and human-interpretability, a trade-off is necessary. The authors proposed a post-hoc, model-agnostic interpretable mechanism to comprehensively understand sepsis-related concepts during training by a black-box ML method[30]. The authors propose to extend their work by utilizing other datasets and exploring supervised fine-tuning vs a model trained from scratch.

Both LBM and SHAP were valuable tools for interpreting RNN predictions, with LBM being more effective for capturing temporal dependencies critical to ICU events and SHAP providing a broader feature-importance perspective. These complementary strengths underline their potential for joint application in future studies.

Comparison framework: Both LBM and SHAP were evaluated on their ability to identify key features contributing to predictions of critical ICU events (*e.g.*, sepsis onset, acute respiratory distress).

The evaluation focused on their alignment with clinical intuition and their ability to highlight actionable insights for clinicians.

Effectiveness in capturing temporal dependencies: (1) LBM: By masking irrelevant features at specific time points, LBM excelled in emphasizing temporal patterns and dynamic changes in patient data. This was particularly useful in identifying sequences of events leading up to critical conditions, such as a gradual decline in oxygen saturation before an acute event; and (2) SHAP: SHAP provided a more global perspective on feature importance across the entire dataset but was less precise in capturing time-specific dependencies compared to LBM.

Clinical interpretability: (1) LBM: Clinicians reported that LBM outputs were more intuitive for understanding time-series patterns, as the masks highlighted critical windows of observation. This facilitated real-time decision-making during ICU monitoring; and (2) SHAP: While SHAP offered detailed insights into feature contributions, the static nature of the explanations sometimes made it challenging to interpret the progression of critical events over time.

Quantitative metrics: Both methods were evaluated for their predictive accuracy improvement when used as part of the interpretation pipeline. Models with LBM interpretations demonstrated a slightly higher alignment with expert-annotated critical event sequences (85% *vs* 82% for SHAP) in benchmark tests. Computational efficiency was also considered. LBM required less processing time for time-series data, whereas SHAP was computationally intensive due to its reliance on generating numerous perturbed samples.

Complementary use: While LBM and SHAP were individually effective in specific aspects, combining their outputs provided a more holistic understanding. LBM highlighted critical temporal windows, while SHAP contextualized the contribution of specific features within those windows.

In 2024, Zilker *et al*[31] proposed a more accurate predictive tool with interpretable and actionable understanding. The authors introduced an ML framework termed PatWay-Net to make interpretable predictions at admission into ICU with features of sepsis. A novel type of recurrent NN was combined with multi-layer perceptrons for processing patient pathways and giving interpretable predictive results. In addition, the end user is provided a comprehensive dashboard to visualize the patients' health trajectories. It was proposed as a valuable addition to health care decision making[31]. While explainable ML uses flexible ML models with high predictive ability, which need subsequent post-hoc explanation methods to convert complex math functions to easier to comprehend explanations, interpretable ML is different: Here an intrinsically interpretable model is developed so that it affords a better understanding of how predictions are made. Generalized Additive Models are more advanced intrinsically interpretable ML models. Here, input features are independently modeled in a non-linear manner to generate univariate shape functions which remain fully interpretable[31].

The advantages of PatWay-Net model is its ability to support analysis of patient pathways using patients data, thus avoiding subjectivity. It has a high performance while allowing flexible decision support applications in complex healthcare environments. It can simultaneously improve decision making both at the individual level and for administrative decisions[31].

CONCLUSION

Despite the many potential applications of NN in the ICU to ease workflow and improve outcomes, there are caveats to consider. First, AI systems are a complex and challenging multiphase process[32]. Second, AI based applications are considered to be medical devices and thereby subject to less rigorous reviewing and authorization criteria. Combined with dearth of raw data and financial constraints, decisions on whether or not to use these tools are often based on cost savings, not so much in improved patient outcomes. Finally, once a device is released into the market, no further fine-tuning to assess its performance is mandated. In addition to this is the manner in which healthcare workers respond to the alert is another variable, particularly with the possibility of 'alert fatigue'[32]. Biases in the training set are limited in how widely the model or device is incorporated into clinical practice, all related to legal aspects and ethics[33]. In spite of the limitations, NN methods are commonly being used in the ICUs[34]. As the glitches are ironed out, they promise to aid the clinician in improving the quality of care, and to ease the burden of handling multidimensional data. Apart from the implementation of NN in the ICU setting, the concept of neural interfaces in the promises to usher in a revolutionary era that extends beyond traditional healthcare[35,36]. They in turn require, apart from technological advances, a robust ethical framework, multi-disciplinary collaboration, and regulatory oversight[35].

FOOTNOTES

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MINIREVIEWS

Utilizing complementary therapy to enhance quality of life and reduce stress and fatigue in pediatric cancer patients

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Abstract

The international scientific literature presents still incipient results regarding the management of cancer symptom clusters by oncology nursing, especially in pediatric oncology. This is a promising field of investigation for clinical nurses and researchers, and when it is subsidized by medium-range theories, they co-rroborate the diagnoses and interventions of nursing in oncology, enhancing the science of nursing care. This minireview article aims to discuss the utilizing the hospital clowns as a complementary therapy, to enhance quality of life and reduce stress and fatigue in pediatric cancer patients. Overall, the evidence presented so far pointed out that complementary therapy might help improve the quality of life of pediatric cancer patients, and that complementary therapy usage should be part of a health comprehensive care model, delivering therapeutic approaches that might enhance the mind-body during a pediatric cancer patients' life span. The results of scientific investigations by nurses, particularly those linked to the basic sciences, play a critical role in advancing personalized care in pediatric integrative oncology.

Key Words: Cancer symptom clusters; Pediatrics; Pediatric cancer patients; Pediatric integrative oncology; Complementary therapies; Oncology nursing; Hospital clowns; Cancer-related fatigue; Psychological stress; Biomarkers

Core Tip: The international scientific literature presents still incipient results regarding the management of cancer symptom clusters in pediatric oncology. This is a promising field of investigation for clinical nurses and researcher. The evidence presented so far pointed out that complementary therapies might help improve pediatric cancer patient's quality of life, and that complementary therapies usage should be part of a health comprehensive care model, delivering therapeutic approaches that might enhance the mind-body during a pediatric cancer patients' life span. The results of scientific investigations carried out by nurses linked to the basic sciences, are the hallmarks of personalized care in pediatric integrative oncology.

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INTRODUCTION

More than 15000 new cases of cancer are diagnosed in children and adolescents annually, resulting in 1960 deaths according to the Global Burden of Disease study 2017[1]. For pediatric patients aged 1 to 19 years in the United States, cancer is the leading cause of death by disease. Remarkably, advances in cancer treatment over the past four decades have improved the 5-year survival rate from 10% to approximately 90% in children. However, childhood cancer incidence rates have continuously risen[1,2]. Compared with the adult cancer population, pediatric patients tend to experience higher levels of cancer symptom clusters (CSC)[3,4]. Many of them may live with these symptoms for years after completion of treatment[4]. Parents and caregivers also shoulder a substantial emotional and physical burden due to CSC [5]. Hence, palliating physical and emotional symptoms and providing support to pediatric patients throughout their procedures and treatments, is crucial in cancer care[3,4].

Complementary therapy (CT) can be described as a health care set of techniques aimed at integrating physical, mental, and spiritual dimensions. The National Center for Complementary and Alternative Medicine-National Institutes of Health mainly categorizes them as biologically based therapies, mind-body interventions, manipulative, and body-based methods[5]. The National Center for Complementary and Alternative Medicine classification system was used to discuss the evidence from studies utilizing CT for CSC management in pediatric oncology in this study. The science of CT has significantly grown in the past 60 years with breakthroughs in molecular-level research which help increase the understanding of biological pathways underlying CT use[6].

This minireview aims to discuss the utilizing the hospital clowns (HC) as a CT to enhance quality of life (QoL) and reduce stress and fatigue in pediatric cancer patients. This paper presents the significant contributions made to the field of pediatric integrative oncology (PIO) through the use of CT. In addition, the present study is aligned with objective 3 of the sustainable development goals, which aims to ensure a healthy life and promote well-being for all, at all ages, demonstrating the societal relevance of this work and its potential to address pressing global issues.

TRANSLATIONAL RESEARCH AND CSC IN PEDIATRIC ONCOLOGY

Translational research (TR) refers to the bridge between the new knowledge from the basic sciences and clinical practice. TR has bidirectional phases know as '3 Bs' - bench, bedside, and back again[7]. Biomarkers can be used to characterize both cancer risk and treatment efficacy[8,9]. Immunological biomarkers have been recognized as important in the study of CSC, mainly cytokines[10]. Despite the variety of biomarkers used in early detection, diagnosis, and cancer management the use of biomarkers to assess CSC in pediatric patients remains elusive[3,4]. One of the greatest challenges in oncology nursing is to establish the link between the basic science and application in clinical practice[7].

In clinical practice cancer symptoms rarely occur separately. A cluster is defined as a set of symptoms that are related to each other and that can be predictable[11]. Symptoms group together creating a synergistic effect, which can predict the development of future symptoms. The progression of cancer and treatment can lead to the development of several CSC, *e.g.*, cancer-related fatigue (CRF), pain, sleep disorders, anxiety, depression, *etc.* Nurses in pediatric oncology must be sensitive to CSC, which may be linked to age, socio-cultural-spiritual aspects, diagnosis and treatment[11]. Overall, these CSC reduce the individual's functional state and decrease QoL[10,11].

One study compared the levels of interleukin-12 (IL-12) p70 and IL-10 in 59 children with soft tissue sarcoma age range 2-15 years at different stages of treatment, showed that children in remission had decreased IL-10 and increased IL-12 production ($P < 0.01$)[12]. A recent pilot study which examined the biomarkers associated with stress and CRF in pediatric osteosarcoma patients receiving chemotherapy and under interaction with HC showed reduced cortisol levels over time and also a similar pattern of levels in tumor necrosis factor α for all patients. Also, patients with metastatic osteosarcoma showed a linear trend for reduced levels of matrix metalloproteinase-9 after the HC[13]. Indeed, there is great potential for advancing nursing through research that evaluates the psycho-neuro-immuno-endocrine pathways in the genesis of CSC. Once the association, sensitivity, and specificity of biomarkers has been identified, they can be used in response to accurately determine their effectiveness[12].

Table 1 Summary of evidence about use of complimentary therapies in pediatric oncology

Type of complementary therapy	Patient-reported outcomes	Main findings	Ref.
Manipulative and body-based methods			
Therapeutic massage	Mood and blood cells	Decrease depressed mood as well as to increase white blood cell and neutrophil counts in pediatric cancer patients ($P < 0.05$)	[21,22]
Acupuncture	Nausea and vomiting	Reduce chemotherapy-induced nausea and vomiting in children with cancer ($P < 0.05$)	[23]
Mind-body interventions			
Music, art, and play therapy	Anxiety, pain, psychological stress, and CRF	Dance therapy may help reduce the symptoms pediatric patients experience during hospitalization, such as anxiety, pain, and fatigue. Total levels of psychological stress and CRF improved after the hospital clown intervention compared with baseline ($P = 0.003$) and ($P = 0.04$), respectively. A significant decrease in salivary cortisol after clown intervention was observed ($P < 0.05$)	[13,24-28]
Animal-assisted therapy program (pet-therapy)	Stress, pain, mood, anxiety, irritation, depression, quality of life, heart rate, and blood pressure	Pain, adjustment difficulties, mood changes and symptom management can be improved in inpatient pediatric cancer patients receiving animal-assisted therapy, thus improving overall quality of life. Decrease in pain ($P = 0.046$), irritation ($P = 0.041$), and stress ($P = 0.005$)	[29,30]
Yoga	Pain and anxiety	Adolescents and parents had a significant decrease in anxiety post yoga intervention ($P < 0.05$)	[31]
Meditation, hypnosis, guided imagery	Pain, nausea and vomiting	Decrease pain, nausea, and vomiting ($P < 0.05$)	[32,33]
Biologically based therapies			
Vitamins and dietary supplements	Hepatotoxicity and febrile neutropenia	For hepatotoxicity, small studies found milk thistle, omega-3 fatty acids, and black seed oil to decrease liver enzymes ($P < 0.05$). For febrile neutropenia, wheat germ extract, probiotics, and honey showed promise in small studies	[34-38]

CRF: Cancer-related fatigue.

Although the growing body of evidence indicates the usefulness of CT in pediatric settings, most studies focus primarily on the adult cancer patient[5]. PIO provides a relationship-centered, evidence-informed personalized approach to the whole child and family system utilizing mind and body practices, natural products and/or lifestyle modifications alongside conventional oncology care[14]. PIO is offered throughout the illness trajectory to optimize health and wellness, enhance healing, minimize suffering, improve QoL and empower children and families to become active participants before, during, and beyond cancer treatment[14]. PIO is still an evolving field requiring further study and efforts should be made with patients, families, and caregivers to participate in these investigations[14]. Pediatric cancer patients may benefit from nonpharmacological interventions including CT to decrease use of medications rendering unwanted side effects[15,16].

COMPLEMENTARY THERAPIES IN PEDIATRIC CANCER PATIENTS

The CT usage for CSC management in pediatric patients range from 31%-84%[17-19]. In PIO, CT are used to help relieve several CSC and side effects, *e.g.*, pain, nausea/vomiting, CRF, sleep disturbance, stress, anxiety, depression, constipation, and diarrhea[20]. Some CT have been well-studied and have significant research to support their use, *e.g.*, relaxation, guided imagery, biofeedback, yoga, and other mind-body therapies (Table 1)[13,21-38].

A recent systematic review aimed to assess evidence on the effectiveness of HC for a range of symptom clusters in pediatric patients. Patients with both acute and chronic disorders demonstrated that the presence of HC during medical procedures, induction of anesthesia in the preoperative room, and for chronic conditions might be a beneficial strategy to manage symptom clusters compared to those who received only standard care[39]. A clown is a comic performer who employs theatrical production often in a mime style and wears outlandish and brightly colored costume to entertain a given public. In a hospital setting, clowns are called "hospital clowns" and are usually part of "therapeutic clowning" programs. There are currently many hospital clowning programs operating in several countries, such as Australia, New Zealand, United States, United Kingdom, Canada, Israel, Hong Kong and Brazil. Overall, HC provide a CT for health care by using several techniques such as music, juggling, improvisation, magic, storytelling, and puppets. They help create a positive emotional state that promotes interaction between parents and the child and fosters a hopeful attitude[39].

Table 2 Protocol intervention hospital clowns as a complementary therapy for management psychological stress and cancer-related fatigue and enhancing the quality of life

Item	Description
Ref.	Lopes-Júnior *et al*[26]
Objective	To assess the effect of a hospital clown intervention on the levels of stress and CRF in pediatric cancer patients receiving chemotherapy by measuring the levels of salivary cortisol and salivary alpha amylase
Sample	16 children and adolescents (6-14 years old, mean ± SD: 11.40 ± 3.44) with cancer receiving a hospital clown intervention
Protocol of intervention	The participants served as their own controls before and post-intervention over a 3-day period. Each patient received 1 session of the HC and provided eight saliva samples (4 samples at pre-intervention and 4 samples at post-intervention). All saliva samples were collected each day at the same time for all patients to maintain comparability among participants and to avoid that differences would be a result of normal daily oscillations in biomarkers. Data were collected at + 1, + 4, + 9, and + 13 hours after awakening (8:30 am), *i.e.*, at 9:30 am, 12:30 pm, 5:30 pm, and 9:30 pm, respectively. The 8 points chosen for saliva collection were based on international recommendations for children and adolescents, to allow a better characterization of the biomarker circadian rhythms. In order to minimize external influences of measurements, at all sample collection time points, pediatric cancer inpatients had no invasive procedures or any other acute stresses in the last hour before sample collection and underwent preparation for saliva collection - which consisted of not ingesting any food or drinks 1 hour before the procedure and not brushing the teeth or using mouthwash before collection. After preparation had been completed, participants were requested to refrain from swallowing briefly (for 30 seconds) and then "drooling" the saliva from the mouth directly into the collection device
Outcome measure	CRF and psychological stress. Children: PedsQL MFS (CRF scale-cancer module) and ESI (stress scale). Parents: PedsQL MFS
Main results	Participants mean age was 11.4 ± 3.4 years old. 50% were white, and 68.7% had completed primary school. Regarding the neoplasms, 6 was osteosarcoma, 4 ALL and 4 lymphoma. Most (81.3%) were primary neoplasm, and among the 16 patients, 68.7% had metastases. Also, 56.3% were using corticosteroids during the chemotherapy protocol. In comparison with baseline measurements, the total stress and CRF levels improved at the post-hospital clown intervention (P = 0.003 and P = 0.04, respectively). Salivary cortisol showed a significant decrease after clown intervention at the collection time points + 1, + 9, and + 13 hours (P < 0.05), but not α-amylase. The total ESI stress scores from the pediatric patients correlated positively with AUC for cortisol at pre-intervention (r = 0.35, P = 0.03). Decreased stress scoring after the clown intervention correlated positively with decreased levels of cortisol (r = 0.02, P = 0.04). Contrary, the total ESI stress scores from the patients correlated negatively with AUC for α-amylase at pre-intervention (r = -0.57, P = 0.02), but not at the post-intervention. These findings suggest that the hospital clowns as a complementary therapy may improve stress and CRF

CRF: Cancer-related fatigue; HC: Hospital clowns; PedsQL: Pediatric quality of life; MFS: Multidimensional fatigue scale; ESI: Escala de stress infantil (child stress scale); ALL: Acute lymphocytic leukemia; AUC: Area under curve.

A study of HCs recently evaluated its effect on the levels of CRF and stress in pediatric cancer patients receiving chemotherapy[26]. The results demonstrated that the total psychological stress and CRF levels improved after the HC compared to baseline (P = 0.003 and P = 0.04, respectively)[26]. A significant decrease in salivary cortisol after the HC visit was observed. In this study, the HC intervention was performed by volunteer clowns from the University of São Paulo, Brazil, and were members of the Laugh Company, which is an outreach project aimed to lift pediatric patient mood levels during hospitalization[26]. Their families and the staff were present during the clown visits and were delighted. Children accompanied by their parents interacted simultaneously with two volunteer clowns in the pediatric oncology ward for 30 minutes at a time. In this period, the clowns performed several activities while adapting their techniques to the best of their ability to each patient's age and psychological condition. The 2 clowns arranged common play sessions with patients in their ward and used different methods for entertaining the children such as singing, dancing, magic tricks, gags, puppets, games, mostly using improvisation and their distinctive humor and charisma. All these HC attended specific training sessions focused on practical work situations to develop theatrical and artistic clown competences in addition to psychosocial and pedagogical skills (Table 2)[26].

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

Perhaps the addition of an HC to the play therapy portion of patient care could be a key addition to the oncology team and could be a valuable supplement to current play therapy practices. This could also be considered for outpatient treatment areas as well. HC have been a mainstay in a child's life for decades[40-43] and may actually be an underused resource[13,26] for improving the oncology child's daily regime while undergoing treatment in the any setting[39]. Nurses play a pivotal role in the identification, monitoring, and risk evaluation of CSCs, including the assessment of biomarkers[44,45]. The understanding of how neuro-immunoendocrine pathways regulate cancer development and the underlying aspects of treatment using biomarkers is urgent to incorporate into clinical practice.

One of the major challenges is to improve the preparation and training of nurses in omics sciences and disruptive technologies for the provision of personalized care, especially adapting curricula at different levels of academic training for these professionals, from undergraduate to postgraduate studies[46,47]. It is worth noting that for this century, one of the main challenges in nursing training is the integration of omics sciences into professional practice, which includes the analysis of biomarkers[47,48]. Therefore, there is an urgent need for extensive continuing education for nursing professionals, undergraduate/postgraduate course teachers and, mainly, the reformulation of more integrated nursing curricula, to adequately prepare the workforce for precision nursing in global health systems[46-48]. One of the main areas

of application and development in precision nursing is oncology, where oncology nurses are already faced with the universe of omics sciences directly in the care of cancer patients, from prevention, diagnosis and oncological treatment through biomarkers, genetic tests, and pharmacogenomics, proteomics, metabolomics, genomics, and bioinformatics[49]. This understanding can contribute to elucidating the diagnosis and prognosis of several cancer types and assist in the selection of personalized CT for each patient and tumor type.

Another challenge is to ensure the transfer of these research results, so that they facilitate clinical decision-making towards personalized care[48]. In the last decade, the substantial growth of TR has opened up perspectives of knowledge in several directions, since they greatly assist in the elucidation of many pathophysiological processes associated with clinical practice and the singularities of patients[49]. Therefore, it is important that nursing is also involved in this type of research, since the application of the discoveries and results of TR carried out by these professionals supports evidence-based nursing[46,49].

CONCLUSION

It is crucial that nurses participate in identifying strategies to accelerate TR for assisting the understanding of the underlying pathophysiological mechanisms associated with CSC to intervene effectively. Overall, the literature suggests that CT may help improve pediatric cancer patient's QoL as part of a comprehensive cancer care model. HCs may be a unique, useful intervention that could be integrated into patient's care to decrease stress, CRF and improve QoL. Finally, oncology nurses using trained qualified CT therapists for various CT interventions can support the patient's recovery from life-threatening illness.

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FOOTNOTES

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MINIREVIEWS

Nipah virus: Preventing the next outbreak

Satvik Tyagi, Shalini Upadhyay, Tanisha Bharara, Sanjeev Sahai

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Abstract

Nipah is a deadly viral infection which has come to the news highlight recently, due to its fresh onslaught in Southern India. As the world continues to recover from coronavirus disease 2019, the World Health Organization has identified a list of high-priority pathogens with the potential to cause future pandemics. Among them is the Nipah virus (NiV), which poses a significant threat. Even a small outbreak could trigger widespread panic among the public. The emergence and re-emergence of NiV among other zoonotic infections is a stern reminder of the importance of One health concept.

Key Words: Encephalitis; Pandemic potential; Re-emergence; One health; Zoonosis

Core Tip: Nipah is a bat borne, zoonotic virus that is notorious to cause serious human outbreaks. The recent coronavirus disease 2019 (COVID-19) pandemic has shed light on the One Health approach and is a stark reminder of the indolent threat of emerging and re-emerging zoonotic infections. Lessons learned from the global COVID-19 pandemic can be applied to managing infections limited to regional outbreaks, such as Nipah, to help prevent recurrent re-emergences. Further studies on Nipah virus, disease development, diagnostic modalities, and treatment options, are need of the hour.

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INTRODUCTION

Emerging and re-emerging zoonotic infections have been threatening human race since time immemorial[1]. Several of these outbreaks have high pandemic potentials. In 2014, the center of disease control (CDC) and prevention defined high-consequence pathogens as microorganisms which cause high mortality but have infrequent spillover from animals, and human to-human transmission is rare[2]. Common high-consequence pathogens like coronavirus, ebolaviruses, henipaviruses and monkeypox virus have challenged this understanding; re-emerged; spread rapidly and killed millions of people[3-5]. United States National Institutes of Health guidelines for managing risky pathogens categorized SARS and MERS in the risk 3 category group, while Nipah virus (NiV) is classified in the risk 4 group[6]. NiV has also been classified as a possible bio- and agroterrorism pathogen. Till date large NiV outbreaks has not been reported. This could probably be attributed to rapid containment initiatives or perhaps because of the virus's intrinsic inability for mass transmission in a population[7,8]. Similar to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), NiV has also originated from bats, with cross-species transmission occurring *via* various intermediate hosts such as pangolins, rats, civets and camels[9,10]. While NiV may currently seem like a regionally confined infection with a low probability of becoming a global threat, the same was true of the coronavirus before it brought the world to a standstill, struggling to overcome its impact. The ability of NiV to spread to patient caregivers has raised concern that the virus might adapt to more efficient human-to-human transmission.

NiV: THE INCITANT

NiV is an RNA virus of genus Henipavirus, family Paramyxoviridae. It has a non-segmented negative-stranded RNA genome which consists of helical nucleocapsids enclosed inside an envelope. NiV like HEV has a genome larger than other paramyxoviruses. The RNA codes for 6 structural protein and 3 non-structural proteins. The structural proteins are nucleocapsid protein (N), phosphoprotein (P), the matrix protein (M), fusion protein (F), glycoprotein (G), large protein or RNA polymerase (L). The 3 non-structural proteins are C, V, W all of which are coded by the phosphoprotein gene. The genome has the arrangement of 3′-N-P-M-F-G-L-5′[5,11,12].

Two strains of NiV have been reported till now, namely, Bangladesh (NiV_B) and Malaysia (NiV_M). Compared to NiV_M, NiV_B strain shows human to human transmission as well as a higher mortality rate, thus making it more pathogenic[12].

Global warming and biodiversity loss over the years have led to emergence and re-emergence of infectious agents over the last two decades. Figure 1 illustrates deforestation, urbanization and the subsequent human invasion of natural animal habitat. The disturbed habitats favor opportunistic species to flourish, and transmission events occur.

Genetic factors also contribute to the zoonotic spillovers, as most of the causative viruses are RNA viruses, including SARS, NiV, influenza and SARS-CoV-2[11-13]. These RNA viruses have exceptionally short generation times without proof reading mechanism and faster mutation rates, which increases the probability of causing infection in new host species. Furthermore, since these viruses mutate so frequently, it is difficult to predict time of emergence of the next strain of NiV within the next 5 years or later[14,15].

PATHOGENESIS

NiV enters the human body through the oro-nasal route. There are various speculations about its early replication site, as most of the investigations on human tissues have been done only in the later stage of the disease. Although, high antigen load in lymphoid and pulmonary tissues makes them likely site of early replication. NiV glycoprotein G interacts with the receptor Ephrin-B2 or Ephrin-B3, highly expressed on the endothelium and smooth muscle cells of the brain, placenta, lungs, prostate and arteries in other organs as shown in Figure 2. Ephrin-B2 has a significant role in the migration of neuron precursors during embryogenesis explaining the clinical and pathological aspects of NiV infection[16]. The receptor Ephrin B2 shows about 96% similarities between bats and pigs. This extensive distribution among various animal species corroborates the wide host range of NiV[17]. The central nervous system may be either infected by NiV through hematogenous route or direct invasion *via* olfactory nerves. The high fatality rate of NiV is because it evades the innate immune response[18].

NiV survives up to three days in fruits and around seven days in artificial date palm sap. The main reservoir host of NiV are fruit bats or flying foxes of genus Pteropus, family Pteropodidae. Virus spillover is based on various factors related to disease ecology from infective stages in the reservoir host, genetic constitution of the virus to population dynamics of the affected host. It has been observed that a bat shedding NiV infects only one or a few people, the amplification and divergent spread is initiated by infected individuals who spread the virus through person-to-person transmission leading to outbreaks[19-22]. The interventions required to curtail NiV infection include preventing farm animals from eating fruit contaminated by bats. Farm designs to minimize overcrowding to control the infection from spreading at rapid rate between animals. Culling of infected animals followed by disposal by deep burial with quick lime, along with other control measures has been found to stop the chain of transmission[23].

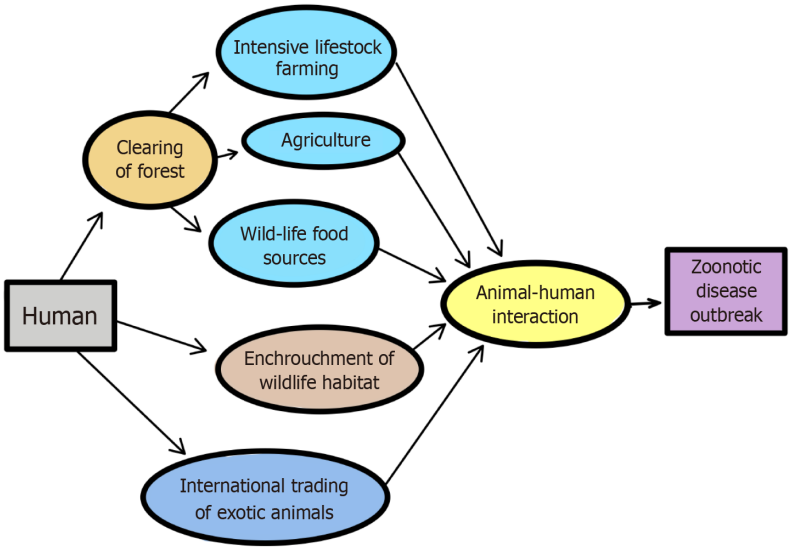

Figure 1 Anthropogenic factors promoting zoonotic spillover. The menace of zoonotic spillover is result of consortium of factors which determine the interplay of ecological dynamics of infection in reservoir hosts, its' transmission, and exposure among susceptible host. The geographical distribution of reservoir hosts, its propensity for human interaction, human behavior towards the reservoir and viral load carried by it are factors determining the possible site of attack. Host immunity and health status in conjunction with the viral load and virulence of the pathogen decide the probability and severity of infection.

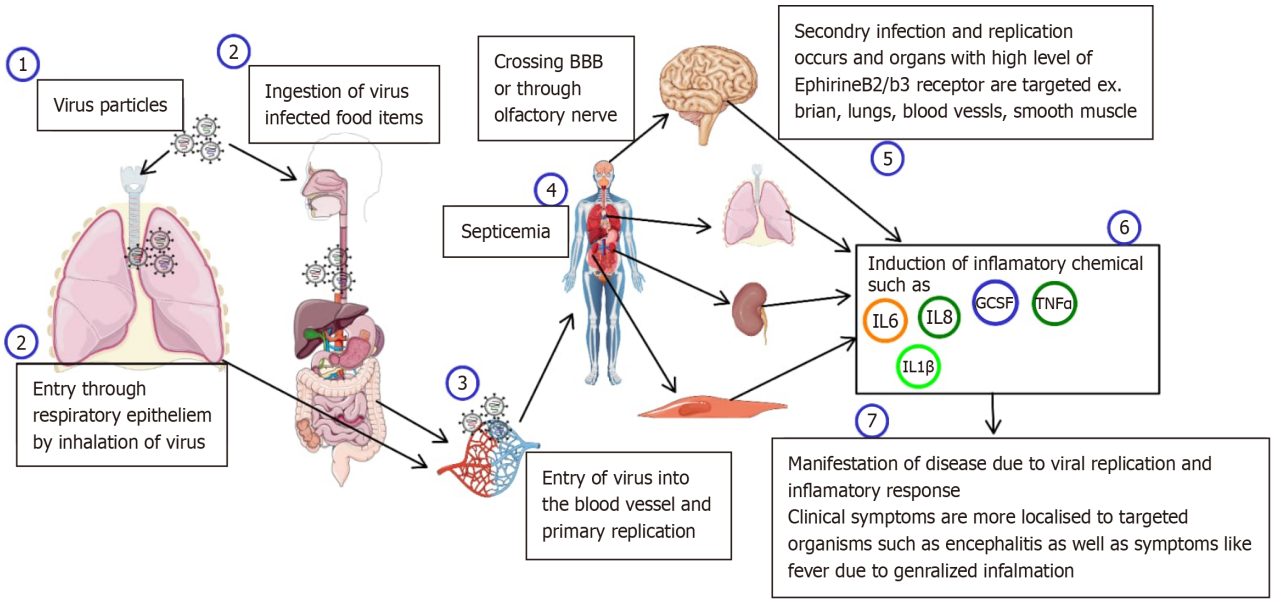

Figure 2 Pathogenesis of Nipah virus. The Nipah virus (1) may enter the human body through oral or nasal route (2). From these sites it reaches the blood stream (3) and gets carried away to brain either by crossing the blood brain barrier or through the olfactory nerve. While in the blood stream it may cause generalized septicemia (4). So the secondary infections (5) can occour in organs with epinephrin b2/b3 receptors *i.e.* brain, blood vessels and smooth muscles. Inflammatory cytokine come into play like IL-6, IL-8, TNF-α. BBB: Blood brain barrier; IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; G-CSF: Granulocyte colony-stimulating factor.

THE OUTBREAK SERIES

NiV infection was first reported in Kampung Sungai Nipah, Malaysia, in 1998. The Malaysian government in collaboration with the CDC reported around 258 cases with a case fatality rate of almost 40%. Mass culling of more than a million pigs in the outbreak areas, led to control of the epidemic and finally the ordeal was over in May 1999. The next blow came very shortly in Bangladesh (2001), and also in Siliguri, West Bengal, India. Around 65 people were infected, out of which 45 patients died. The origin of infection was pigs in Malaysia and presumptively bats, in India[24,25]. From thereupon there has been no stopping for NiV, frequent fatal outbreaks have been documented mostly form South and South-East Asia.

Table 1 Comparative analysis of Nipah and coronavirus disease 2019

Features	Nipah virus disease	COVID-19
Agent	Nipah virus	SARS-CoV-2
Transmission	Fruit bats to humans, eating contaminated fruit or juice, date palm, fluids from infected animals like pigs, dogs, horses, cats. Few cases of person-to-person transmission	Origin speculated to be from bats or pangolins. Further transmission through respiratory droplets or airborne
Human-to-human transmission	Limited, but can occur through close contact with an infected person	Efficient
Incubation period	4 to 14 days	2 to 14 days
Symptoms	Fever, headache, muscle aches, sore throat, dizziness, nausea, vomiting, acute respiratory syndrome, encephalitis and in severe cases, coma, or death	Fever, dry cough, fatigue, shortness of breath, body aches, loss of taste or smell, sore throat, headache, chills, congestion or runny nose, nausea or vomiting, diarrhea
Severity	Variable, ranging from asymptomatic or mild illness to severe respiratory or neurological symptoms	Variable, ranging from asymptomatic or mild illness to severe pneumonia and acute respiratory distress syndrome
Case fatality rate	40% to 75%	Generally lower, estimated around 1%-3%
Vaccination	No specific vaccine available	Vaccines available
Treatment	Supportive care to relieve symptoms and prevent complications; no specific antiviral drugs available	Supportive care, oxygen therapy, antiviral drugs like Remdesivir, and in severe cases, corticosteroids and immunomodulators
Preventive measures	Avoiding exposure to sick pigs or bats, avoiding consuming raw date palm sap, culling of infected animals and decontamination of their remains, standard precautions	Vaccination, standard precautions, quarantine, and isolation measures
Global impact	Outbreaks, mainly in Southeast Asia	Recent pandemic

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

In India, after the first outbreak in Siliguri, second occurred in Nadia district of West Bengal which was a minor one with 5 cases in 2007 but the case fatality was 100%. Both these districts are at the border of the Nipah belt in Bangladesh. However, the outbreak of 2018 occurred in Kerala (Kozhikode and Malappuram) which is a southern state on the west coast, geographically distant to previously affected areas and date palm sap intake is not widespread there. Since then, Kerala has become an endemic site with the latest outbreak in Kozhikode district (2023) being the sixth incident in the state. The outbreak was contained with vigorous public health measures with 6 cases and 2 fatalities[26-28].

The index case in the 2001 outbreak remained undetected in Siliguri but it infected 11 patients, 25 employees and eight visitors. In 2007, the index case started with a person consuming date palm-derived alcohol later infecting a healthcare professional caring for him. In 2018 epidemic, there was a case of NiV in a 12-year-old boy in Kerala, which was hypothesized to have eaten infected tropical fruit, rambutan. In the same episode, healthcare practitioners got infected with the virus while caring for the boy[26,27].

EPIDEMIOLOGY OF NIV AS COMPARED TO CORONAVIRUS DISEASE 2019

NiV, being less widespread as compared to coronavirus disease 2019 (COVID-19), still poses a significant threat to cause a pandemic due to its high mortality rate, infrequently sprouting outbreaks, and practically no treatment or vaccines as depicted in Table 1. When compared to SARS-CoV-2, NiV infection has a high fatality rate, which ranges from 40% to 75%, depending upon the level of outbreak and the robustness of healthcare system of the affected areas. The severity of the infection and its clinical complications including severe respiratory and neurological symptoms are far worse for NiV. Like COVID-19, NiV is also a zoonotic infection, meaning it can be transmitted from animals to humans. Fruit bats are the main reservoir of NiV, like the speculated theory for zoonotic spill of COVID-19. NiV can also be transmitted from person to person, especially in healthcare setting or through close contact with infected people. Unlike COVID-19, which is highly transmissible through respiratory droplets, the transmission of NiV among humans is less efficient but still is a significant risk, especially during outbreaks. Currently, there are no approved vaccines or specific antiviral treatments for the NiV infection. While supportive care can manage symptoms, there is an urgent need for the development of vaccines and antiviral drugs to combat NiV. Although there are quite a few COVID vaccines, time will tell whether they actually worked, or they were detrimental to human health in long term scenario. Various treatment strategies were tried during the pandemic some of which added to the complication and mortality. Lastly, NiV outbreaks have occurred sporadically in several countries, including Malaysia, Bangladesh, India, and Singapore. The potential for outbreaks, combined with globalization and increased travel, is concerning for the global spread of the virus. NiV infections can be devastating for global public health, economies, and healthcare systems.

In 2019, a conference of researchers conducted in Singapore analysed the outbreaks and the recent epidemiologic data, vaccines and management strategies for NiV[5]. The deliberations also pondered upon the fact that NiV could become an

agent responsible for the next pandemic while in the backdrop COVID-19 pandemic still brewing. Many previous studies have also indicated that NiV has the potential to cause a pandemic or epidemic[13,28]. In a recent publication, Moore *et al* highlighted the significant global threat posed by the Nipah virus and other henipaviruses. The authors emphasized the urgency of addressing this issue and supported the World Health Organization's advanced draft proposal for developing medical countermeasures against the Nipah virus. They underscored the critical need for an internationally coordinated effort to accelerate the development of rapid point-of-care diagnostic tests, as well as affordable vaccines and therapeutics, to combat Nipah virus and related pathogens[29].

CONCLUSION

NiV outbreaks have mostly been confined to Indo-Bangladesh region till now but the chronicles of emerging infectious diseases have shown such infections to find newer hotspots as part of their evolution. The origins of such infections are substantially associated with socio-economic and geographical factors with increased global travel being the driving force of further dissemination. The NiV outbreaks in India shifting from western parts to the southern India is an austere reminder of the possibility of spill over episodes to sites where risk variables were hitherto unknown. The strategies of prevention and management apprehended from the global COVID disaster should become the rule book to follow for further such infections. One Health approach is required for comprehending the transmission risk and preventing NiV from becoming the next disease of global concern.

FOOTNOTES

Author contributions: Tyagi S, Upadhyay S, Bharara T, Sahai S contributed to this paper; Upadhyay S and Bharara T designed the overall concept and outline of the manuscript; Sahai S contributed to the discussion and design of the manuscript; Tyagi S and Upadhyay S contributed to the writing, illustrations, and review of literature; Bharara T and Upadhyay S contributed to edit the manuscript.

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META-ANALYSIS

Exercise rehabilitation on patients with non-small cell lung cancer: A meta-analysis of randomized controlled trials

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Abstract

BACKGROUND

Lung cancer is one of the most common and deadly cancers worldwide. As the disease progresses and due to the side effects of treatment, patients' physical activity significantly decreases.

AIM

To systematically review and conduct a meta-analysis on the effects of exercise rehabilitation on the physical activity of lung cancer patients and determine the best implementation methods to provide clinical guidance.

METHODS

Literature was searched through multiple electronic databases. A random effects model was used to combine effect sizes through standardized mean difference (SMD). The Cochrane risk of bias tool was used to assess the quality of the literature, sensitivity analysis was used to ensure the robustness of the results, and Egger's test was used to detect publication bias and asymmetry.

RESULTS

A total of 11 studies involving 541 patients were included in this study. The physical endurance, muscle function and cardiopulmonary function of non-small cell lung cancer (NSCLC) patients were evaluated. The overall effect size of the six-minute walk test (6MWT) was not statistically significant. However, subgroup analysis found that endurance significantly improved when exercise duration exceeded 0.5 hours ($P \leq 0.05$). In terms of muscle function, the overall effect size was SMD = 0.619. Subgroup analysis showed that strength training, respiratory training, and cross-training (XT) significantly improved muscle function. Exercise

rehabilitation significantly enhanced cardiopulmonary endurance (SMD = 0.856, P = 0.002), and the effect was better when the single exercise duration was more than 1 hour, age was over 65 years, and the intervention period was more than 3 months.

CONCLUSION

Exercise rehabilitation effectively improved muscle function in NSCLC patients, especially strength training, respiratory training, and cross-training. Cardiopulmonary function also showed improvement, particularly when exercise duration exceeded 1 hour, age was ≥ 65 years, and the intervention period was more than 3 months. A single exercise duration of more than 0.5 hours can enhance patients' physical endurance. Appropriately increasing exercise duration and selecting suitable exercise forms can effectively improve the physical activity of NSCLC patients.

Key Words: Non-small cell lung cancer; Physical activity; Physical endurance; Muscle function; Cardiopulmonary function

Core Tip: This study conducted a meta-analysis on the effects of exercise rehabilitation for lung cancer patients. It found that exercise, especially strength, respiratory, and cross-training, significantly improved muscle function. Cardiopulmonary function also improved, particularly with exercise exceeding 1 hour. A single exercise duration over 0.5 hours enhanced physical endurance. Increasing exercise duration and choosing suitable forms can improve non-small cell lung cancer patients' activity.

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INTRODUCTION

Lung cancer is a malignant tumor occurring in the lungs. It is one of the most common cancers globally and a leading cause of cancer-related deaths[1]. Lung cancer typically forms due to genetic mutations in lung cells, causing uncontrolled cell growth[2]. These abnormal cells continuously divide, forming tumors. Lung cancer is generally classified into two major types: Small cell lung cancer and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all lung cancer cases[3]. NSCLC patients typically experience persistent coughing and expectoration, hemoptysis, along with symptoms like shortness of breath or dyspnea, chest pain, hoarseness, unexplained weight loss, and continuous fatigue and weakness[4]. According to Global Cancer Statistics 2020 data, there were an estimated 2.2 million new lung cancer cases globally in 2020, accounting for 11.4% of all cancer cases, and nearly 1.8 million lung cancer deaths, making up 18.0% of all cancer deaths[5]. The World Health Organization reports that in countries with a high human development index (HDI), the age-standardized incidence and mortality rates are more than three times higher than in countries with medium/low human development index[6].

The current main treatments for NSCLC include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. These treatments significantly impact patients' lung function decline and respiratory muscle weakness, leading to postoperative cardiopulmonary function impairment, respiratory system disorders, decreased exercise tolerance, and limited physical activity, severely affecting patients' quality of life and postoperative recovery. Maintaining and improving exercise capacity during treatment is crucial for enhancing their quality of life and prognosis[7]. This involves not only the patient's physical functions but also directly impacts their daily activities and social participation. Patients often face varying degrees of reduced exercise capacity due to the disease itself and psychological factors such as fear and anxiety. Symptoms like chest tightness, coughing, and shortness of breath caused by surgical trauma further affect their exercise capacity. Due to pain, fatigue, and other symptoms, patients may find it challenging to adhere to regular rehabilitation training, significantly impacting NSCLC patients' exercise self-efficacy. Therefore, rehabilitation training and improving exercise capacity for lung cancer patients are essential.

Numerous studies have shown that implementing pulmonary rehabilitation training can effectively enhance the exercise endurance and quality of life for lung cancer patients[7]. Preoperative exercise training helps improve patients' surgical tolerance and reduces postoperative complications, while systematic postoperative exercise rehabilitation accelerates recovery, enhances lung function, reduces the occurrence of pulmonary complications, and promotes early return to daily life and social activities. Some studies indicate that exercise rehabilitation for lung cancer patients can significantly improve their exercise endurance and quality of life[8]. However, other studies point out that due to cardiovascular and pulmonary comorbidities often accompanying lung cancer patients, exercise rehabilitation may pose risks. Additionally, there is ongoing debate regarding the optimal form of exercise [strength training, aerobic exercise (AE), cross-training], frequency, and duration[9]. Some studies suggest that the benefits of exercise rehabilitation are only

positive for specific groups, and it remains unclear whether exercise therapy has consistent effects across different age groups in NSCLC patients[10]. This uncertainty limits the widespread clinical application of exercise rehabilitation. There is a lack of systematic reviews on the improvement of exercise capacity through exercise rehabilitation in lung cancer patients, necessitating further research to verify its effectiveness and applicability. In light of this, the present study aims to conduct a systematic review and meta-analysis, integrating current evidence to investigate the effects of exercise rehabilitation on lung cancer patients. It will also explore the best implementation methods and the rehabilitative efficacy for lung cancer patients across different age groups to address existing controversies and gaps in research, providing clearer clinical guidance and determining supplementary rehabilitation protocols in clinical practice. The goal is to enhance the exercise capacity and quality of life for NSCLC patients.

MATERIALS AND METHODS

This study has been registered in the International Prospective Register of Systematic Reviews and Meta-Analyses Database[11] with the registration number CRD42024546506. To ensure the integrity and reproducibility of the research, the writing of this study strictly follows the PRISMA 2020 checklist.

Inclusion and exclusion criteria

Inclusion criteria: (1) Participants: Patients who have been diagnosed with lung cancer, including symptomatic and asymptomatic patients, and all included patients must have undergone surgical treatment; (2) Study type: Only randomized controlled trials (RCTs) are included; (3) Interventions: The experimental group undergoes various forms of exercise rehabilitation, including AE, strength training, respiratory training (RT), and cross-training; and (4) Control group: No form of exercise intervention is given.

Exclusion criteria: (1) Non-randomized or uncontrolled studies are excluded; (2) Case studies or special case reports are excluded; (3) Studies with incomplete outcome data or data that cannot be extracted are excluded; (4) Review articles and animal studies are excluded; and (5) Non-English literature is excluded.

Search strategy and study selection

Multiple electronic databases were used for literature retrieval, including PubMed, EMBASE, Cochrane Library, EBScohost, and Web of Science. Based on the PICOS principle, both Medical Subject Headings and free terms were used to determine the search terms (Table 1), with P: Pulmonary neoplasms, and I: Exercise rehabilitation. To ensure comprehensiveness and relevance, no restrictions were placed on the control group, outcome indicators, or type of literature during the search, and logical operators were used to combine search terms. Additionally, citations from relevant reviews and meta-analyses were traced to expand the search depth. The search timeframe was set from the establishment of each database to October 2023, and the search language was limited to English.

Study selection

We implemented a detailed literature screening process to ensure the accuracy and systematic nature of the research. In the initial screening stage, we managed the search results using the EndnoteX20 reference management software. After deduplication, studies were excluded based on titles and abstracts according to the inclusion and exclusion criteria, eliminating studies that did not align with the research objectives. Subsequently, the studies that met the preliminary screening criteria underwent full-text review to further assess their eligibility. Exclusion criteria included non-RCTs, case studies, and studies with incomplete data. To ensure transparency and reproducibility, all information and results from the screening process were recorded and managed *via* EndnoteX20. The study selection process was independently conducted by two researchers, Xiao KW and Xu SH. Any discrepancies or disputes were resolved by a third party, Xu H, aiming to enhance the credibility and scientific rigor of the research results through stringent standards and transparent processes.

Data collection process

In this study, the data collection and extraction process was strictly conducted according to the Cochrane data extraction protocol[12]. Data extraction was independently performed by two researchers, Xiao KW and Xu SH, using customized data extraction forms, which helped standardize information collection and reduce bias. The extraction forms included several key areas: Baseline characteristics of lung cancer patients, surgical status, details of the intervention measures, outcome indicators, and information on whether the control group participants were taking specific medications. Researchers first independently extracted data from the literature and then compared their results to identify any inconsistencies. If discrepancies or disputes arose during the data extraction process, they were reviewed and decided upon by a third researcher, Xu H. Extracted baseline characteristics included patients' age, gender, disease stage, and other relevant health indicators. Surgical status was recorded as whether surgery had been performed. Details of the interventions included the type (AE, strength training, cross-training, breathing exercises), frequency, and duration.

Study indicators

In this meta-analysis, we included indicators related to exercise capacity to evaluate the impact of exercise rehabilitation on lung cancer patients. Functional strength, muscle strength, endurance, and cardiopulmonary function collectively reflect the overall exercise capacity of lung cancer patients. The six-minute walk test (6MWT) demonstrated an indi-

vidual's ability to perform daily activities and complex tasks, emphasizing the muscle's power output in practical applications[13]. Muscle strength and endurance described the capacity for sustained muscle activity, crucial for prolonged physical activity. Cardiopulmonary function, as an indicator of heart and lung efficiency, directly affected oxygen transport and energy production, forming the foundation for sustained physical activity.

Specific indicators included in this study were the 6MWT, predicted percentage, and walking distance to comprehensively evaluate the patients' functional endurance. Muscle strength test indicators included thigh muscle strength, grip strength test, Timed Up and Go test, 30-second sit-to-stand test, and one-leg stand test to explore patients' muscle strength and endurance[14]. By observing maximal oxygen consumption (VO2max) peak and maximum values, exercise thresholds, and their predicted percentages, we aimed to clarify the effects of exercise rehabilitation on lung cancer patients' exercise capacity and further explore its role and potential benefits in the rehabilitation of lung cancer patients.

Risk of bias and quality assessment

In this study, to ensure the quality of the included literature and reduce the risk of bias, we employed quality assessment and bias risk evaluation methods. All included RCTs were assessed for quality using the Cochrane risk of bias[15] Tool *via* Revman 5.4. This tool specifically evaluates potential bias risks in RCTs, including random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other biases. "Other biases" refer to potential sources of bias beyond the six domains mentioned above. According to the Cochrane Handbook guidelines, other biases may include baseline imbalance bias, early termination bias, learning effect bias, duplicate publication bias, and funding source bias, among others, which could impact study outcomes. Each study was classified as "low risk", "uncertain", or "high risk" based on these dimensions.

To assess potential publication bias, we performed Egger's test to detect small study effects and asymmetry risk, commonly used in meta-analyses to evaluate bias. To further verify the robustness of our results, we also conducted sensitivity analyses using the leave-one-out approach. This involved re-performing the meta-analysis by sequentially excluding each study to examine the impact of any single study on the overall effect estimate and to identify studies that might excessively influence the overall analysis results.

Statistical analysis

In this meta-analysis, we used Stata16.1 statistical software, employing both fixed-effect and random-effect models to combine effect sizes. Preliminary statistical tests (I^2 statistics) were used to assess heterogeneity among studies. If heterogeneity was not significant ($I^2 < 40\%$), a fixed-effect model was used; otherwise, if heterogeneity was significant ($I^2 \geq 40\%$), a random-effect model was applied. Due to differences in the units of measurement for the included study indicators, we calculated effect sizes and heterogeneity using the standardized mean difference (SMD), and generated forest plots, publication bias graphs, and sensitivity analysis charts.

Subgroup analyses were performed based on the classification of participants' age, intervention duration, exercise type, and single intervention duration to explore the potential impact of these factors on the overall effect estimate. This aimed to more accurately understand the effects of exercise rehabilitation on lung cancer patients under different conditions. To verify the robustness of our research results, sensitivity analyses were conducted on the included studies, which helped identify and confirm key factors affecting the study conclusions and ensure the reliability of the results. Throughout the meta-analysis process, we strictly adhered to the Cochrane Handbook's data analysis standards to ensure the transparency and scientific integrity of the analysis.

RESULTS

Literature search results

This study searched databases such as PubMed, EMBASE, Web of Science, and the Cochrane Library. A total of 12643 articles were retrieved, along with 16 additional articles from other sources. After removing duplicates, 9306 articles remained. Initial screening based on titles and abstracts, following inclusion and exclusion criteria, resulted in 490 articles for further review. After full-text screening, 479 articles were excluded, and ultimately, 11 RCTs on exercise rehabilitation for improving exercise capacity in NSCLC patients were included in this meta-analysis (Figure 1).

Basic characteristics of included studies

This meta-analysis included 11 RCTs on exercise rehabilitation improving exercise capacity in lung cancer patients (Table 2), involving 541 patients, all of whom had NSCLC. The exercise rehabilitation interventions included AE, RT, high-intensity interval training (HIIT), and XT. The experimental groups' ages ranged from 56 to 72 years, with exercise intervention durations varying from less than 0.5 hours to over 1 hour per session, and frequencies ranging from twice weekly to six times weekly. Most intervention periods lasted 12 weeks, with control groups typically receiving standard care or no specific intervention.

Risk of bias assessment

This study evaluated the quality of the included studies using the Cochrane risk of bias tool. The quality assessment chart displays the scores of each study across seven risks of bias items. As shown in Figure 2A, "+" represent low risk; "?" represent unclear risk, and "-" represent high risk. Overall, Gill (2010) showed low risk only in random allocation, with other items not clearly described. Most studies had a high risk in blinding of participants and personnel due to the nature

Table 1 Literature search strategy

Search strategy	Subject terms	Mesh terms
T1	Lung neoplasms	Pulmonary neoplasms OR neoplasms, lung OR lung neoplasm OR neoplasm, lung OR neoplasms, pulmonary OR neoplasm, pulmonary OR pulmonary neoplasm OR lung cancer OR cancer, lung OR cancers, lung OR lung cancers OR pulmonary cancer OR cancer, pulmonary OR cancers, pulmonary OR pulmonary cancers OR cancer of the lung OR cancer of lung
T2	Exercise	Exercises OR physical activity OR activities, physical OR activity, physical OR physical activities OR exercise, physical OR exercises, physical OR physical exercise OR physical exercises OR acute exercise OR acute exercises OR exercise, acute OR exercises, acute OR exercise, isometric OR exercises, isometric OR isometric exercises OR isometric exercise OR exercise, aerobic OR aerobic exercise OR aerobic exercises OR exercises, aerobic OR exercise training OR exercise trainings OR training, exercise OR trainings, exercise
T3	T1 and T2	
Search strategy	Subject terms	Medical Subject Headings terms

of lung cancer patients and the interventions, making blinding impractical. Most studies showed low risk in random sequence generation and allocation concealment, while other biases were not specified (Figure 2B). From the summary of publication bias results (Figure 3), most studies showed low risk in random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. However, there was some uncertainty and high risk in blinding of participants and personnel, as well as other biases. Other biases identified include incomplete reporting of baseline characteristics and inconsistent standardization of intervention implementation. These bias risks might affect the reliability and interpretability of the overall analysis results.

Meta-analysis results

Effect of exercise rehabilitation on physical endurance in lung cancer patients: The 6MWT is a recognized standard test for measuring patients' physical endurance, effectively reflecting the maximum distance a patient can walk within a specified time, thereby assessing their cardiopulmonary endurance and functional status. In this study, we evaluated the physical endurance of lung cancer patients by combining the 6MWT indicators, finding high heterogeneity (I^2 = 85.4%), thus choosing to use a random effects model. Due to the inclusion of both time and distance units, the SMD was used for effect size consolidation (Figure 4A). The results of this meta-analysis showed that the combined effect size SMD = 0.14, P = 0.558, with no statistical significance. Further subgroup analysis revealed that when the exercise duration per session was between 0.5 and 1 hour, the SMD = 0.44, $P \leq 0.05$; and when it was more than 1 hour, the SMD = 0.5, $P \leq 0.05$. This indicates that when the exercise duration exceeds 0.5 hours, there is a significant improvement in the physical endurance of lung cancer patients. This result supports that longer exercise durations in rehabilitation can enhance physical endurance in lung cancer patients (Table 3).

Effect of exercise rehabilitation on muscle function in lung cancer patients: In this study, we conducted a combined effect size analysis of multiple muscle function indicators in lung cancer patients. Considering the high heterogeneity among the included studies (I^2 = 71.5%), a random effects model was chosen. The main muscle function tests involved in the analysis included thigh muscle strength tests, grip strength tests, Timed Up and Go tests, 30-second sit-to-stand tests, and single-leg stand tests, thus using SMD as the combined effect size (Figure 4B). The results of the muscle function evaluation showed an overall combined effect size SMD = 0.619 (P = 0.001), which was statistically significant, indicating that exercise intervention effectively improved muscle function in lung cancer patients overall. Subgroup analysis further revealed differences in the effects of various intervention forms, with strength training, RT, and XT all showing significant improvements in muscle function ($P < 0.05$), while AE did not reach statistical significance ($P > 0.05$). Additionally, the effect was significant when exercise duration exceeded 1 hour or was less than 0.5 hours ($P \leq 0.05$), reflecting that exercise within these time ranges is particularly effective in enhancing physical endurance in lung cancer patients. When exercise duration was between 0.5 and 1 hour, the effect was not significant ($P > 0.05$) (Table 3). These findings emphasize the need to consider the form and duration of exercise when designing rehabilitation programs to optimize therapeutic effects.

Impact of exercise rehabilitation on cardiopulmonary function in lung cancer patients: This study assessed the cardiopulmonary function of lung cancer patients using peak VO2, maximum VO2, exercise threshold, and their predicted percentages. Due to the different measurement units for each indicator, the SMD was used to combine effect sizes. High heterogeneity among the studies (I^2 = 82.7%) necessitated the use of a random effects model for the meta-analysis (Figure 4C). The results show that exercise rehabilitation significantly improves the cardiopulmonary function of lung cancer patients, with an SMD of 0.856, 95% confidence interval (CI) = 0.307-1.406, P = 0.002, indicating statistical significance. This demonstrates the effectiveness of exercise rehabilitation in enhancing the cardiopulmonary endurance of lung cancer patients. Further subgroup analysis found that when the single session exercise duration was between 0.5 to 1 hour using HIIT, and the patients were under 65 years of age, the P values were all > 0.05, suggesting that under these specific conditions, the exercise intervention does not significantly improve cardiopulmonary function. Conversely, when the exercise duration exceeded 1 hour, the age was over 65, and the interventions included RT and XT with an intervention period ≥ 3 months, the P values were ≤ 0.05, indicating significant effects of exercise on cardiopulmonary

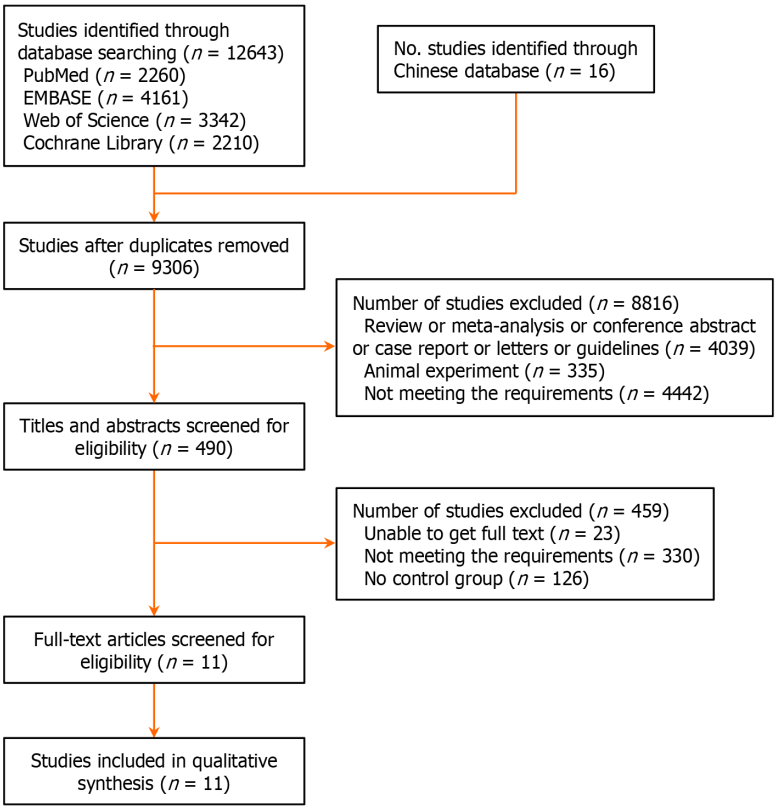


Figure 1 Literature search flowchart.

function under these conditions (Table 3). Thus, it can be seen that appropriately increasing exercise duration and selecting suitable forms of exercise can more effectively enhance cardiopulmonary endurance, and exercise rehabilitation is particularly effective in improving outcomes for older adults.

Sensitivity analysis

This study employed influence analysis and the leave-one-out method for sensitivity analysis. Influence analysis confirmed that the results were consistent with the combined effect sizes (Figure 5), indicating no potential outliers had a significant impact on the meta-analysis results, thus demonstrating the stability of the study outcomes. The leave-one-out method was used, and recalculating the meta-analysis statistics showed that the results remained stable after this process, with no single study significantly influencing the overall conclusions, affirming the reliability of the study results.

Publication bias assessment

In the Egger's test analysis, no significant publication bias was observed in the data related to physical endurance, muscle function, or cardiopulmonary function. The publication bias analysis for physical endurance showed that both the slope and bias were not statistically significant (slope $P = 0.30$, bias $P = 0.47$), indicating no obvious publication bias. The 95%CI for the slope ranged from -0.72 to 2.11, and for the bias from -6.79 to 3.41, both encompassing zero, further supporting the conclusion of no significant bias. The muscle function Egger's test results showed an estimated slope of -0.05, standard error of 0.28, t value of -0.18, P value of 0.86, indicating no statistical significance for the slope, with a 95%CI ranging from -0.67 to 0.57, indicating no significant publication bias. The analysis of cardiopulmonary function data also showed no significant publication bias. The P values for the slope and bias analyses were 0.87 and 0.25, respectively, indicating no statistical significance, showcasing the stability and reliability of the data. The confidence intervals for both slope and bias included zero, further confirming the consistency of the research results and the absence of systematic bias.

DISCUSSION

The exercise capacity of patients with NSCLC plays a crucial role in their overall health and quality of life. Maintaining and enhancing exercise capacity not only helps them cope better with the side effects of treatment but also improves their daily activity levels and mental health. However, there is still considerable debate regarding the applicability and programs of exercise rehabilitation. Our meta-analysis found that exercise rehabilitation effectively enhances muscle function and cardiopulmonary function; moreover, a single session of exercise rehabilitation lasting more than 0.5 hours significantly improves patients' physical endurance. This meta-analysis demonstrates that exercise rehabilitation

Table 2 Literature feature table

Authors	Year	Preoperative/ postoperative	Type	Medication	Experimental group age, mean ± SD	Experimental group gender (male/female)	Intervention method	Duratio (hour/time)	Frequency (time/week)	Period (week)	Control group age, mean ± SD	Control group gender	Control method
Gill Arbane	2010	After surgery	NSCLC	Analgesia	65.4 ± 8.75	N/A	ST	< 0.5	2	12	62.6 ± 3.75	N/A	UC
Denise Shuk Ting Cheung	2021	Preoperative	NSCLC	N/A	61.00 ± 12.12	5/5	AE	0.5-1	2	12	58.36 ± 9.32	5/6	SM
Denise Shuk Ting Cheung	2021	Preoperative	NSCLC	N/A	61.11 ± 7.01	6/3	RT	0.5-1	2	12	58.36 ± 9.32	5/6	SM
Raquel Sebio García	2017	Preoperative	NSCLC	N/A	70.9 ± 6.1	9/1	ST	0.5-1	3-5	According to actual condition	69.4 ± 9.4	11/1	UC
Chueh-Lung Hwang	2012	Preoperative + after surgery	NSCLC	N/A	61.0 ± 6.3	5/8	HIIT	0.5-1	3	< 12	58.5 ± 8.2	7/4	UC
Marcus Jonsson	2019	Preoperative + after surgery	NSCLC	Analgesia	68.7 ± 7.4	29/25	HIIT	< 0.5	6	12	68.4 ± 8.3	18/35	N/A
Marta K. Mikkelsen	2022	Preoperative + after surgery	NSCLC	N/A	72.1 ± 1.8	19/22	XT	0.5-1	2	12	71.5 ± 1.625	17/26	UC
Maria T. Morano	2013	Preoperative	NSCLC	N/A	68.8 ± 7.3	5/7	RT	< 0.5	4	< 12	64.8 ± 8	4/8	UC
Morten Quist	2020	Preoperative	NSCLC	N/A	65.2 ± 8.2	55/55	XT	> 1	2	12	63.5 ± 8.7	52/56	UC
Anna Rutkowska	2019	Preoperative	NSCLC	N/A	59.1 ± 6.8	18/2	XT	0.5-1	5	< 12	61.3 ± 8.8	9/1	UC
Francesco Stefanelli	2013	Preoperative	NSCLC	Improve lung function	65.5 ± 7.4	N/A	RT	> 1	5	< 12	64.8 ± 7.3	N/A	UC
Rui-Chen Ma	2021	Preoperative	NSCLC	N/A	56.97 ± 7.09	13/21	AE	0.5-1	2	According to actual condition	54.91 ± 10.09	8/27	UC

NSCLC: Non-small cell lung cancer; ST: Strength training; AE: Aerobic exercise; RT: Respiratory training; HIIT: High-intensity interval training; XT: Cross training; UC: Usual care; SM: Self-management; N/A: Not applicable.

significantly enhances the muscle function of NSCLC patients, aligning with previous research findings. Appropriate exercise rehabilitation not only strengthens muscle power but also improves overall physical function. Research by Peddle-McIntyre *et al*[16] has shown that cancer patients can significantly increase muscle strength and physical endurance through strength and endurance training. Lung cancer patients participating in systematic exercise rehabilitation programs have shown significant improvements in muscle strength and function. Exercise rehabilitation also significantly enhances the cardiopulmonary function of NSCLC patients. Numerous studies indicate that cardiopulmonary function is a critical factor affecting the quality of life and prognosis of lung cancer patients[17,18]. Research by

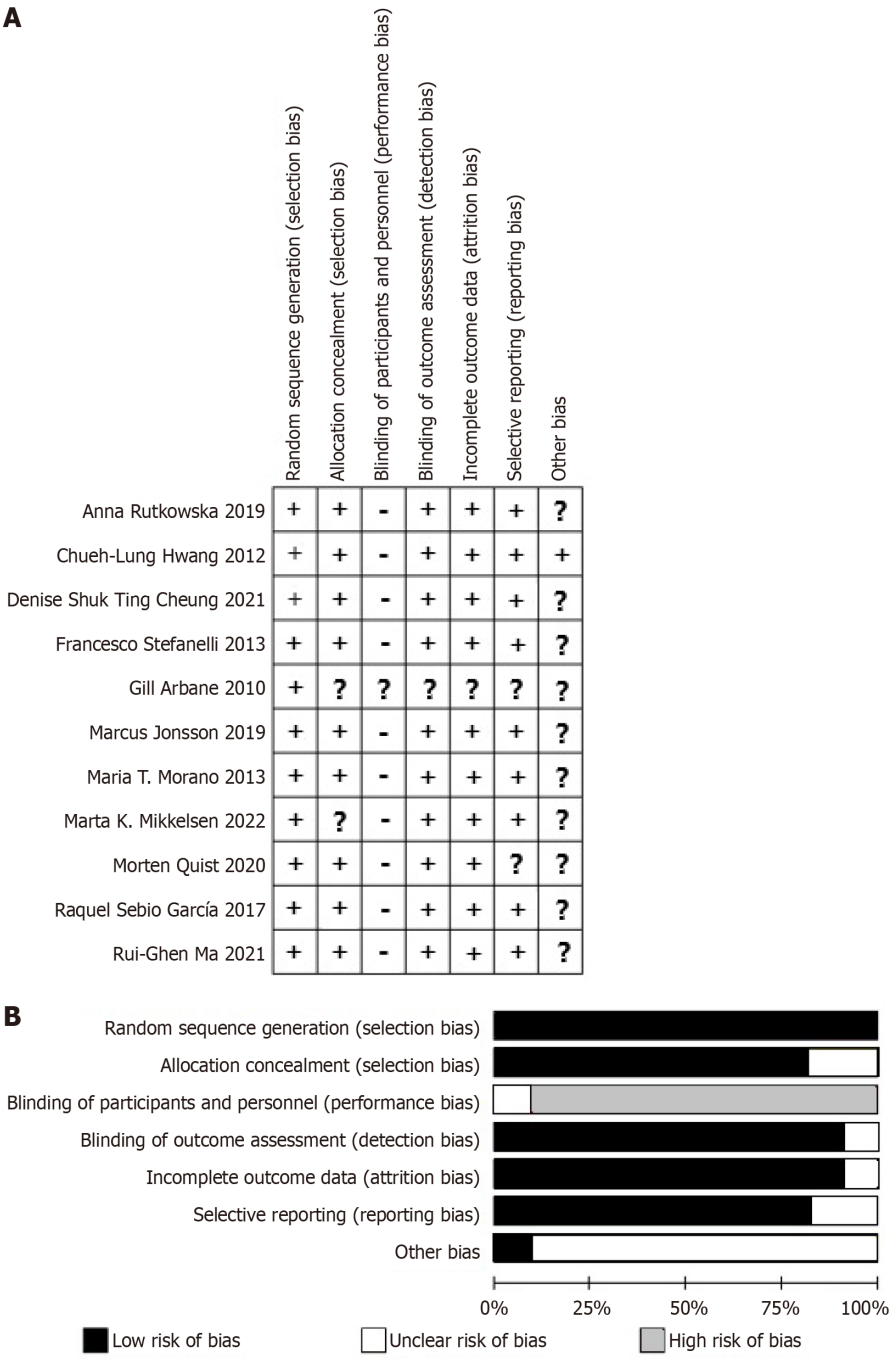


Figure 2 Risk of bias assessment. A: Summary of quality assessment; B: Quality assessment of included studies.

Lindenmann *et al*[19] in 2020 has found that lung cancer patients significantly improve their peak VO2 and maximum heart rate through postoperative aerobic training, consistent with the results of this study.

Our meta-analysis found that when the duration of a single exercise rehabilitation session exceeds 0.5 hours, there is an improvement in the 6MWT scores of NSCLC patients. Research by Rodríguez-Cañamero *et al*[20] in 2022 has shown that prolonged aerobic training significantly enhances the physical endurance of lung cancer patients. A large-scale epidemiological survey found that more than 150 minutes of moderate-intensity exercise per week can significantly improve the physical endurance and survival rates of lung cancer patients[21]. However, some studies have noted that short-duration, HIIT can also effectively improve physical endurance. This inconsistency may relate to factors such as research design, patient characteristics, and the intensity and frequency of exercise.

Exercise rehabilitation can improve and enhance muscle function; exercise promotes the balance of muscle protein synthesis and degradation, making muscle fibers stronger and more enduring. The mechanical load induced by exercise stimulates the growth of muscle fibers, enhancing muscle protein synthesis rates through signaling pathways such as mammalian target of rapamycin and adenosine 5'-monophosphate-activated protein kinase[22]. Exercise also enhances mitochondrial function in muscles, improving energy metabolism efficiency, and overall muscle endurance and function [23]. Due to the prolonged disease and treatment process, NSCLC patients often experience muscle atrophy and strength decline. Exercise rehabilitation can reduce inflammatory cytokines' damage to muscles through its anti-inflammatory

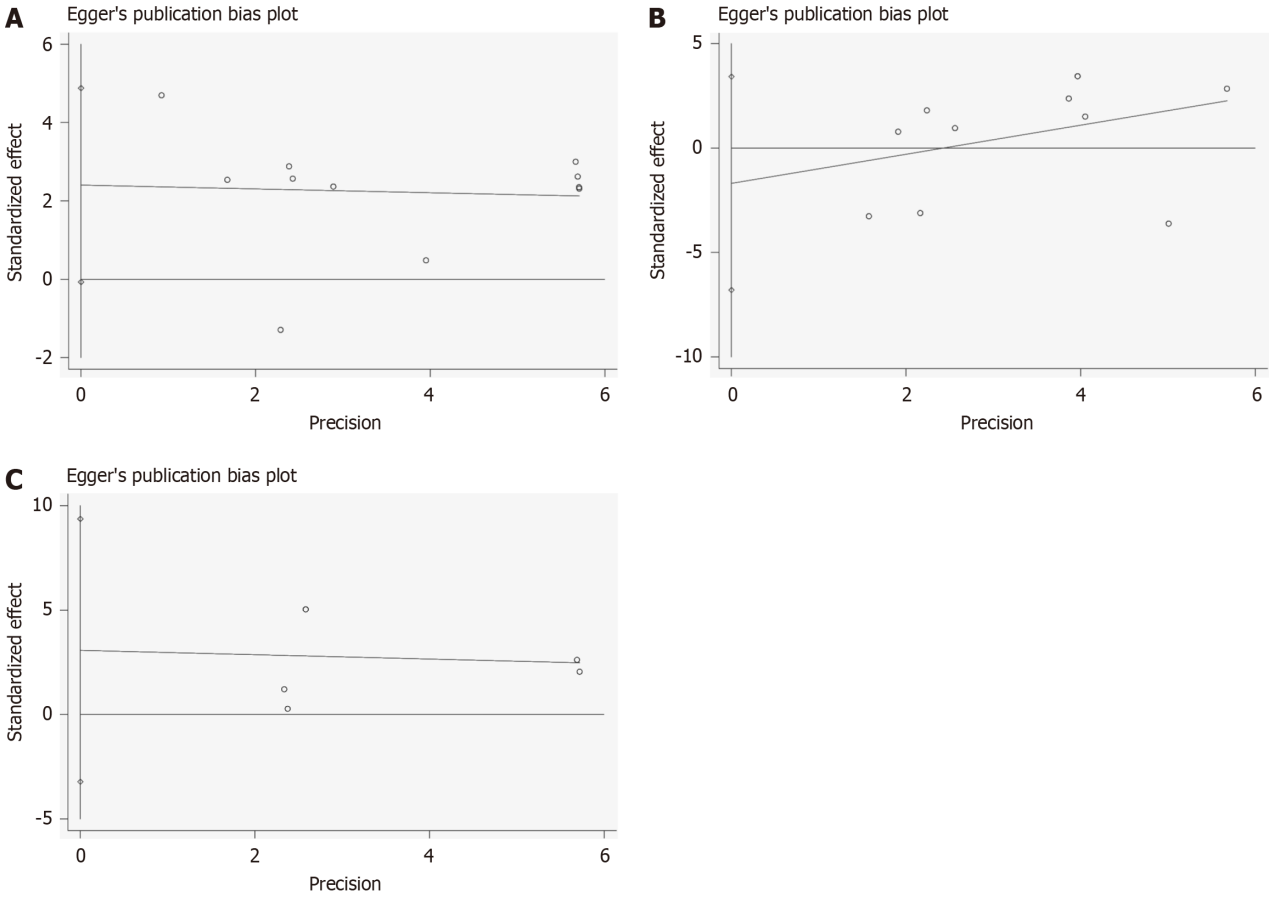
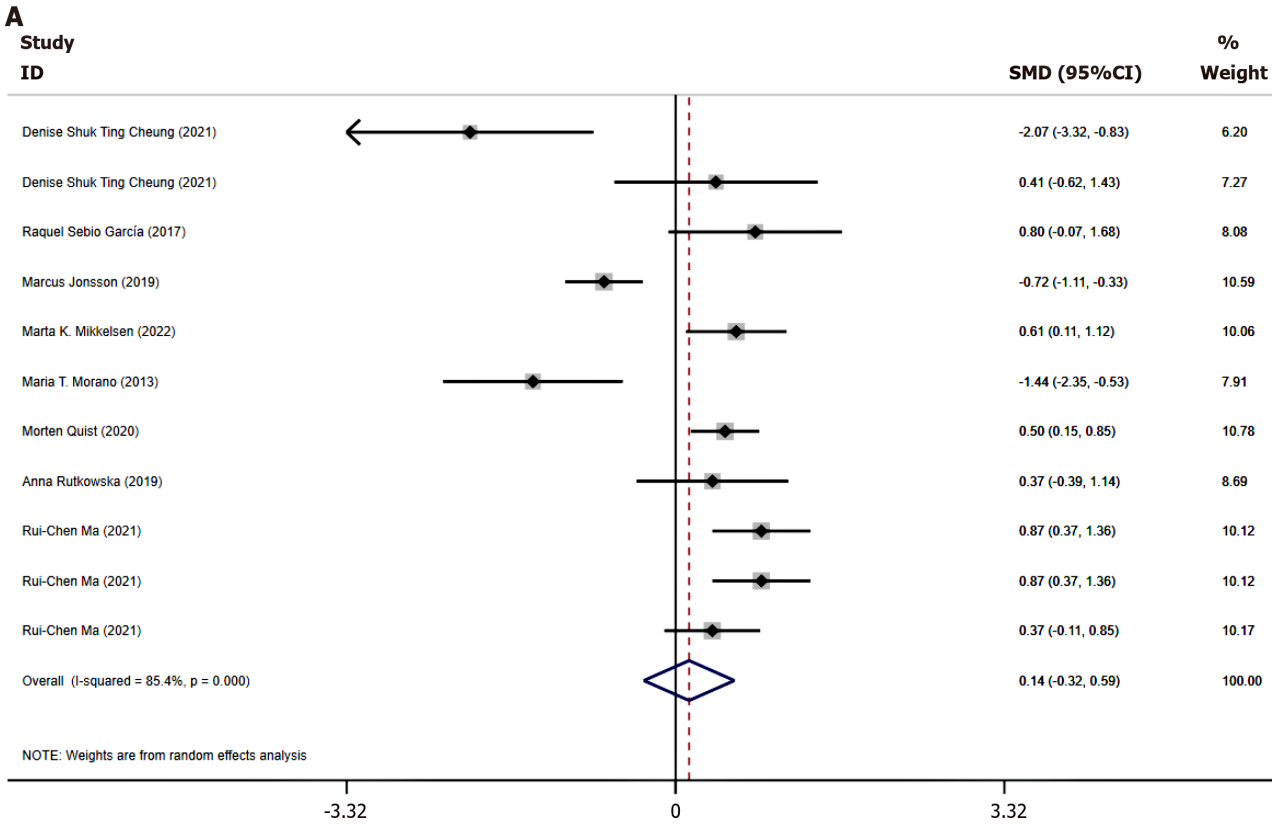


Figure 3 Funnel plot of publication bia. A: Funnel diagram of muscle strength sensitivity analysis; B: Funnel diagram of six-minute walk test sensitivity analysis; C: Funnel diagram of cardiopulmonary endurance.



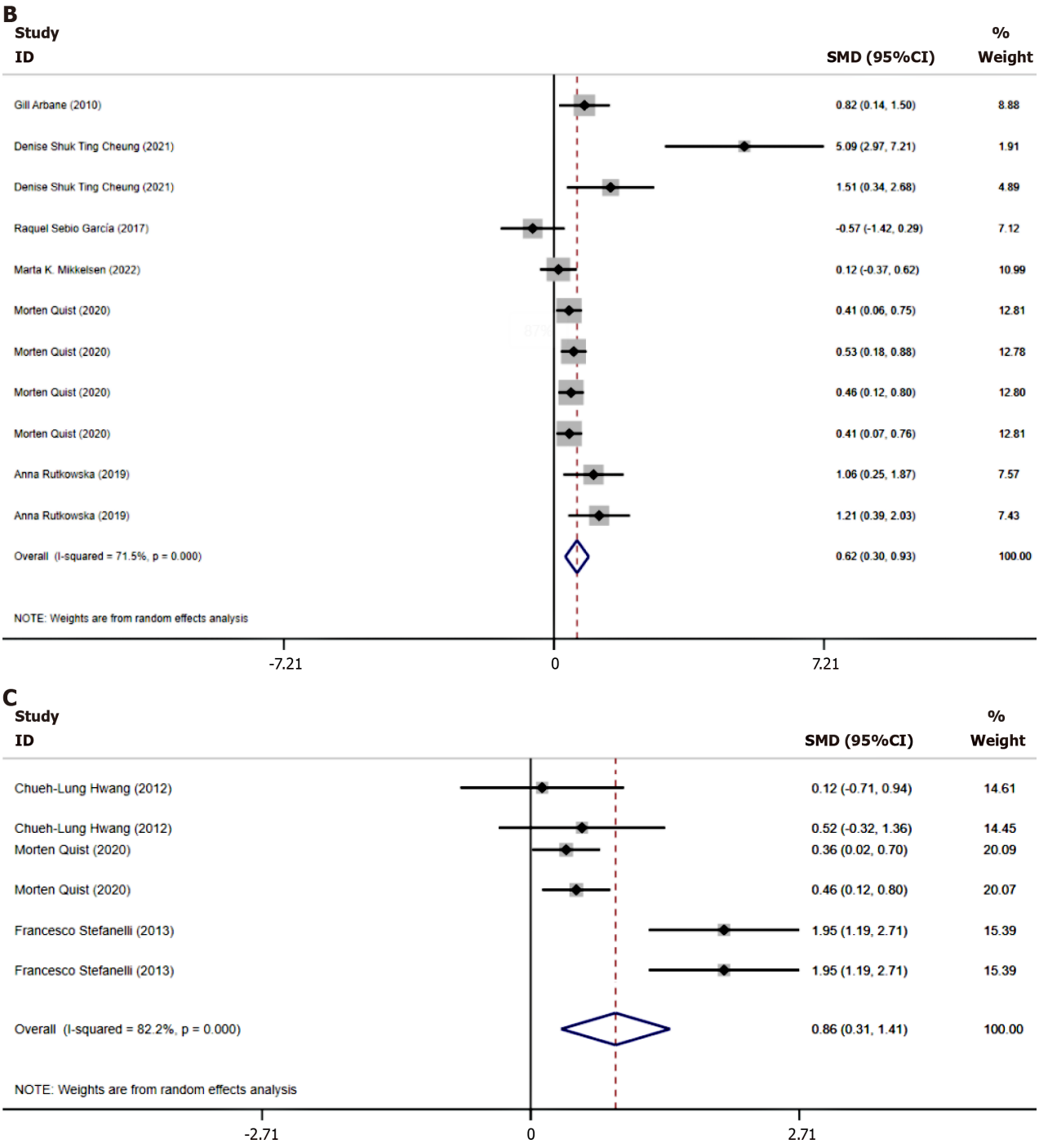


Figure 4 Meta-analysis results. A: Meta-analysis forest plot concerning R1 resection rate; B: Forest plot of muscle strength; C: Forest plot of analysis for cardiorespiratory endurance.

effects and decrease oxidative stress to muscle tissues through its antioxidant actions, thereby protecting and restoring muscle function. Personalized exercise rehabilitation programs can effectively enhance the muscle function of NSCLC patients, with gradually increasing loads stimulating the adaptive enhancement and strength improvement of muscles. Large-scale epidemiological surveys have found that cancer patients participating in exercise rehabilitation significantly outperform non-participants in physical, psychological, and social functions. Compared to traditional drug treatments, it not only improves muscle function but also enhances their quality of life, alleviates adverse reactions from treatment, and improves patient survival quality.

This study, through subgroup analysis, found that exercise durations exceeding 1 hour or less than 0.5 hours significantly improved muscle function in lung cancer patients, suggesting a potential nonlinear relationship between exercise duration and outcomes. Short-duration, high-intensity exercise (< 0.5 hours) may enhance muscle function by rapidly activating the mammalian target of rapamycin signaling pathway, promoting the secretion of anabolic hormones, and optimizing neuromuscular recruitment. In contrast, prolonged exercise (> 1 hour) may induce chronic adaptive changes by increasing mitochondrial density, promoting capillary formation, and improving energy metabolism

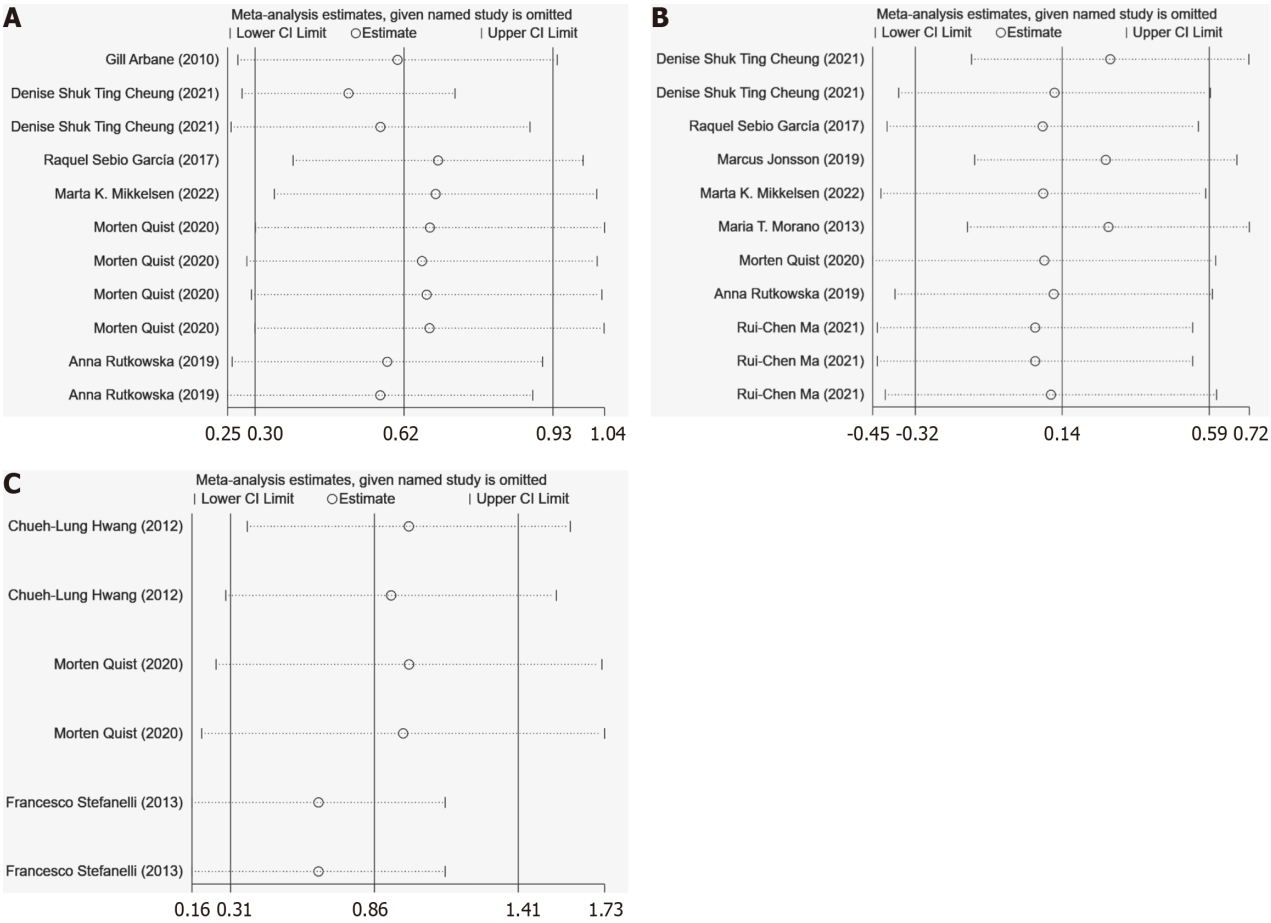


Figure 5 Sensitivity analysis plot. A: Muscle strength sensitivity analysis chart; B six-minute walk test sensitivity analysis chart; C: Cardiovascular endurance tesls sensitivity analysis chart.

efficiency. Medium-duration exercise (0.5-1 hour), however, may fall into a "transition zone", neither achieving the acute stimulation threshold of high-intensity exercise nor generating cumulative adaptive effects. Additionally, patients may reduce exercise intensity due to fatigue, further diminishing the benefits. The unique physiological state of lung cancer patients, coupled with the heterogeneity of studies included in the meta-analysis (variations in exercise type, intensity, and frequency), may obscure the true effects of medium-duration exercise. Moreover, the small sample size and lack of standardized evaluation methods increase uncertainty. Future studies should aim to optimize research design to clarify the mechanisms and clinical significance of exercise duration and its effects.

The mechanism by which exercise enhances the cardiopulmonary function of NSCLC patients primarily involves adaptive changes in the cardiovascular and respiratory systems. Physical activity increases cardiac output and blood oxygen transport capacity, enhancing alveolar gas exchange efficiency and thereby improving oxygenation capabilities [24]. Long-term physical activity can strengthen myocardial contractility, lower heart rates, and enhance cardiac efficiency. These physiological changes not only improve patients' exercise endurance but also reduce respiratory distress during physical activities. NSCLC patients often face a decline in cardiopulmonary function due to cancer and its treatments, including cardiotoxicity induced by chemotherapy drugs and pulmonary fibrosis. Exercise training has been proven to alleviate these adverse effects through anti-inflammatory and antioxidant mechanisms, reducing inflammation markers, decreasing tumor-related systemic inflammatory responses, and enhancing antioxidant enzyme activity[25]. Furthermore, physical activity effectively improves metabolic function, reduces insulin resistance, and enhances overall health, thereby boosting cardiopulmonary function[26]. Past studies have shown that patients who participate in exercise rehabilitation experience significant improvements in cardiopulmonary function, quality of life, and functional independence[27]. Exercise can reduce the recurrence and complication rates in NSCLC patients, improving long-term prognosis[28-30].

This study found that when exercise interventions exceed 0.5 hours, patients' physical endurance improves. This may be due to the continuous exercise stimulus that promotes adaptive changes in the cardiovascular and muscular systems [31]. Extended periods of exercise increase cardiac output, enhance blood oxygen transport efficiency, and promote alveolar gas exchange, improving oxygenation capabilities. NSCLC patients often suffer from systemic inflammation and oxidative stress, which can affect their physical endurance and rehabilitation outcomes[32]. Long-term exercise rehabilitation can improve the cellular microenvironment by reducing inflammation markers and oxidative stress levels, promoting tissue repair and functional recovery. Past studies have indicated that sustained AE significantly reduces levels of C-reactive protein and interleukin-6 in NSCLC patients, decreasing systemic inflammation[33]. Past research has

Table 3 Results of meta-analysis included indicators

Included indicators	Analysis indicators	Group	SMD	95%CI	*P* value	I^2
Physical endurance	Age subgroup analysis	Age < 65	0.31	-0.25 to 0.86	0.28	76.20%
		Age ≥ 65	0.14	-0.32 to 0.59	0.95	89.90%
	Intervention, method, subgroup	AE	-2.07	-3.32 to -0.83	0.01	-
		RT	-2	-1.34 to 0.94	0.733	-
		ST	0.8	-0.07 to 1.68	0.07	-
		HIIT	-0.72	-1.11 to -0.33	0.0001	-
		XT	0.65	0.43 to 0.86	0.0001	0%
	Single intervention duration	< 0.5 hours	-0.96	-1.62 to -0.30	0.034	50.60%
		0.5-1 hour	0.44	0.03 to 0.85	0.004	67.30%
		> 1 hour	0.5	0.15 to 0.85	0.005	-
	Intervention period	< 3 months	0.27	-0.39 to 0.93	0.421	80.80%
		≥ 3 months	0.04	-0.60 to 0.68	0.906	87.50%
	Overall		0.14	-0.32 to 0.59	0.558	85.40%
Muscle function	Age subgroup analysis	Age ≥ 65	0.394	0.205 to 0.582	0.0001	26.80%
		Age < 65	1.842	0.725 to 2.960	0.001	76%
	Intervention, method, subgroup	AE	5.09	2.965 to 7.215	0.825	-
		RT	1.514	0.345 to 2.684	0.011	-
		ST	0.152	-1.203 to 1.508	0.001	83.80%
		XT	0.477	0.298 to 0.656	0.0001	71.50%
	Single intervention duration	< 0.5 hours	0.818	0.140 to 1.497	0.018	-
		0.5-1 hour	1.087	0.154 to 2.021	0.022	85.10%
		> 1 hour	0.451	0.279 to 0.624	0.0001	0
	Intervention period	< 3 months	2.197	0.330 to 4.064	0.021	0.86
		≥ 3 months	0.437	0.213 to 0.661	3.83	0.453
	Overall		0.619	0.304 to 0.933	0.0001	0.715
Cardiorespiratory function	Age subgroup analysis	Age < 65	0.313	-0.275 to 0.902	0.297	0
		Age ≥ 65	1.097	0.370 to 1.824	0.003	88.70%
	Intervention, method, subgroup	HIIT	0.313	-0.275 to 0.902	0.297	0
		RT	1.950	1.413 to 2.487	0.001	0
		XT	0.409	0.166 to 0.652	0.0001	0
	Single intervention duration	0.5-1 hour	0.313	-0.275 to 0.902	0.297	0
		> 1 hour	1.097	0.370 to 1.824	0.297	0
	Intervention period	3 months	0.313	-0.275 to 0.902	0.003	88.70%
		≥ 3 months	1.097	0.370 to 1.824	0.002	82.7%
	Overall		0.856	0.307 to 1.406	-	-

SMD: Standardized mean difference; CI: Confidence interval; AE: Aerobic exercise; RT: Respiratory training; ST: Strength training; HIIT: High-intensity interval training; XT: Cross training.

shown that regular and prolonged exercise rehabilitation significantly reduces mortality and recurrence rates in NSCLC patients[34], enhancing quality of life and functional independence. However, short-term exercise interventions often fail to provide sufficient stimulus and may not significantly reduce inflammation markers and oxidative stress levels, thus limiting their effectiveness in improving overall patient health[35].

In this meta-analysis, the results of the subgroup analysis should be interpreted with caution due to methodological limitations. The subgroup analysis in this study was conducted at the study level, based on 11 RCTs, rather than at the individual level of the 541 patients. Although the original studies were designed as RCTs, key baseline characteristics (age, gender ratio, disease stage, comorbidities) were not fully balanced across subgroups after stratification. Uneven sample sizes across subgroups may have further reduced statistical power. Additionally, the distribution of potential confounding factors (chemotherapy regimens, nutritional status, and complications) was not effectively controlled among the subgroups. Therefore, the results of this subgroup analysis should be regarded as hypothesis-generating rather than definitive conclusions.

The research limitations of this article are as follows: (1) This study included only 11 RCTs, which is a small sample size that may limit the generalizability and external validity of the results. Future research should expand the sample size and conduct more RCTs for different types and stages of lung cancer patients; (2) Due to the limitations of the included studies, this research did not perform subgroup analyses for preoperative and postoperative interventions. This may lead to an incomplete understanding of the effects at different intervention time points. Future studies should explore in detail the specific impacts of preoperative and postoperative interventions on the rehabilitation of lung cancer patients; and (3) Due to the specificity of lung cancer patients and the nature of exercise rehabilitation interventions, it is difficult to implement blinding for participants and personnel administering the interventions, posing a high risk of bias. Although bias is reduced through subgroup analysis and sensitivity analysis, it cannot be completely eliminated.

CONCLUSION

This meta-analysis assessed physical endurance, muscular function, and cardiopulmonary function to explore the impact of exercise rehabilitation on the exercise capacity of NSCLC patients. The results indicate that exercise rehabilitation significantly enhances muscular function, with an overall effect size of SMD = 0.619, $P = 0.001$. Subgroup analyses further reveal that strength training, RT, and XT significantly improve muscular function ($P < 0.05$), while the effect of AE did not reach statistical significance ($P > 0.05$). Moreover, interventions lasting more than one hour per session showed more significant effects. In terms of cardiopulmonary function, exercise rehabilitation also demonstrated significant improvements (SMD = 0.856, 95%CI = 0.307-1.406, $P = 0.002$). Subgroup analyses showed particularly significant improvements in cardiopulmonary function when the exercise duration exceeded one hour, the patients were older than 65 years, and the interventions used respiratory and XT over periods longer than three months ($P \leq 0.05$). For physical endurance, although the overall effect size was not statistically significant, subgroup analyses indicated that NSCLC patients' physical endurance significantly increased when exercise sessions lasted more than 0.5 hours. Increasing exercise duration and selecting appropriate forms of exercise can significantly enhance the physical endurance, muscular function, and cardiopulmonary function of NSCLC patients, particularly in elderly patients. The findings of this study aid in developing personalized exercise rehabilitation plans, enhancing clinical complementary therapies, and improving the overall health status and quality of life of NSCLC patients.

FOOTNOTES

Author contributions: Xu SH, Xu H, and Mao SJ acquisition of data, analysis and interpretation of data, drafting the article; Xu H conception and design of the study, critical revision; Xu SH and Xu H contributed equally to this article, they are the co-first authors of this manuscript; Xiao KW interpretation of data, revising the article; and all authors thoroughly reviewed and endorsed the final approval the manuscript.

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CASE REPORT

Rapid improvement in postpartum pulmonary hypertension associated with hereditary hemorrhagic telangiectasia: A case report and review of literature

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Abstract

BACKGROUND

Postpartum pulmonary arterial hypertension (PAH) complicated with hereditary hemorrhagic telangiectasia (HHT) is a rare condition. Diagnosing and treating PAH in patients with HHT can be challenging. To the best of our knowledge, no previous reports have investigated the efficacy of pulmonary vasodilators in improving hemodynamics in postpartum patients with this disease.

CASE SUMMARY

In this paper, we report a postpartum case of HHT combined with PAH, presenting with worsening dyspnea. Genetic testing revealed that the patient carried a heterozygous variant of activin receptor-like kinase 1. The patient received various treatments, including diuretics, anticoagulants, sildenafil, macitentan, inhalation of nitric oxide, and iloprost. Changes in PaO_2/FiO_2, pulmonary artery systolic pressure as assessed by echocardiography, and N-terminus pro-brain natriuretic peptide levels suggested that, except for iloprost inhalation, the other treatments appeared to have limited efficacy.

CONCLUSION

To our knowledge, this is the first report on efficacy of pulmonary vasodilators in postpartum patients with HHT and PAH.

Key Words: Pulmonary hypertension; Hereditary hemorrhagic telangiectasia; Dyspnea; Postpartum; Iloprost inhalation; Case report

Core Tip: This case report examines pulmonary vasodilators in a postpartum patient with hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension carrying an activin receptor-like kinase 1 mutation. Despite treatments with diuretics, sildenafil, and nitric oxide, the efficacy was limited. Inhaled iloprost, however, rapidly relieved symptoms and improved hemodynamics. The study underscores the importance of genotype in treatment responses and highlights the need for personalized management of hereditary hemorrhagic telangiectasia-related pulmonary arterial hypertension, especially during pregnancy and postpartum. Further research is needed to explore underlying mechanisms and drug interactions.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is a dominantly-inherited disorder with an estimated prevalence of 1 in 5000-8000 individuals[1]. The underlying pathology of HHT involves a lack of capillary beds, resulting in arteriovenous malformations (AVMs), which can lead to spontaneous epistaxis, multiple mucocutaneous telangiectasias, and arteriovenous shunts in various organs[2]. HHT can be diagnosed through genetic testing or following the Curaçao Criteria, which includes the presence of epistaxis, telangiectasias, visceral lesions, or a family history. A diagnosis of HHT is considered "definite" if at least three criteria are present and "possible" if two are met[3]. The main genetic mutations responsible for HHT are endoglin and activin receptor-like kinase 1 (*ACVRL1*), resulting in HHT type 1 (HHT1) and HHT2, respectively. Mutations in the growth differentiation factor 2 gene, which belongs to *HHT5*, and in the decapentaplegic homolog 4 have also been reported. All these genes play a role in the transforming growth factor beta (TGF-β) signaling pathway involved in angiogenesis[4].

Pulmonary arterial hypertension (PAH) is a condition characterized by elevated mean PAH resulting from various underlying pathologies[5]. PAH is a rare but severe complication of HHT. The pathophysiological mechanisms linking HHT to PAH include interference with the TGF-β pathway and systemic vasculopathy[4]. Heritable PAH (HPAH) is a subtype of PAH, with less than 1% of HHT patients developing HPAH due to mutations in the *ACVRL1* gene. Because of the association between PAH and genetic mutations in HHT, heritable diseases are now classified as group 1 PAH[6]. Patients with HHT complicated by PAH are thought to have worse outcomes than those with PAH alone. Notably, PAH patients with an *ACVRL1* mutation are diagnosed at a younger age and have a worse prognosis, despite receiving similar therapy and demonstrating better hemodynamics at the time of diagnosis[7]. The management of HHT involves medical or interventional therapy, which can be challenging in HHT-PAH patients. Postpartum PAH complicated with HHT is a rare condition. Diagnosing and treating PAH in pregnant or postpartum HHT patients can be particularly challenging. There are few reports investigating the efficacy of pulmonary vasodilators in improving hemodynamics in postpartum patients with this condition. In this case report, we present the effects of different pulmonary vasodilators on a postpartum woman with an *ACVRL1* mutation who was diagnosed with both HHT and PAH.

CASE PRESENTATION

Chief complaints

A 28-year-old woman, who had recently given birth, was admitted to our hospital with complaints of dyspnea on exertion for the past five months, as well as chest tightness and shortness of breath for the past ten days.

History of present illness

At 24-week gestation, the patient experienced a cold and fever, followed by a dry cough that persisted for about a month. Her dyspnea on exertion worsened over time. Ten days prior to admission, she delivered a healthy baby boy vaginally, after which her dyspnea became markedly more severe.

History of past illness

The patient reported having giving birth to a healthy girl three years ago. Her first pregnancy was uneventful, except for recurrent episodes of epistaxis, for which she did not see medical treatment. During her second pregnancy, she

experienced recurrent epistaxis, as well as episodes of dizziness and ocular blurring.

Personal and family history

The patient disclosed that her mother had also experienced recurrent epistaxis during both of her pregnancies.

Physical examination

Upon admission, the physical examination showed a pulse rate of 111 beats per minute, blood pressure of 134/80 mmHg, body temperature of 36.5 °C, and a respiration rate of 30 breaths per minute. Despite receiving high-flow oxygen therapy (FiO_2: 80%, flow rate: 50 L/minute), the pulse oxygen saturation remained at 88%. Cyanosis of the lips and facial erythema were observed.

Laboratory examinations

Upon arrival at the hospital, the patient's arterial blood gas (ABG) test revealed type I respiratory failure (PaO_2/FiO_2 ratio: 134.75 mmHg, PaO_2: 53.9 mmHg, $PaCO_2$: 26.8 mmHg, PH: 7.42). She was subsequently admitted to the intensive care unit. Her complete blood count was within normal limits, but her hemoglobin level was elevated (151 g/L). Liver, kidney and cardiac indicators showed slightly decreased albumin (37 g/L), increased lactate dehydrogenase (276 U/L), alanine aminotransferase (106 U/L), uric acid (458 μmol/L), and N-terminus pro-brain natriuretic peptide (NT-proBNP) (140.8 pg/mL). Immunological markers and immunoglobulin levels were normal. Coagulation function tests revealed elevated D-dimer (1.59 mg/L) and fibrinogen (4.33 g/L). Genetic testing identified a mutation in *ACVRL1* [chr12: 52308295, M_000020.3, c.698C>G, (p.S233W)] (Figure 1).

Imaging examinations

Initial imaging raised concerns about pulmonary embolism. However, chest computed tomography angiography performed on the day of arrival revealed multiple bilateral pulmonary AVMs (PAVMs) (Figure 2A and B). Cyanosis and telangiectasias were observed on the patient's fingertips (Figure 2C-F) and lips.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient declined endotracheal ventilation and central venous catheterization, and did not tolerate non-invasive positive pressure ventilation. She was therefore given supplemental oxygen *via* nasal cannula at a flow rate of 5 L/minute. Echocardiography showed an elevated pulmonary artery systolic pressure (PASP: 51 mmHg).

FINAL DIAGNOSIS

Based on the patient's positive family history, the presence of PAVMs, epistaxis, and telangiectasias, she was clinically diagnosed with HHT.

TREATMENT

The alterations in PASP, NT-proBNP, and ABG levels under different treatments are depicted in Figure 3. Specifically, within the first seven days of admission, the patient was treated with diuretics (hydrochlorothiazide, triamterene) and anticoagulant (low molecular weight heparin calcium). However, her dyspnea continued to deteriorate, accompanied by a decrease in PaO_2/FiO_2 ratio (from 134.75 mmHg to 82 mmHg), an increase in PASP (from 51 mmHg to 80 mmHg), and a rise in NT-proBNP (from 162 pg/mL to 461 pg/mL). Considering her PAH diagnosis, treatment was initiated with sildenafil 18.75 mg three times a day, a phosphodiesterase type 5 inhibitor, and macitentan 5 mg once daily, a dual endothelin receptor antagonist for four days. This was followed by 24-hour nitric oxide (NO) inhalation administered *via* high flow nasal cannula. The oxygen supplement of high flow nasal cannula (FiO_2 increased from 0.8 to 0.9, flow from 30 L/minute to 50 L/minute) was provided for her instead of mask (flow: 10 L/minute). Despite these interventions, there was no significant improvement in her dyspnea or clinical indicators. As a result, Ventavis® (iloprost) inhalation therapy was introduced (1.25 μg in 3 mL of 0.9% NaCl solution per administration every three hours) for eight days. During this period, the patient's PaO_2/FiO_2 ratio improved significantly (from 68 mmHg to 133 mmHg), and her PASP decreased (from 85 mmHg to 70 mmHg). Due to limited availability of Ventavis®, the dosage was reduced (1.25 μg in 3 mL of 0.9% NaCl solution every six hours) and continued for five days. The patient was discharged on the 27th day with improved symptoms and indicators, as shown in Figure 3 (PaO_2/FiO_2 ratio: 297 mmHg, NT-proBNP: 123 pg/mL, and PASP: 50 mmHg). By discharge, she was able to walk 100 m with assistance without experiencing dyspnea or requiring oxygen supplementation. However, the patient declined to continue taking medication post-discharge.

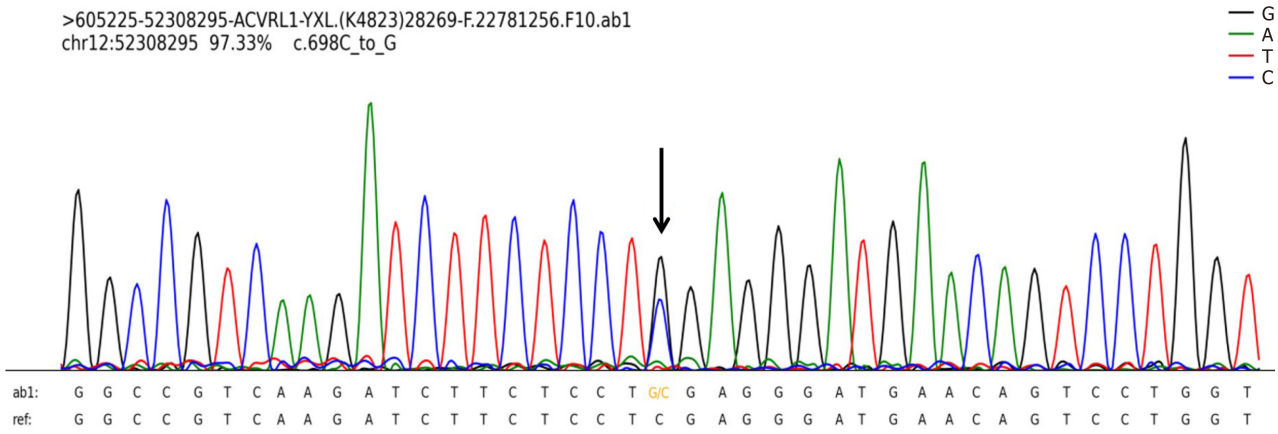

Figure 1 Identification of a heterozygous variant of *ACVRL1* in the patient.

OUTCOME AND FOLLOW-UP

At a telephone follow-up on day 100 post-discharge, the patient was found alive with a resting SpO_2 of 90%-92%, measured by finger oximeter. On day 132 post-discharge, she revisited and underwent successful arteriovenous fistula closure. Notably, the patient's oxygen saturation remained stable at 96% both pre-procedure and post-procedure. However, right heart catheterization showed improvement in PAH (pulmonary artery systolic pressure/pulmonary artery diastolic pressure/mean pulmonary artery pressure (PAP) from 70/23/42 mmHg to 52/21/33 mmHg).

DISCUSSION

We hereby present a case report on a postpartum woman with concurrent pulmonary hypertension and HHT, complicated by an *ACVRL1* mutation. Notably, inhalation of iloprost led to a prompt amelioration of symptoms and improvement in examination findings, ultimately resulting in a successful hospital discharge. Several intriguing clinical manifestations were observed in this case, which may provide valuable insights into the management of similarly afflicted patients. HHT is a systemic disease that affects multiple organ systems, including the brain, liver, and lungs, leading to diverse clinical presentations[8]. Its management depends on the organs involved and the specific clinical manifestations, with treatment options including blood transfusion, surgery, embolization, drainage, and diuretics[9]. During pregnancy or delivery, HHT patients are at increased risk of developing life-threatening complications, including bleeding (0.8%-4.3%), stroke (1.3%), and myocardial infarction (0.5%)[10]. In the case presented, the patient experienced progressively worsening dyspnea during her pregnancy, which became more severe after delivery. Echocardiography revealed significantly elevated PAP, along with typical HHT features including epistaxis and PAVMs, presenting considerable challenges in both diagnosis and management.

PAH, as a complication of HHT, is gaining increasing recognition. Mutations in *ACVRL1* genes have been associated with PAH and HHT[11]. A study evaluating *ACVRL1* genotype and PAP in adult HHT patients found that, among 68 patients, 27 had a mutation in *ACVRL1*, and 9 had elevated PASP. Further investigation confirmed that 7 of the 9 patients with elevated PASP also had a mutation in *ACVRL1*[12]. While these patients did not exhibit severe pulmonary hypertension, many had coexisting vascular anomalies detected by contrast echocardiography, which could complicate the estimation of pulmonary vascular resistance[12]. Further investigation is necessary to determine whether HHT is a consequence of PAH or whether the two conditions coexist. Although research on postpartum changes in pulmonary blood flow is limited, hormonal and hemodynamic alterations during pregnancy are known to exacerbate PAVMs[13]. Pulmonary arteriovenous fistulas, frequently associated with HHT, may exhibit increased pulmonary shunts during pregnancy[14]. When PAVMs expand beyond the capacity of normal pulmonary capillary beds, the proportion of pulmonary shunts may increase due to the elevate blood volume in late pregnancy[15]. Pulmonary shunting and resultant hypoxemia may lead to pulmonary vascular constriction and an increased PAP, creating a vicious cycle of pulmonary arteriovenous shunting.

In this case, the patient's dyspnea worsened gradually at 24-week pregnancy and continued to deteriorate after delivery. Our assessment suggests that the patient's PAH and hypoxia may be linked to postpartum fluid volume expansion and HHT-related PAVMs. Diuretics were administered to address potential fluid overload, but the patient's symptoms persisted, indicating that additional factors may have been contributing. One possibility is that the patient had HPAH, which was aggravated during pregnancy. The presence of HHT may induce arteriovenous shunting in the patient's pulmonary circulation *via* AVM, thereby reducing pressure on the right heart, similar to the effect of balloon atrial septostomy. Although PAVM embolization is a common treatment method for pregnant patients with HHT, in this case, we believe that occluding these open pulmonary AVMs could potentially worsen the patient's PAH, or leading to the opening or worsening of other arteriovenous fistulas post-occlusion.

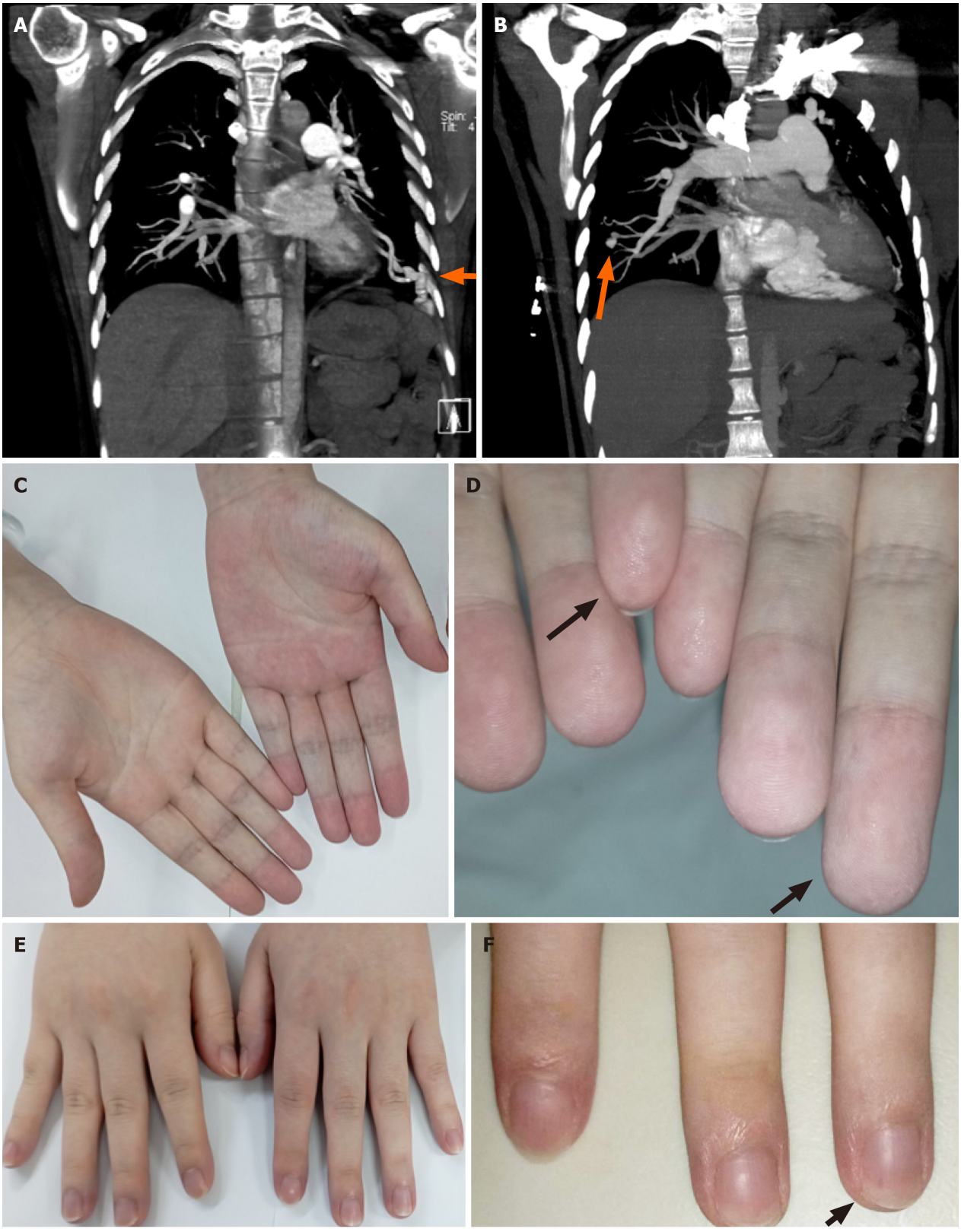

Figure 2 The patient's clinical manifestations at admission. A and B: The patient's imaging presentation on admission, bilateral pulmonary arteriovenous malformations shown by the orange arrows; C and D: Telangiectases (black arrows) are observed in both distant and closer views of the palm of the patient's hands; E and F: Telangiectases (black arrows) are observed in both distant and closer views of back of the patient's hands.

A recent literature review identified 24 cases of severe complications in HHT pregnant women between 1986 and 2022 [16]. Among them, seven women had hypoxemia but were not monitored with echocardiography or PAP assessments. Three patients had received PAVM treatment for HHT prior to pregnancy, but the PAVMs reoccurred during pregnancy, resulting in hemoptysis. In addition, three patients with both PAH and HHT were reported, all of whom had *ACVRL1* mutations. Two of them developed symptoms of PAH before being diagnosed with HHT. None of these three patients

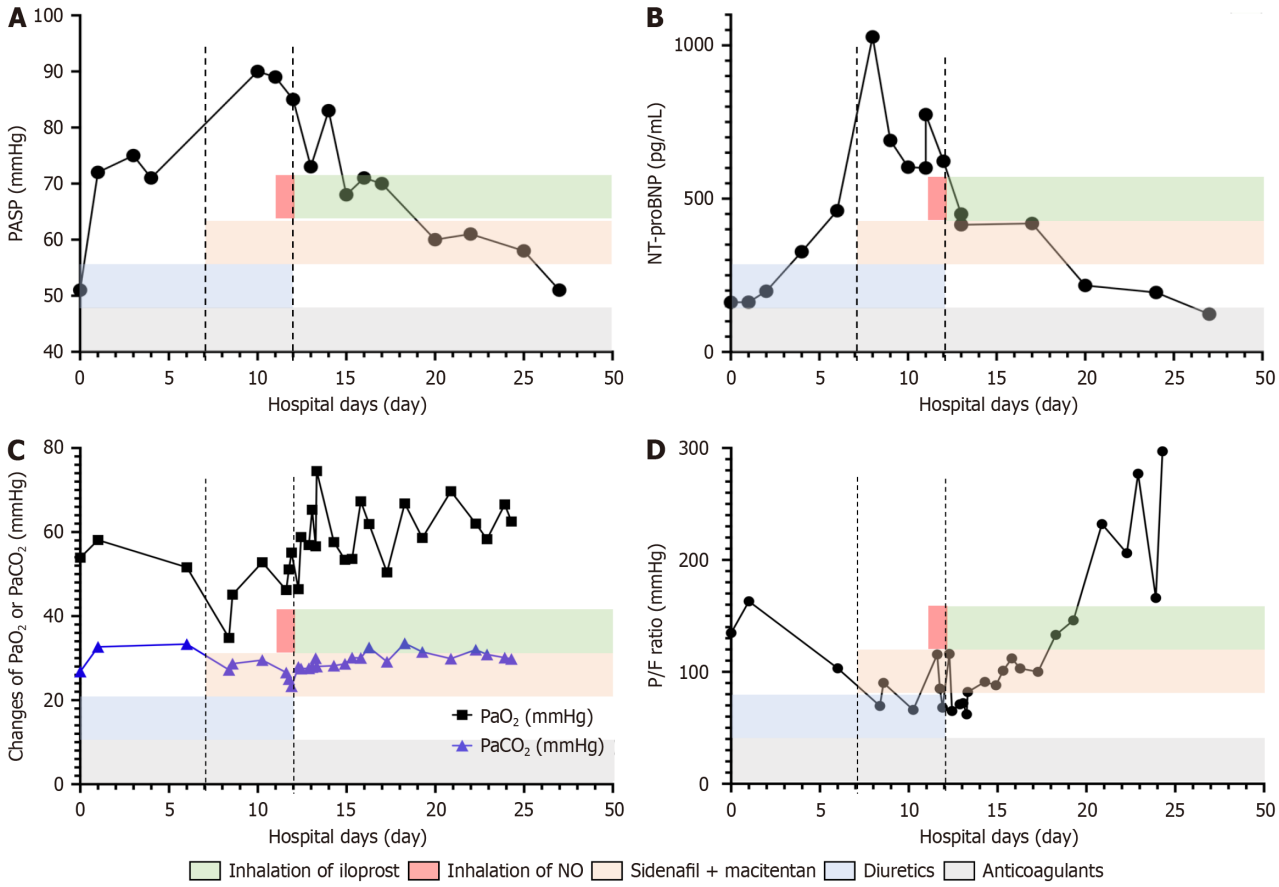

Figure 3 Changes in this case at the time of treatment. A: Changes in pulmonary artery systolic pressure ratio of this case under treatments; B: Changes in N-terminus pro-brain natriuretic peptide ratio of this case under treatments; C: Changes in PaO_2 or $PaCO_2$ ratio of this case under treatments; D: Changes in PaO_2 /FiO_2 ratio of this case under treatments. PASP: Pulmonary artery systolic pressure; NT-proBNP: N-terminus pro-brain natriuretic peptide; P/F: PaO_2/FiO_2; NO: Nitric oxide.

responded to acute vasodilator testing, and did not initially respond to treatment with oxygen and/or inhaled NO[17]. Managing pregnant women with severe hypoxia due to PAH and HHT is particularly challenging. Following consultations with the radiology, cardiology, and obstetrics and gynecology departments, and considering the patient's lack of obvious bleeding symptoms and the ineffectiveness of diuretics, we decided to proceed with PAP reduction treatment.

The pathophysiology of PAH is complex. Current therapeutic strategies focus on targeting the three primary molecular pathways: Prostacyclin, endothelin-1, and NO. All of these pathways primarily function by modulating the tone of the pulmonary vasculature, leading to vasodilation[18]. Phosphodiesterase 5 inhibitors block the degradation of cyclic guanosine monophosphate, enhancing NO signaling to produce significant vasodilation and antiproliferative effects, particularly in the pulmonary vasculature[19]. Ambrisentan, tadalafil, and sildenafil are phosphodiesterase 5 inhibitors that have been used in the treatment of cases with HHT-PAH associated with *ACVRL1* mutations[20,21]. Endothelin receptor antagonists, such as bosentan, inhibit endothelin-1 activity, leading to vasodilation, and have been reported in case studies for treating PAH in HHT patients with *ACVRL1* mutations[22-24]. Case reports also describe the use of intravenous or oral epoprostenol in treating PAH in these patients[25]. Prostacyclin, a potent vasodilator produced by endothelial cells, and its synthetic derivatives (epoprostenol, treprostinil, and iloprost) also induce pulmonary vasodilation. *ACVRL1* is a type I receptor of the TGF-β family. Its mutation can disrupt TGF-β signaling, leading to dysfunction of pulmonary endothelial and/or smooth muscle cells and the proliferative features of PAH[22,26]. Jerkic *et al*[27] reported that endothelial cell dysfunction and reduced NO production were observed in *ACVRL1* gene knockout mice but not in wild-type mice. There are few reports on the treatment of HHT-PAH with *ACVRL1* mutations, and even fewer cases in the postpartum context. While the drugs mentioned above are theoretically effective based on their mechanisms, this may not always be the case in practice. For example, inhaled NO has been reported as ineffective in all cases of HHT-PAH with *ACVRL1* mutations. Wu *et al*[28] reported a 45-year-old female with HHT-PAH and *ACVRL1* mutations who, despite treatment with ambrisentan, died of heart failure within ten months. Jamindar *et al*[25] reported that a female patient, after three months of sildenafil treatment, still exhibited signs of right heart failure, and her symptoms only stabilized after switching to bosentan and intravenous epoprostenol. Some reports also suggest that personalized treatment, and combination therapy might be effective in improving patient conditions in HHT-PAH. However, these reports do not focus on the postpartum state, and there are no detailed reports on the immediate improvement in oxygenation or symptom relief. Bleeding and anemia have been reported in these case studies, but it remains unclear whether they are adverse effects of systemic treatments (*e.g.*, endothelin receptor antagonists, which may compromise endothelial integrity and increase bleeding risk) or a consequence of the underlying disease. Inhaled nebulized medications offer several

advantages, such as the ability to deliver the drug directly to the target organ, resulting in higher local concentrations and reduced systemic toxicity. Additionally, inhalation has minimal impact on the ventilation-perfusion ratio in the lungs, thereby exerting only a minimal effect on gas exchange. Lastly, for the same drug, the inhaled dosage is typically lower, which helps reduce costs and alleviate the patient's financial burden[29].

In this case, sildenafil and macitentan were used to target the endothelin receptors and inhibit phosphodiesterase-5, but no significant improvement was seen in either PAP or ABG levels. Inhaled NO also failed to alleviate the patient's condition, consistent with previous reports. In Bonderman *et al*'s report[30], two female patients with HHT-related PAH showed improved PAH after one year of bosentan treatment. However, these patients were not genetically tested, and they were not pregnant at the time. Regarding our case, the limited duration of treatment with sildenafil and macitentan may help explain the lack of significant improvement observed. In contrast, inhaled iloprost has shown promising efficacy in the treatment of PAH. According to the guidelines[31], it is recommended as a class I monotherapy for patients with PAH in World Health Organization functional class III (with level B evidence) and as a class IIb monotherapy for those in World Health Organization functional class IV (with level C evidence). Our case reports that inhalation of iloprost led to significant improvements in symptoms and indicators in a patient with HHT-PAH associated with an *ACVRL1* mutation. Furthermore, no bleeding symptoms, such as epistaxis, gastrointestinal bleeding, or hemoptysis, were observed during the treatment.

CONCLUSION

There remain numerous unresolved issues in this field, such as the factors influencing the occurrence of PAH in patients with HHT, recommendations for pregnancy among HHT patients, and treatment strategies for pregnant HHT-PAH patients. It is worth noting that not all HHT patients, even those with *ACVRL1* gene mutations, progress to PAH. In this case, the patient had a successful childbirth during her first pregnancy, while PAH symptoms developed in the later stages of her second pregnancy. In managing pregnancy complicated by PAH, inhaled NO and iloprost have demonstrated effectiveness. However, in pregnant HHT-PAH patients with *ACVRL1* mutations, inhaled NO has shown no efficacy. In contrast, inhaled iloprost has led to rapid relief of hypoxia symptoms and a reduction in PAP. Nonetheless, further research is necessary to investigate treatment endpoints and long-term effects on both the fetus and the mother.

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FOOTNOTES

Author contributions: Hao SY, Muhetaer Y, and Zheng X collected the patient's information, summarized the literature data, and wrote the manuscript; Hao SY and Muhetaer Y contributed equally to this article, they are the co-first authors of this manuscript; Long YL followed up with the patient and collected the patient's information; Song JQ and Zhong M were the major contributors in revising the manuscript, they contributed equally to this article, they are the co-corresponding authors of this manuscript; and all authors have read and approved the final manuscript.

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CASE REPORT

Parietal peritoneal hernia after abdominal hysterectomy for forty years: A case report

Ya-Chen Chou

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Abstract

BACKGROUND

Internal hernia is a rare complication following abdominal surgery, primarily resulting from structural defects caused by anastomosis. We report a unique case of a late abdominal wall internal hernia highly suspected as resulting from insufficient peritoneal closure.

CASE SUMMARY

A 72-year-old woman presented with symptoms of intestinal obstruction 40 years after undergoing an abdominal hysterectomy. Abdominal computed tomography revealed a suspicious closed loop of intestine; then, a laparotomy was performed for suspected internal hernia. During the procedure, herniation of intestine into the preperitoneal space through a parietal peritoneal defect between rectus abdominis and sigmoid colon was identified. Intestinal reduction, resection of the ischemic segment and closure of the peritoneal defect were performed. The patient recovered well.

CONCLUSION

Non-closure of peritoneum might lead to late internal hernias. Meticulous peritoneal closure should be considered to prevent this potentially lethal complication.

Key Words: Peritoneal hernia; Internal hernia; Incisional hernia; Intestinal obstruction; Case report

Core Tip: We report a unique case of an abdominal wall internal hernia, a late complication that is highly suspected to be related to insufficient peritoneal closure. In the context of the current dominant practice of not closing the peritoneum, our case highlights a potential challenge in lower abdominal surgeries, particularly those involving organ resection or transabdominal preperitoneal inguinal herniorrhaphy. It emphasizes the need for heightened awareness among clinicians regarding long-term surgical outcomes, and advocates for meticulous peritoneal closure to prevent this potentially lethal issue, despite the limited existing evidence.

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INTRODUCTION

Internal hernia is a rare condition related to either natural or acquired defects, which can lead to intestinal obstruction, ischemia, necrosis and even mortality. As a surgical complication, it accounts for 0.5% to 6% of various operations, primarily resulting from anastomosis[1-5]. Internal hernias occurring through abdominal wall peritoneal defects are extremely rare and have predominantly been reported as acute complications[6-8]. We describe a case of such a condition as a late complication occurring 40 years after a hysterectomy.

CASE PRESENTATION

Chief complaints

A 72-year-old woman complained of abdominal distension for three days.

History of present illness

A 72-year-old female presented to the emergency room with abdominal distension lasting for three days. She also complained about vomiting and a lack of flatus and defecation, but denied having had similar discomfort in the past.

History of past illness

She had undergone a hysterectomy *via* lower midline laparotomy 40 years previously, although no documentation regarding the operation was available.

Personal and family history

There is no relevant personal and family history.

Physical examination

Physical examination revealed mild abdominal distension with stable vital signs and no signs of peritoneal irritation.

Laboratory examinations

Blood tests indicated dehydration (hemoconcentration, pre-renal azotemia and hyperlactatemia) and signs of intra-abdominal infection (leukocytosis with left shift and hyperlactatemia).

Imaging examinations

Abdominal computed tomography (CT) revealed segmental dilation of the small bowel with a transitional zone of mid-ileum in right lower quadrant, as well as a segment of suspicious closed loop of the small bowel with edematous change and focal ascites in the left lower quadrant (Figure 1).

FINAL DIAGNOSIS

The final diagnosis is high suspicion of internal herniation.

TREATMENT

The CT scan indicated suspicious internal herniation. Although the patient did not exhibit signs of peritoneal irritation

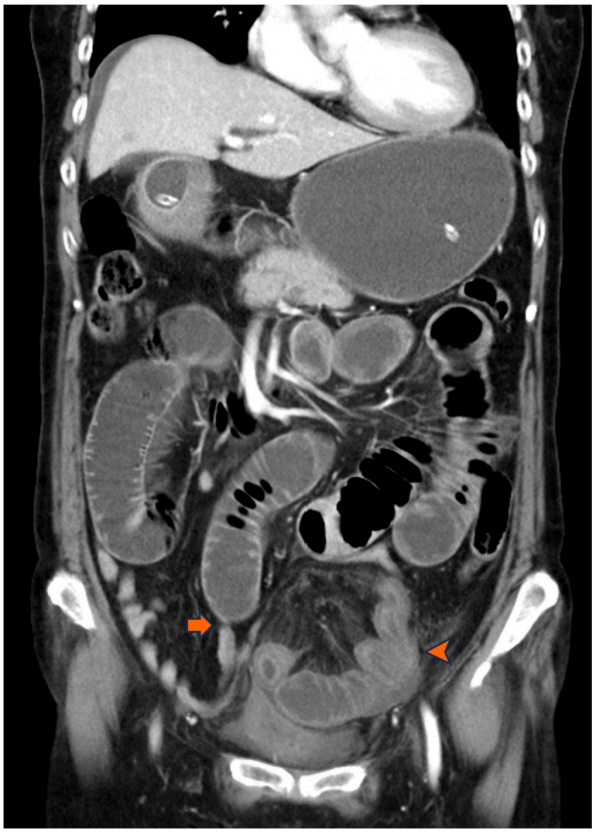

Figure 1 Pre-operative abdominal computed tomography scan. Abdominal computed tomography revealed segmental dilatation of the small bowel with a transitional zone (arrow), as well as a segment of suspicious closed loop of the small bowel (arrowhead).

and her vital signs were relatively stable, clinical deterioration could have been delayed due to obstruction of venous return from internal herniation. Considering its high risk of morbidity and mortality, low likelihood of spontaneous reduction and the patient's advanced age with limited compensatory ability, exploratory laparotomy was recommended. After a thorough explanation and discussion, the patient and her family consented to surgery.

An urgent exploratory laparotomy was performed. After incising along the previous hysterectomy scar, a large segment of distal jejunum was found herniated into the preperitoneal space in the pelvis through a peritoneal defect at the prior scar, located between the rectus abdominis and sigmoid colon. A complete hernia sac under intact muscular integrity was identified (Figure 2A and B). Upon reviewing CT, the situation was also documented (Figure 2C) in a perspective drawing illustrating the spatial relationship of the hernia in a simple way (Figure 2D). The herniated intestine was reduced, and a ten-centimeter segment of bowel resection was performed due to suspected partial wall ischemic changes. The peritoneal defect (hernia sac) was closed using continuous non-absorbable sutures.

OUTCOME AND FOLLOW-UP

The patient was transferred to intensive care unit for sepsis and atrial fibrillation with rapid ventricular response postoperatively. She had a smooth recovery from the sepsis, and her intake was gradually resumed with the postoperative course being largely normal, except for urinary retention due to deconditioning. She was discharged after two weeks.

DISCUSSION

Internal hernia is a rare, surgery-related condition that can be potentially lethal, possibly resulting from congenital or postoperative defects or weak points. The incidence varies between surgical procedures and methods of anastomosis, with significantly higher rates observed in upper gastrointestinal surgeries (0.7% to 6%)[1,2,4], lower rates in lower gastrointestinal surgeries (0.5% to 0.65%)[3,5], and even lower rates in other types of surgery. Most cases are caused by ring-structured defects produced by anastomosis[1-5]. Diagnosis is challenging due to non-specific clinical symptoms and findings, with accurate diagnosis requiring a high level of awareness from physicians.

In our case, we report an extremely rare presentation of an incisional internal hernia. The exact cause of this hernia was unclear and there were no records regarding the hysterectomy, particularly concerning peritonealization. However, it

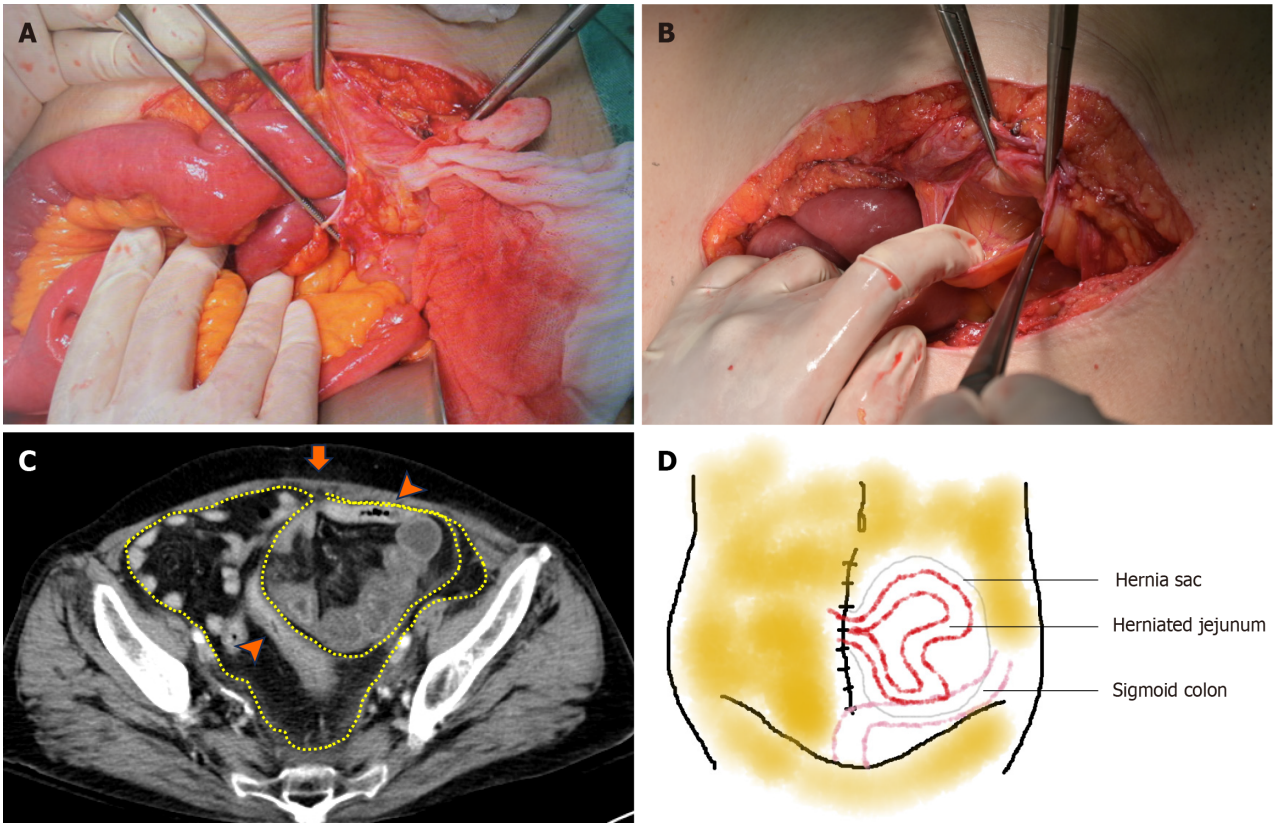

Figure 2 Findings of parietal peritoneal hernia. A: After laparotomy, a large segment of distal jejunum was found herniated into the retrorectus preperitoneal space; B: After reduction of the herniated intestine, a complete hernia sac was observed through a peritoneal defect on the prior scar; C: Pre-operative computed tomography showed the hernia sac located between the intact rectus abdominis (arrow) and sigmoid colon (arrowhead, representing part of the dome of the sac). The yellow line indicates the parietal peritoneum; D: This perspective drawing illustrates the spatial relationship of the hernia in a simple way.

was assumed that a peritoneal defect - whether peritonealized or not - was created by the prior abdominal hysterectomy, leading to chronic migration of the intestine. This is similar to the acute complication of intestinal herniation through a small peritoneal defect after abdominal hysterectomy, as proposed by Kwon *et al*[6]. Other similar cases in transabdominal preperitoneal (TAPP) herniorrhaphy have also demonstrated acute herniations due to improper peritoneal approximation[7,8].

Peritoneal closure remains a topic of controversy, with a trend towards non-closure in both obstetric and non-obstetric surgeries in recent decades. In the case of acute peritoneal hernia after hysterectomy mentioned above, the surgeons ultimately decided to leave the peritoneum open and only closed the fascial layer[6]. The reasons favoring non-closure included equivalent major complications - such as mortality, burst abdomen, incisional hernia, and length of hospitalization - as well as shorter surgical times and reduced anesthesia exposure[9-11]. Similar findings regarding postoperative pain and recurrence have been observed in TAPP surgeries[12]. Our case highlights the possibility of a significant late complication of internal herniation, which can lead to high morbidity. Despite the limited evidence, we propose that non-peritonealization could result in peritoneal herniation with acute onset associated with smaller defects and late onset with larger ones.

Accordingly, parietal peritoneal hernia emerges as a possibly delayed challenge in the context of current practices of non-peritonealization or large-distance closure of the peritoneum. It is anticipated that this type of hernia might occur in lower abdominal surgeries involving organ resection such as hysterectomy or cystectomy, where there is no fascial restriction and additional preperitoneal space. Inguinal hernias following TAPP repair could also represent a potential source, given the disease-related space, a relatively weak abdominal wall, and compromised peritoneal integrity due to absorbable tacks or non-closure. Given the high morbidity and mortality associated with internal hernias compared to their low primary detection rates, we advocate for more meticulous closure of the peritoneum in these situations, even in light of the limited available evidence. Further investigation is necessary.

CONCLUSION

Non-closure of the peritoneum may lead to internal hernia developing over time. This late complication may pose an increasing challenge, especially in lower abdominal surgeries; accordingly, when treating patients with a long history of lower abdominal surgery, awareness needs to be raised and meticulous peritonealization should be considered to avoid this potentially lethal problem, even in the absence of extensive evidence. Further research into the long-term outcomes of

non-closure of the peritoneum is necessary.

FOOTNOTES

Author contributions: Chou YC contributed to data collection, data analysis and drafting of the manuscript.

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CASE REPORT

Treatment of thymoma with low-dose glucocorticoids before surgery for significant tumor shrinkage: A case report

Jin-Kun Yao, Zi-Yi He, Zheng Zhu, Hai-Tao Huang

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Abstract

BACKGROUND

Thymic epithelial neoplasms are rare malignant neoplasms originating in the thymus gland. There have been case reports of patients with advanced thymomas treated with a methylprednisolone pulse or with glucocorticoid (GCs) shock before surgery, followed by surgical treatment, all of whom achieved good results. The effect of GCs on thymomas is related mainly to the action on GC receptors in thymic lymphocytes and epithelial cells. GC receptor expression has been associated with a better prognosis in patients with thymomas, including those with surgically removed thymomas.

CASE SUMMARY

We report a case of a patient with thymoma who had a significant response to preoperative low-dose GC therapy. A mediastinal tumor was detected in the patient *via* computerized tomography upon admission. The tumor was initially suspected to be a thymic tumor, but lymphoma could not be ruled out. The tumor shrank significantly after low-dose (5 mg/day) GC therapy. Thoracoscopic thymoma resection was performed after puncture pathology was confirmed. The patient recovered well after the operation and is currently performing well with no recurrence of the tumor.

CONCLUSION

This case highlights that low-dose GCs are effective in the treatment of thymomas, and we believe that GCs should be applied more frequently and studied more thoroughly in the treatment of thymomas.

Key Words: Thymoma; Glucocorticoid; Diagnosis; Shrinkage; Treatment; Case report

Core Tip: This study reports a case of a thymoma patient whose tumor significantly shrank following preoperative treatment with low-dose glucocorticoids (GCs). The low-dose GC therapy demonstrated promising efficacy, promoting tumor reduction, minimizing intraoperative adhesions, and facilitating smooth postoperative recovery without recurrence. This study highlights the potential of GCs in the management of thymoma and calls for further investigation into their application in therapeutic strategies.

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INTRODUCTION

Thymic epithelial tumors are rare malignant tumors originating in the thymus[1]. The overall incidence of thymomas in the United States is 0.13 per 100000 person-years[2]. Histologically, thymic epithelial tumors are classified into various subtypes, including type A, AB, B1, B2, B3, and C thymic carcinomas[3]. Thymomas can present with various manifestations, such as myasthenia gravis and local symptoms, or are asymptomatic and detected as mediastinal masses on chest X-ray[4-6]. For resectable thymomas, especially for invasive thymomas, postoperative radiotherapy is recommended[7]. Complete thymectomy is typically performed in specific cases[8]. Platinum chemotherapy is still the standard treatment for advanced thymomas that cannot be completely resected by surgery[9]. Initiation of chemotherapy to optimize surgical excision and consolidation to control residual lesions may improve the prognosis of patients with advanced thymomas [10-12].

At present, there are case reports that advanced thymomas can be controlled by methylprednisolone pulse therapy with good efficacy[13]. Moreover, preoperative glucocorticoid (GC) impact therapy has a significant effect on stage B1 thymoma, and the preoperative tumor burden in patients is significantly reduced[14]. However, there are currently almost no clinical studies on the application of low-dose GCs in the treatment of thymoma. We hope that this report on the preoperative use of low-dose GCs in the treatment of a thymoma will provide new ideas for the application of GCs in the treatment of thymomas.

CASE PRESENTATION

Chief complaints

A 44-year-old young patient with chest tightness examined chest computed tomography (CT) and found anterior mediastinal space.

History of present illness

In August 2023, a 44-year-old patient with chest tightness was examined *via* chest CT and an anterior mediastinal space tumor was detected. The patient was admitted with a temperature of 38.2 °C. The patient was healthy in the past and had no bad habits, such as smoking or drinking. The patient had occasional chest tightness and pain but no related clinical symptoms of myasthenia gravis and sought treatment at our hospital because of the aggravation of chest tightness symptoms.

History of past illness

The patient had no specific past medical history.

Personal and family history

The patient had no personal and family history.

Physical examination

He had a physical examination but found no obvious positive signs.

Laboratory examinations

Routine blood tests revealed that the white blood cell count was 15.97 × 10^9/L, the lymphocyte count was 3.11 × 10^9/L, and the monocyte count was 2.25 × 10^9/L. Other blood tests showed no obvious abnormality.

Imaging examinations

Chest CT revealed a soft-tissue shadow that was visible on the right side of the anterior mediastinum.

FINAL DIAGNOSIS

The patient was eventually diagnosed with thymoma.

TREATMENT

The cooling effect of daily intravenous injection of 5 mg of dexamethasone sodium phosphate was significant, as shown in Figure 1, and chest CT reexamination revealed a significant reduction in the thymic mass.

OUTCOME AND FOLLOW-UP

When professor Huang's expert team discussed the condition, they consulted the relevant literature and found that in other countries, the preoperative application of GCs could effectively reduce the thymus tumor volume and improve the surgical effect; thus, dexamethasone sodium phosphate was used for 2 weeks. Considering that the patient's disease could not exclude the possibility of lymphoma, B-ultrasound-guided transesophageal mediastinal mass puncture was performed after admission. Thymoma was pathologically confirmed (Figure 2), and surgery was scheduled. Extubation was performed 3 days after surgery, and routine pathology revealed a type B2 anterior mediastinal thymoma (Figure 3). To date, the patient has recovered well, and the tumor has not returned. The entire process of patient treatment, from admission to discharge, is shown in Figure 4.

DISCUSSION

In this case, the patient experienced excellent GC therapy outcomes before surgery. The mass was significantly reduced, there was less intraoperative adhesion, and the separation of the pericardium and thymus tissue was smooth. These findings suggest that the GC promoted a significant shrinkage of the thymoma in this patient. Indeed, there have been previous reports of thymoma regression after GC therapy[14,15], which is consistent with the findings reported in this case. These findings suggest that GCs can promote the obvious shrinkage of thymomas in patients. After the patient was admitted to the hospital, we consulted the relevant literature and found many case reports of GC shock therapy for thymomas. Some scholars have conducted prospective studies with the administration of GC shock therapy for 2 weeks before surgery and reported that the effects on B1, B2 and B3 thymomas were significant, and most patients experienced partial remission before surgery and no recurrence after surgery[14]. In Nakamura *et al*'s report[13], a patient with a metastatic thymoma that was well controlled by methylprednisolone pulse therapy plus immunosuppressants was described. In patients with metastatic thymomas, especially in those with myasthenia gravis, the use of GCs has been affirmed by many studies for their positive effects[16]. However, no studies have discussed in detail the influence of the duration of GC use and its benefits before and after surgery. In addition, these studies were based on high-dose corticosteroid shock therapy, while our patient achieved significant tumor shrinkage with 5 mg of a corticosteroid per day. In previous studies, only one patient with thymoma-induced pleural effusion was reported to have been treated with a low dose of GCs, but the effect was significant[17]. These findings suggest that it may be possible to achieve good results with small amounts of hormones in patients with preoperative thymoma.

GCs, a class of steroid hormones, are important regulatory molecules that control inflammation, cell growth and differentiation through the activity of specific intracellular GC receptors (GRs)[18,19]. In the normal thymus, GRs are expressed not only in immature thymus cells but also in epithelial cells, and high GR expression can also be detected in thymoma cells. Therefore, the effect of GCs on thymomas is related mainly to the effects of GRs on thymoma cells and epithelial cells. A study by Mimae *et al*[20] revealed high GR expression rates in thymomas, and multivariate analysis revealed that GR expression was associated with a better prognosis in patients with thymomas, including those with surgically removed thymomas.

In our case, there were positive pathological changes before and after hormone therapy, which provided effective case support for our study of the effects of GCs on thymoma. We report the case of a patient who was hospitalized for a large thymoma, with a pre-steroid biopsy showing immature TdT (+) and CD5 (+), CD20 (+), and CD3 (+) T lymphocytes, and post-steroid resection pathology revealing TdT (-), CD5 (-), CD20 (-), and CD3 (-) cells. These findings suggest that GCs cause the loss of immature lymphocytes in thymus tumors. This finding is consistent with the findings of Tateyama *et al*[21], who reported that corticosteroids might cause degenerative changes in epithelial cells and immature T lymphocytes. Kobayashi *et al*[14] noted that the reduction in the size of thymomas rich in these immature lymphocytes with steroid treatment could be explained by the reduction in the number of most lymphocytes. This could explain why the tumors shrunk so much after GC therapy. Kobayashi *et al*[14] also reported that preoperative GC pulse treatment resulted in a much greater reduction in B1 thymomas than in other types of thymomas because B1 thymomas have large numbers of

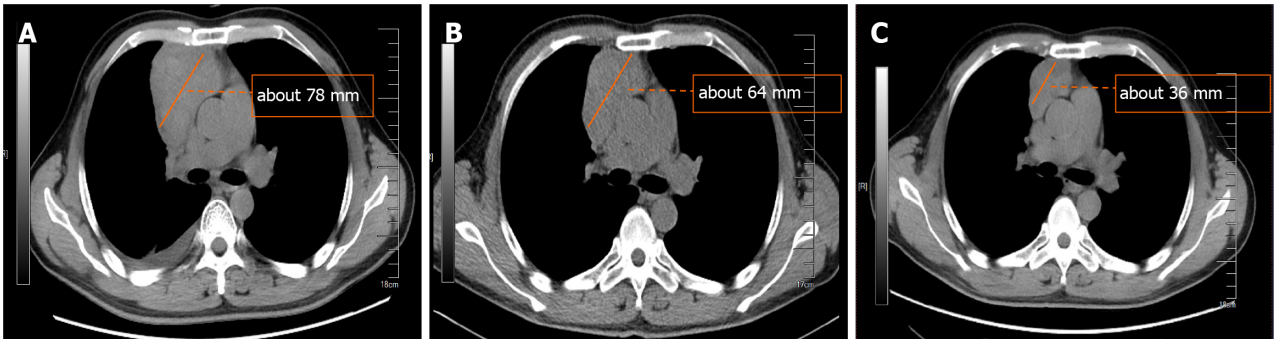

Figure 1 Computed tomography examination of the patient. A: On August 23, 2023, enhanced chest computed tomography (CT) revealed a soft-tissue shadow that was visible on the right side of the anterior mediastinum, with a size of approximately 78 mm × 53 mm. After enhancement, the mass was uneven and mildly enhanced, the surrounding fat space was blurred, and the superior vena cava and the right atrium were compressed; B: On August 28, 2023, chest CT revealed a soft-tissue shadow that was visible on the right side of the anterior mediastinum; the size of the mass was approximately 64 mm × 55 mm, the surrounding fat space was blurred, and the superior vena cava and the right atrium were compressed; C: On September 11, 2023, chest CT revealed a soft-tissue shadow that was visible on the right side of the anterior mediastinum; the size of the mass was approximately 39 mm × 54 mm, the surrounding fat space was blurred, and the sizes and shapes of the large blood vessels of the heart were normal.

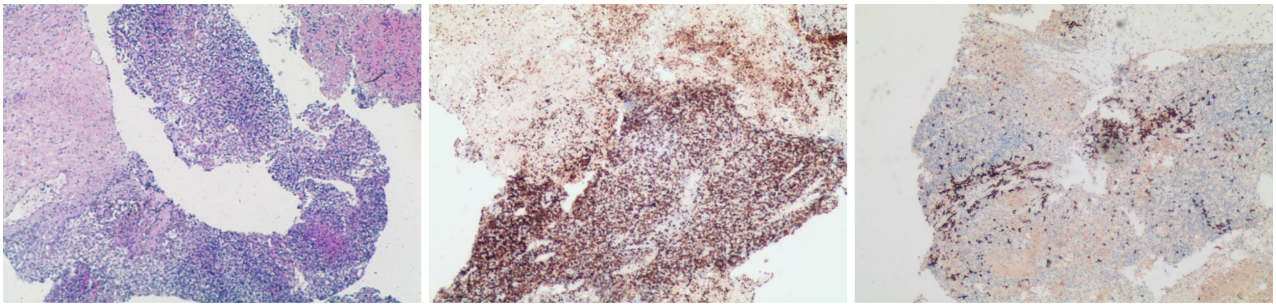

Figure 2 Preoperative pathology. Preoperative pathology revealed a small amount of lymphoid tissue and epithelioid cells with necrosis. When combined with immunohistochemical results, which were consistent with thymoma, and considering that there was little tissue, it was recommended that specimens be further classified after surgery. The immunohistochemistry results were as follows: TdT (partial +), CD5 (partial +), CD20 (small +), CD3 (partial +), CK (AE1/AE3) (+), CK19 (+), p63 (+), Ki-67 (20% +), CDla (partial +), CD117 (individual +), CK (+), and p53 (minor +). HE: Hematoxylin and eosin.

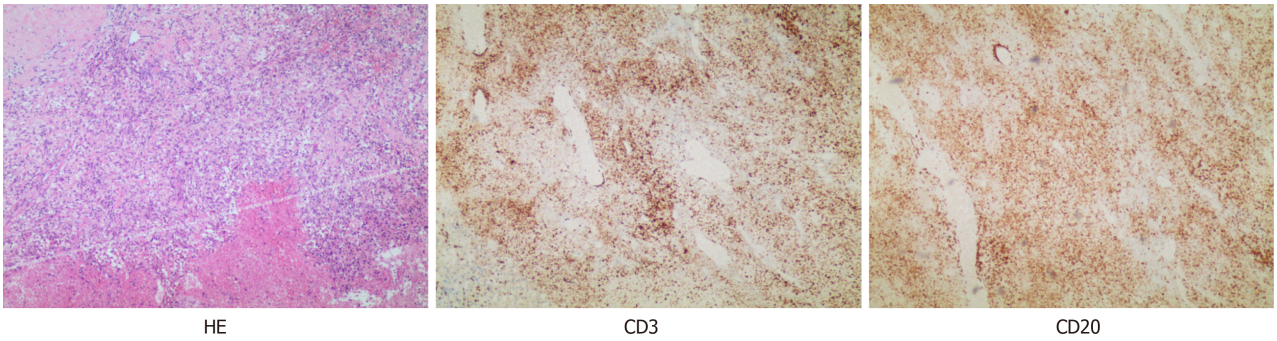

Figure 3 Postoperative pathology. Postoperative pathology revealed anterior mediastinal thymoma (type B2), cyst formation in some areas, fibrosis and large necrosis, and infiltration of the capsule. Immunohistochemistry revealed the following: CK (AE1/AE3) (+), CK19 (+), CK5/6 (+), p63 (+), Ki-67 (+), TdT (-), CD5 (-), CD20 (-), CD3 (-), CDla (-), and CD117 (-). HE: Hematoxylin and eosin.

immature double-positive [CD4 (+) and CD8 (+)] lymphocytes, which are very sensitive to GC-induced apoptosis.

Notably, studies have shown that GCs can also directly inhibit the proliferation of tumor cells. This may be because GCs affect tumor cells by inducing G1 phase cell cycle arrest in human thymus tumor epithelial cells[22]. In this study, there were a small number of cases in which tumors still grew slowly after steroid therapy, which the authors believe may be related to the short duration of steroid hormone use and the type of pathology. We hope that further studies will confirm the appropriate duration of preoperative steroid use and analyze its benefits depending on the pathological types in patients. In summary, we believe that GCs can effectively control the progression of thymomas. We also believe that for thymoma patients with large tumor volumes or chest tightness, the use of low-dose GC therapy can be considered

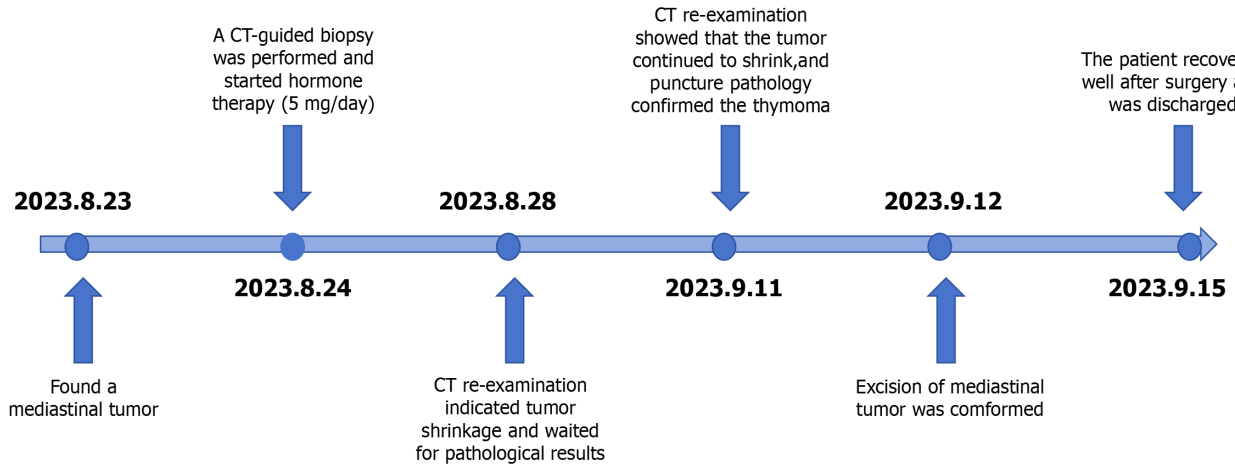

Figure 4 Patient treatment flowchart. CT: Computed tomography.

before surgical treatment, which may be conducive to curing patients. We also look forward to more similar cases or studies to provide clinical evidence for preoperative GC therapy. At present, there are no authoritative guidelines for the preoperative use of hormone therapy for thymomas. This case provides a better idea for the treatment of thymoma and has certain reference value for clinicians. The explanation of the mechanism of action of hormones in the treatment of thymoma could be improved in the future, and the application of hormone therapy in the treatment of thymoma could be supported by a systematic theory. In the future, we may conduct more in-depth research on the timing of hormone therapy before thymoma surgery and whether to use hormone therapy after surgery so that patients with thymomas can receive better treatment.

CONCLUSION

This report reports a case of thymoma sensitive to low dose GCs. It highlights the need to consider preoperative trials of low-dose GC therapy in patients with significant discomfort or large, suspected thymomas.

FOOTNOTES

Author contributions: Yao JK drafted the manuscript; He ZY, Zhu Z, and Huang HT revised and approved the manuscript and provided guidance and technical support; Huang HT's surgical team evaluated the patient and participated in the entire treatment of the patient; He ZY and Huang HT they contributed equally to this article, they are the co-corresponding authors of this manuscript; and all of the authors have contributed to this article and have approved the submitted version.

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CASE REPORT

Dystrophic epidermolysis bullosa caused by novel frameshift mutation in the *COL7A1* gene: A case report

Yan Yang, Zhi-Wei Guan, Qin-Feng Li

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Abstract

BACKGROUND

Dystrophic epidermolysis bullosa is characterized by fragile ulcerations of the skin caused by mutations in specific genes. However, genetic typing of this condition is rare.

CASE SUMMARY

An 11-year-old female suffered from recurrent fever, visible ulcerations of the entire skin, and severe malnutrition. Genetic testing revealed a frameshift mutation in the coding region 4047 of the 35th intron region of *COL7A1*, and she was diagnosed as malnutrition-type epidermolysis bullosa. Drug therapy (immunoglobulin, fresh frozen plasma), topical therapy (silver ion dressing), fever reduction, cough relief, and promotion of gastrointestinal peristalsis are mainly used for respiratory and gastrointestinal complications. The patient's condition improved after treatment.

CONCLUSION

Dystrophic epidermolysis bullosa caused by a new framework shift mutation in *COL7A1* should be taken seriously.

Key Words: Dystrophic epidermolysis bullosa; Frameshift mutation; Genetic testing; *COL7A1* gene; Genetic typing; Immunoglobulin; Case report

Core Tip: A new frameshift mutation in the *COL7A1* gene caused dystrophic epidermolysis bullosa (DEB). Genetic testing of the patient showed a frameshift mutation in the coding region 4047 of the 35th intron of the *COL7A1* gene, which was improved after symptomatic drug treatment. Indicating the role of genetic testing in DEB diagnosis and providing clinical data for DEB gene therapy.

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INTRODUCTION

Based on the classification of inherited epidermolysis bullosa, dystrophic epidermolysis bullosa (DEB) is an inherited genetic variant with clinical manifestations of skin fragility and ulceration[1], especially in areas such as the hands, feet, and knees, where the skin is fragile and prone to blisters and scars after slight friction or trauma[2]. DEB is mainly caused by abnormal changes in the *COL7A1* gene, which encodes a complex COL7 protein that maintains skin structure and function. Herein, we report a case of DEB associated with a novel frameshift mutation in the *COL7A1* gene. This report aimed to draw doctors' attention to genetic testing in DEB diagnosis and promote the progress of DEB gene drug therapy.

CASE PRESENTATION

Chief complaints

The patient presented with unexplained fever symptoms before admission, with a maximum body temperature of 39 °C and no convulsions. After oral treatment with ibuprofen, the body temperature decreased to normal levels but subsequently showed multiple increases. This fever lasting 8 days.

History of present illness

An 11 years old female presented for a fever lasting 8 days.

History of past illness

The patient had a history of congenital epidermolysis bullosa for > 10 years.

Personal and family history

The patient and her parents denied a family history of hereditary diseases.

Physical examination

After admission, physical examination revealed scattered ulcerations and erosions of the child's entire skin; peeling of the skin on the face, shoulders, back, waist, and thighs, with local exudation and visible scabbing; the gap between the palms and fingers of both hands disappeared; and both toes were missing (Figure 1). The child was 124 cm tall and weighed 18.5 kg, showing significant physical underdevelopment, poor nutritional status, and a relatively thin and weak physique.

Laboratory examinations

No significant abnormality was found in biochemical routine, calcitoninogen, blood sedimentation, liver and kidney function, coagulation function. Immunoglobulin E: 281.7 IU/mL; chest X-ray showed: Heavy texture in both lungs. Electrocardiogram showed non-specific changes in the T-wave, along with incomplete right bundle branch block. Echocardiography showed no significant abnormalities.

Imaging examinations

Genetic testing revealed an abnormal change in the sequence of *COL7A1* with NM-000094.4: Intron35: C.4047 + 1 guanine (G) > adenine (A) (the nucleotide in the coding region 4047 changed from G to A). The mother harbored a heterozygous mutation at this site, whereas the father did not (Figure 2).

FINAL DIAGNOSIS

Based on the patient's clinical symptoms and genetic test results, the final diagnosis was malnourity-type bullous epidermal lysis.

Figure 1 Patient full body check-up. A: Scattered ulceration and erosion can be seen on the skin of the patient's entire body; B: Locally visible exudation and scabbing.

TREATMENT

After the patient was admitted to the hospital, she was given linezolid and ertapenem for one week to treat recurrent high fever. Drug treatment: The patient was treated with immunoglobulin at approximately 0.4 g/kg, albumin was given to maintain blood volume and blood pressure, fresh frozen plasma was used to treat coagulation disorders and supplement protein, and ulinastatin was used to reduce inflammation and promote wound healing. External treatment: External medications, laser, wet compresses, medication baths, scab removal, dressing changes of the patient's wounds, iodine disinfection, physiological saline flushing, silver ion dressing (antibacterial), and external application of freeze-dried recombinant human acidic fibroblast growth factor and mupirocin ointment were also done. On the 20th day of admission, the patient's chest X-ray showed consolidation shadows in the right middle lung field, and she was treated with a cephalosporin laxative. However, the child had a persistent cough and was treated with nebulization, an oral solution of eucalyptus palmatum, and ambromoterol oral solution for symptomatic cough relief. The child's immunoglobulin E levels were > 2500 IU/mL in the serum, allergy level to milk in allergen testing is at level 2. Cetirizine hydrochloride drops were also administered for anti-allergy purposes. The patient's mother was also encouraged to show the patient love and affection to help balance gut microbiota. After treatment, the patient's overall skin exudation decreased, the area of injury became smaller, and the locally visible skin was fresh (Figure 3). The patient was subsequently discharged from the hospital.

OUTCOME AND FOLLOW-UP

The patient was discharged after 28 days of hospitalization, and the wound improved significantly upon discharge. The patient was advised to take home care measures to prevent infection. Regular follow-up visits are conducted through communication such as phone calls.

DISCUSSION

DEB is a rare congenital genetic disorder caused by mutations in many genes, mostly occurs in children, which manifests clinically as dystrophica and a tendency to form blisters and vesicles when subjected to minor trauma or friction, prognosis difficulties, which greatly affects the quality of life of patients[3]. DEB is classified into malnourished, borderline, and simple types based on genetic patterns and lesion depth. Among these, DEB is a relatively rare type caused by the absence or abnormal morphology of anchored fibers in the dermal connective tissue beneath the dense plate of the basement membrane[4]. From a genetic perspective, DEB is caused by abnormal changes in type VII collagen (*COL7A1*), the main component of anchor fibers[5]. The *COL7A1* gene is located at position 3p21.1 on the human

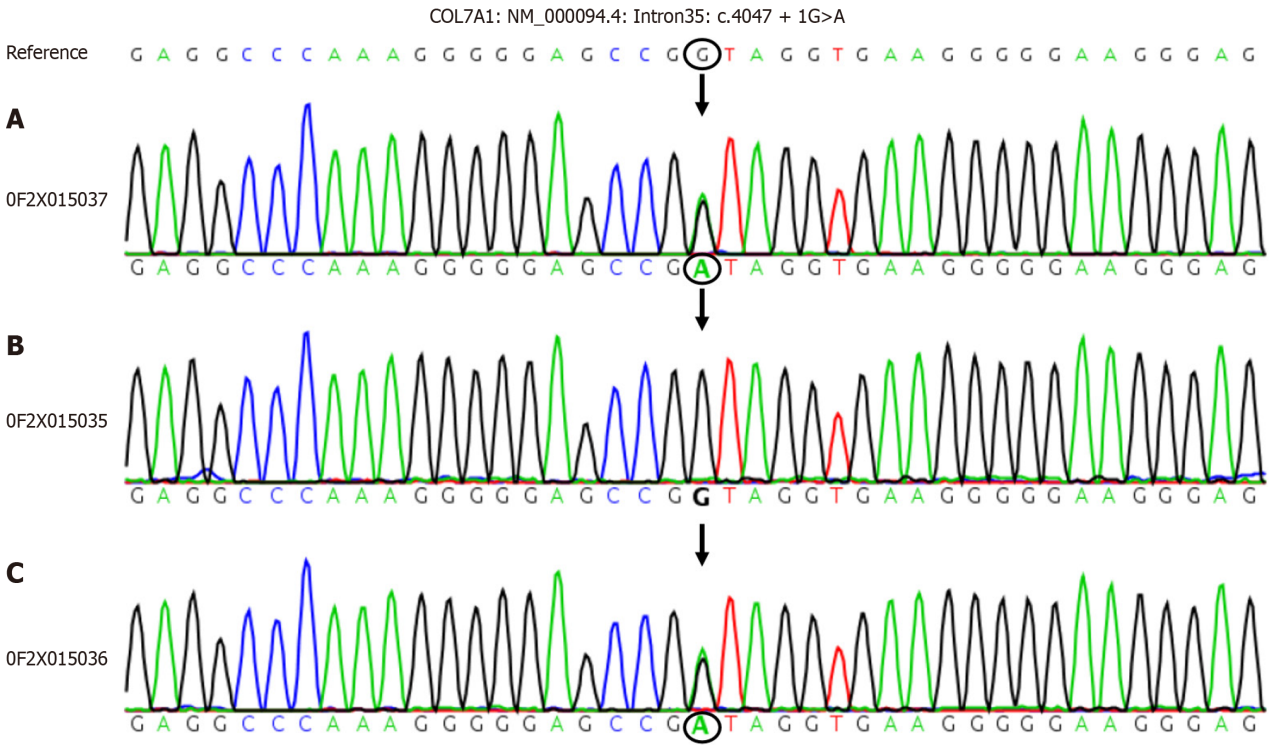

Figure 2 *COL7A1* genetic test. A: The *COL7A1* gene in the patient undergoes a mutation, NM-000094.4: Intron35: c.4047 + 1 guanine > adenine (the nucleotide in the coding region 4047 mutates from guanine to adenine); B: The father did not have a mutation; C: The mother has a heterozygous mutation at this locus. G: Guanine; A: Adenine.

chromosome and is approximately three times the length of the mRNA encoding type VII collagen. The subsequence of this gene is relatively short and the arrangement of exons is relatively compact, which plays an important role in the function of the protein it encodes. However, in patients with DEB, early termination codon mutations or glycine substitution mutations in *COL7A1* cause qualitative and quantitative changes in type VII collagen, thereby affecting the molecular biological characteristics of anchor fibers and leading to instability of the true epidermal junction structure, which can make skin tissue extremely sensitive to friction and pressure; even a slight touch can lead to blisters and skin tearing. However, the condition described in this case is relatively rare. Congenital EB is typically diagnosed during infancy. At the age of 11, an abnormal fever may lead to severe illness. In our case, the patient's skin was ulcerated, especially on the limbs, face, shoulder, back, waist, and thighs. Local exudation and scabbing were observed, the proximal gap between the palms and fingers disappeared, and both toes were missing. These findings were accompanied by severe malnutrition and infections. Genetic testing revealed a code-shifting mutation in *COL7A1*. Based on the medical records, clinical manifestations, and test results, the patient was diagnosed with malnutrition-type bullous epidermal lysis.

Harmful missense mutations and gene function loss mutations can disrupt gene function, thereby reducing an individual's adaptability to survive in the existing environment and leading to a genetic burden. Dang *et al*[6] pointed out that 23 different *COL7A1* allelic variants, nine of which were novel, which involves glycine substitutions within the triple helix of *COL7A1*. Liu and Wang[7] reported *COL7A1* frameshift mutations at C2005T and G7922A, which were identified as autosomal recessive malnutrition bullous epidermal lysis. Han *et al*[8] described cases of heterozygous frameshift mutations occurring in two exon positions of *COL7A1* that were identified and found to be associated with Bart syndrome. However, the mutations identified in our study were different from those mentioned above. The DEB cases in this study were unique and caused by a newly discovered *COL7A1* frameshift mutation. This association was determined by analyzing the clinical manifestations and genotypes of the affected children. From a clinical perspective, the patient presented with systemic lesions, severe ulceration, and loss of both toes. As patients with this condition age, they exhibit worsening skin damage accompanied by severe malnutrition and delayed growth and development. From a genotypic perspective, a heterozygous frameshift mutation was found in the coding region 4047 of the 35th intron of the *COL7A1* gene. The mutation in the coding region 4047 resulted in a substitution of the first nucleotide from G to A, followed by the formation of a stop codon. Therefore, the triple-helix region of type VII collagen in *COL7A1* undergoes changes, synthesizing mutated peptides that affect the recognition of the ultrastructure of anchored fibrils.

Many methods are currently available for treating DEB. Venugopal *et al*[9] used allogeneic fibroblasts cultured in suspension to treat DEB wounds. Gurevich *et al*[10] applied beremagene geperpavec containing *COL7A1* to treat skin injuries in patients with DEB. This treatment method delivers the normal *COL7A1* gene to the patient's skin cells through a viral vector to restore or enhance the function of type VII collagen, thereby improving skin condition. However, there is no fundamental and widespread treatment for DEB that mainly focuses on alleviating symptoms and preventing complications. In terms of treatment, this article highlights the use of immunoglobulin, albumin, fresh frozen plasma, and ulinastatin for the treatment of affected children to improve coagulation disorders, supplement proteins, and promote

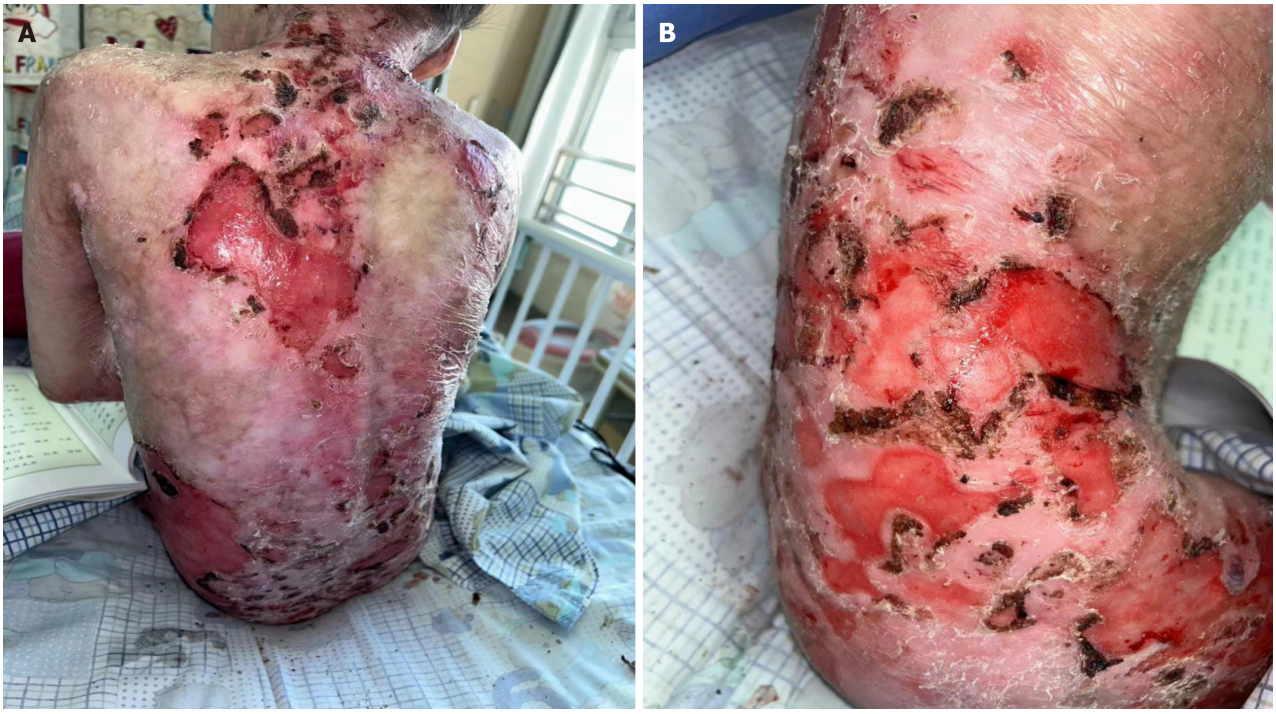

Figure 3 Gradual recovery of the patient's overall skin. A: The patient's overall skin exudation decreased and the area of injury became smaller; B: Locally visible skin was fresh.

wound healing. It also highlighted the use of external treatments such as silver ion dressings supplemented with growth factors and mupirocin ointment for wound scab removal and dressing changes. In our case, the patient's condition worsened due to repeated fever, which affected the gastrointestinal and respiratory tracts. Therefore, treatments such as fever reduction, cough relief, and nebulization may be necessary. After treatment, the patient's symptoms improved, and she was discharged without complications.

The field of genetic medicine has developed rapidly in recent years. With the accumulation of clinical manifestations and genetic testing data for DEB, the precise classification of DEB and methods based on cell and gene therapies may become a reality. Gene therapy differs from traditional therapy, which involves treating hereditary diseases by adding, repairing, replacing, or silencing specific genes. Therefore, it is necessary to study novel heterozygous frameshift mutations in *COL7A1* associated with DEB. Exploring the mutation's effects and responses to gene-targeted therapies is of great significance for deepening our understanding of disease mechanisms and expanding treatment options. Through in-depth analysis of mutated genes and molecular pathways can help us identify potential biomarkers and provide more accurate basis for personalized treatment. In the future, we will further reveal the specific impact of different mutations on the therapeutic effects, so as to optimize the existing treatment protocols, enhance the clinical efficacy, and ultimately improve the prognosis and quality of life of patients.

CONCLUSION

We present a case of DEB caused by novel frameshift mutation in the *COL7A1* gene, which not only plays a key role in the development of complex diseases such as hereditary dermatological disorders and cancers, but may also directly affect the patient's responsiveness to targeted drugs. In the future, we will conduct in-depth research on relevant case genes to provide clinical trial data and theoretical support for DEB gene therapy.

FOOTNOTES

Author contributions: Yang Y and Guan ZW designed the research study; Yang Y, Guan ZW, and Li QF performed the research; Yang Y, Guan ZW, and Li QF analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

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CASE REPORT

Hepatic hemangiomas mimicking gastrointestinal stromal tumors: A case report

Ji-Ze Wang, Hao Chen

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Abstract

BACKGROUND

Hepatic hemangiomas can be challenging to diagnose, particularly when they present with atypical features that mimic other conditions, such as gastrointestinal stromal tumors (GISTs). This case highlights the diagnostic difficulties encountered when imaging subepithelial lesions, especially when conventional methods such as computed tomography (CT) and endoscopic ultrasound (EUS) are used.

CASE SUMMARY

A 44-year-old woman presented with intermittent abdominal distension and heartburn for three months. Her medical history included iron deficiency anemia, menorrhagia, and previous cholecystectomy. One week prior to admission, an endoscopy suggested a bulging gastric fundus, which was likely a GIST, along with chronic nonatrophic gastritis and bile reflux. CT and EUS revealed nodules in the gastric fundus, which were initially considered benign tumors with a differential diagnosis of stromal tumor or leiomyoma. During surgery, unexpected lesions were found in the liver pressing against the gastric fundus, leading to laparoscopic liver resection. Postoperative pathology confirmed the diagnosis of hepatic cavernous hemangiomas. The patient recovered well and was discharged five days later, with normal follow-up results at three months.

CONCLUSION

This case underscores the challenges in the preoperative diagnosis of GISTs, particularly the limitations of the use of CT and EUS for the evaluation of subepithelial lesions. While CT is the primary tool for visualizing abdominal tumors, it is difficult to detect smaller lesions and assess the layers of the gastrointestinal wall on CT. EUS is recommended for the evaluation of nodules smaller than 2 cm and is useful for distinguishing GISTs from other lesions; however, its accuracy with regard to the differential diagnosis is relatively low. In this case, the gastric distension observed on imaging led to the compression of a liver tumor against the stomach, resulting in the misinterpretation of the tumor as a gastric wall

lesion.

Key Words: Hepatic hemangioma; Gastrointestinal stromal tumors; Left lobe tumor; Subepithelial lesions; Extragastric lesions; Case report

Core Tip: Hepatic hemangiomas can be challenging to diagnose, especially when they mimic other conditions like gastrointestinal stromal tumors. This case highlights the limitations of imaging techniques such as computerized tomography and endoscopic ultrasound in diagnosing subepithelial lesions. While computerized tomography is effective for visualizing abdominal tumors, it struggles to detect smaller lesions and assess the gastrointestinal wall layers. Endoscopic ultrasound is helpful for evaluating smaller nodules, but its diagnostic accuracy is limited. This case emphasizes the importance of considering hepatic lesions when gastrointestinal symptoms are present, particularly when imaging findings are inconclusive.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tumors that can occur anywhere in the gastrointestinal tract, with the most common site being the stomach. Approximately 15%-30% of patients with GISTs are asymptomatic, with the most common symptoms including abdominal pain, nausea, and bleeding[1]. GISTs should be diagnosed through immunohistochemical analysis, including the assessment of KIT and CD34 and/or discovered on GIST 1[2]. However, since GISTs are subepithelial lesions (SELs), obtaining a conclusive histologic diagnosis through standard endoscopic forceps biopsy is relatively challenging. The preoperative diagnosis of GISTs relies on imaging examinations such as computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, and endoscopic ultrasound (EUS) [3]. We present a case of hepatic hemangioma that was initially misdiagnosed as a GIST and discuss our findings in relation to the diagnosis of GISTs and hepatic hemangiomas on the basis of a review of the literature.

CASE PRESENTATION

Chief complaints

A 44-year-old female patient was admitted to the oncological surgery department with complaints of intermittent abdominal distension and heartburn for 3 months.

History of present illness

An endoscopic examination one week prior to admission revealed a bulging gastric fundus. A GIST was considered the likely diagnosis, as well as chronic nonatrophic gastritis with bile reflux.

History of past illness

The patient's relevant past medical history included iron deficiency anemia, menoxenia, and cholecystectomy for gallbladder stones.

Personal and family history

The patient had no history of smoking or alcohol consumption. There was no relevant family medical history.

Physical examination

The physical examination did not reveal any abnormalities.

Laboratory examinations

The clinical examination was unremarkable.

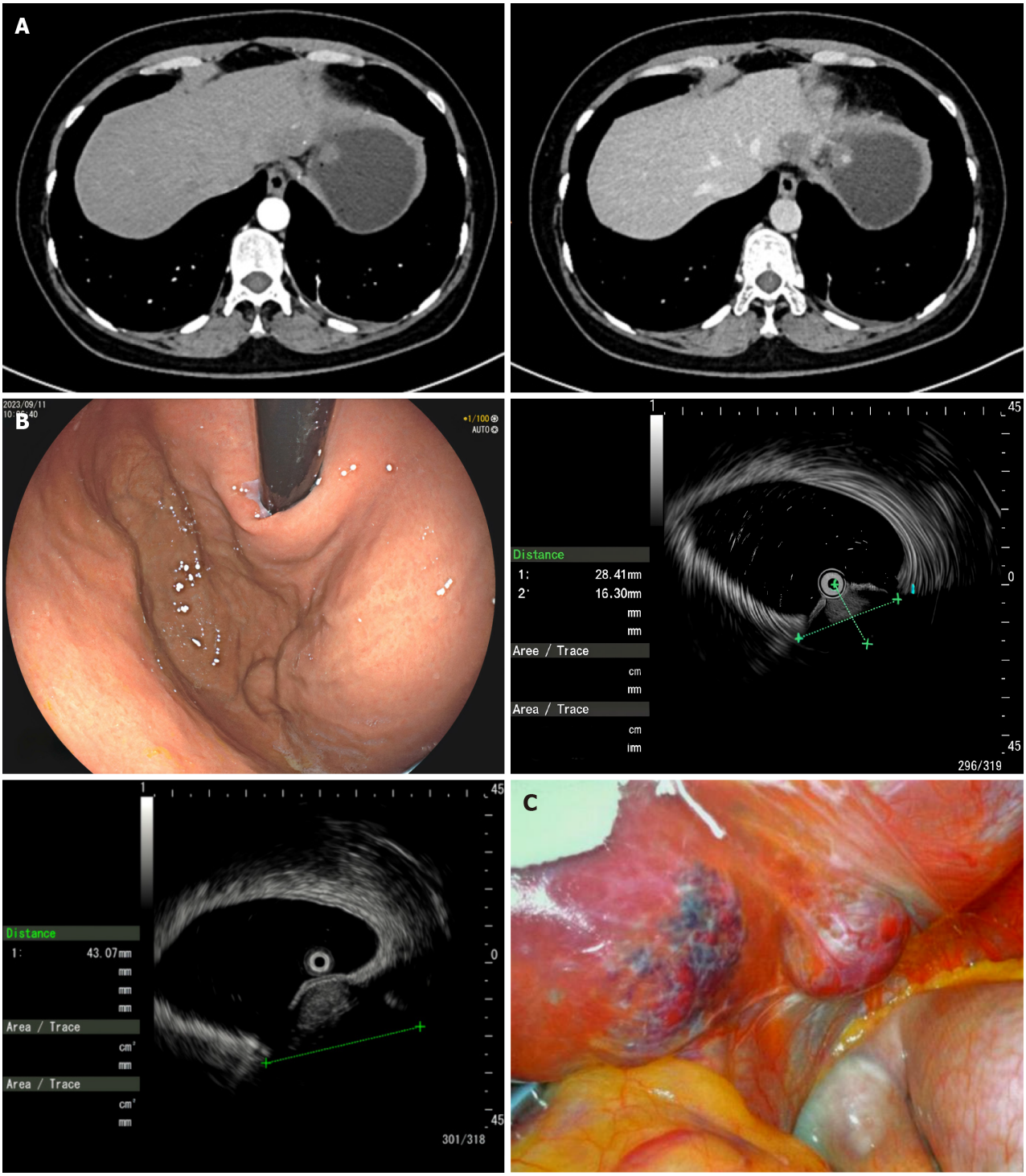

Figure 1 The patient's imaging examination and laparoscopy. A: Enhanced computed tomography image of two circular nodules in the fundus of the stomach; B: Endoscopic ultrasound image of two connected spherical bulges in the anterior wall of the fundus of the stomach; C: Laparoscopic visualization of two unexpected lesions in the left lobe of the liver.

Imaging examinations

An enhanced CT scan revealed two circular nodules in the fundus of the stomach measuring approximately 1.8 cm × 1.3 cm and 2.3 cm × 1.6 cm (Figure 1A), leading to the consideration of a benign gastric tumor, with the differential diagnosis including a stromal tumor and a leiomyoma. EUS revealed two connected spherical bulges in the anterior wall of the fundus of the stomach, with diameters of 28 mm and 43 mm (Figure 1B), both with normal mucosa. The lesions appeared hypoechoic from the muscularis propria and appeared to be growing toward the outer cavity, with uniform internal echo and attenuated rear echo. Combining the findings from CT and EUS, the diagnosis was thought to be GISTs.

FINAL DIAGNOSIS

Patient diagnosed with hepatic hemangioma.

TREATMENT

Preoperatively, an endoscopic injection of indocyanine green was administered to mark the incisal margin during fluorescence laparoscopy. During laparoscopy under general anesthesia, two unexpected lesions were found in the left lobe of the liver, while the gastric surface appeared normal (Figure 1C). These hepatic lesions were pressing on the fundus of the stomach. Intraoperative gastroscopy confirmed that the lesions originated from extragastric compression. Subsequently, laparoscopic liver partial resection was performed.

OUTCOME AND FOLLOW-UP

Postoperative pathological examination confirmed that the hepatic lesions were hepatic cavernous hemangiomas. The patient recovered well after surgery and was discharged 5 days later. Follow-up was normal at 3 months.

DISCUSSION

This report describes a case of misdiagnosis as GISTs despite detailed preoperative examinations involving CT, endoscopy, and EUS. CT is the primary method used to visualize tumors in the abdominal cavity; however, the limitation of CT for the evaluation of SELs is that it cannot easily be used to analyze smaller lesions and does not allow the accurate evaluation of the gastrointestinal wall layers[4]. GISTs larger than 5 cm in diameter typically appear exophytic and hypervascular on CT[2]. In contrast, CT can readily be used to identify hepatic cavernous hemangiomas. These lesions present with early peripheral nodular enhancement in the arterial phase and progress slowly, with centripetal filling in the portal venous phase[5]. Although these imaging features may not be detected when the lesions are smaller than 5 mm in diameter[6], this typical enhancement pattern makes them easy to distinguish from GISTs. The ESMO guidelines recommend EUS assessment as the standard approach for patients with esophagogastric or duodenal nodules measuring < 2 cm in diameter[7]. EUS can be used to accurately discriminate an SEL suspected of being a GIST (hypoechoic solid mass) from other SELs, including lipomas, cysts, varices, and extragastrointestinal compression[8]. The finding of a hypoechoic solid mass on EUS can also be seen with malignant tumors, such as malignant lymphoma, metastatic cancers, neuroendocrine tumors, and SEL-like cancers, as well as in benign conditions such as leiomyoma, neurinoma, and an aberrant pancreas. It is difficult to distinguish among these lesions on the basis of EUS findings alone. The accuracy of the differential diagnosis of SELs on the basis of EUS is extremely poor and ranges from 45.5%-48.0%[4]. The problem lies in the location of the lesion; the left outer lobe of the liver is closer to the anterior wall of the fundus stomach. In this case, both CT and EUS required distention of the stomach, which further pressed the liver tumor against the stomach wall, making it appear as if it were stomach wall lesion. We have outlined the key imaging characteristics used in the differential diagnosis of hepatic hemangiomas and GISTs (Table 1).

However, it is quite rare for a hepatic hemangioma located in the left lobe of the liver to present as a GIST. Some researchers have identified pedunculated hepatocellular carcinoma (P-HCC) as a condition that can mimic GISTs[9,10]. The diagnosis of P-HCC, particularly type II P-HCC, presents significant challenges. P-HCCs located in the left lobe of the liver are more prone to misdiagnosis as GISTs than are hepatic hemangiomas found in the same anatomical region. Some researchers believe that, with the careful analysis of imaging features, MRI can lead to more reliable diagnoses[10-12].

CONCLUSION

This case report highlights the diagnostic challenges faced when distinguishing hepatic hemangiomas from GISTs, particularly when the lesion is located in the left lobe of the liver and exerts pressure on the stomach wall. Despite detailed preoperative evaluations involving CT, endoscopy, and EUS, a hepatic hemangioma can be mistakenly diagnosed as a GIST due to overlapping imaging characteristics. Importantly, while CT and EUS are invaluable tools for assessing gastrointestinal tumors, their limitations with regard to the evaluation of SELs and differentiation among extragastric lesions, such as hepatic hemangiomas, underscore the importance of considering a broad differential diagnosis. The importance of careful imaging analysis and, when necessary, intraoperative exploration to ensure an accurate diagnosis and avoid mismanagement is emphasized. This case also underscores the need for a multimodal approach, incorporating MRI and other advanced techniques, to refine the preoperative diagnosis and guide the selection of appropriate treatments.

Table 1 Key imaging features for differential diagnosis of hepatic hemangioma and gastrointestinal stromal tumor

	CT	MRI	PET/CT	US	EUs
GIST	Initial diagnostic modality, size ≤ 2 cm, low detection; size > 2 cm, peripheral enhancement pattern, exophytic and hypervascular[4]	Similar to CT imaging, low signal intensity on T1WI, high signal intensity on T2WI, and enhanced signal intensity on post gadolinium image[13]	Shows a sensitivity of 89% and specificity of 97%[14]	Use for the diagnosis of hepatic metastases	size < 2 cm, hypoechoic solid mass accurately identifying a SEL[7]
Hepatic hemangioma	High detection, early peripheral nodular enhancement in the arterial phase and slow, progressive centripetal filling in the portal venous phase[9]	Differential diagnosis with other liver tumors, low signal intensity on T1WIs and appear hyperintense on diffusion-weighted imaging[15]	-	Initial diagnostic modality, presents as hyperechoic, or as hypoechoic masses with a hyperechoic rim[15]	-

CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; US: Ultrasound; EUS: Endoscopic ultrasound; GIST: Gastrointestinal stromal tumor; T1WI: T1-weighted imaging; SEL: Subepithelial lesion.

FOOTNOTES

Author contributions: Wang JZ conceptualized and designed the study, collected data, analyzed statistics, wrote the manuscript, and reviewed and edited the manuscript; Chen H supervised the research project, coordinated the study, and approved the final manuscript; and all authors thoroughly reviewed and endorsed the final manuscript.

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LETTER TO THE EDITOR

High-grade pancreatic intraepithelial neoplasia: A commentary of magnetic resonance cholangiopancreatography findings

Alessandro Posa, Enza Genco

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Abstract

Commentary on the role of magnetic resonance cholangiopancreatography findings in diagnosing high grade pancreatic intraepithelial neoplasms.

Key Words: Magnetic resonance; Cholangiopancreatography; Pancreas; Intraepithelial neoplasms; Diagnosis

Core Tip: Magnetic resonance cholangiopancreatography can help in early identification and stratification of high grade pancreatic intraepithelial neoplasms.

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TO THE EDITOR

We read with interest the case report by Furuya *et al*[1], on magnetic resonance cholangiopancreatography (MRCP) findings that helped in diagnosing high-grade pancreatic intraepithelial neoplasia (PanIN).

CASE SUMMARY

The authors presented a case of a 60-year-old female patient with pancreatic cysts detected during a follow-up for uterine cancer[1]. The patient had diabetes mellitus but no history of smoking, alcohol consumption, pancreatic neoplasm, or chronic pancreatitis in her family. Imaging examinations including contrast-enhanced computed tomography, endoscopic ultrasonography (EUS), and MRCP revealed a 5 mm cyst in the pancreatic tail with no evidence of a solid mass nor parenchymal atrophy. EUS also showed hyperechoic spots suggesting early pancreatitis. MRCP described an irregular narrowing of the main pancreatic duct (MPD), with no finding of distal/caudal duct dilation. Follow-up imaging revealed cyst growth and slight MPD dilation over time. Contrast-enhanced EUS and endoscopic retrograde cholangiopancreatography (ERCP) confirmed the findings of irregular MPD narrowing and slight dilation of the caudal portion of the duct. Serial pancreatic juice aspiration cytology examination found neoplastic cells consistent with adenocarcinoma, leading to a final diagnosis of high-grade PanIN. Patient treatment involved a distal pancreatectomy; the patient remained alive without relapse 17 months postoperatively.

DISCUSSION

Pancreatic cancer poses significant challenges in medical research due to its aggressive nature and poor prognosis. PanIN represents an early stage (stage 0) of pancreatic cancer, which is potentially curable if diagnosed early. Unlike typical tumors, PanIN does not form a mass, making its diagnosis challenging. Instead, it can only be identified through indirect findings such as MPD stricture, dilatation, pancreatic cysts, and pancreatic atrophy. The case illustrated by Furuya *et al*[1] highlights the challenges in diagnosing high-grade PanIN, particularly in cases with poor MPD visualization. Despite challenges in diagnostic strategies, serial cytology of pancreatic juice based on changes in MRCP findings over time proved effective in this case, emphasizing the need for an early diagnosis system for pancreatic cancer.

Morphological features

PanIN encompasses a range of morphological changes within the pancreatic ductal epithelium, providing valuable clues for early detection and prognostic assessment[2]. Microcysts, fibrosis, and parenchymal atrophy could be indicators of PanIN; in particular, microcysts that do not communicate with the MPD could serve as predictive factors[3]. A non-communicating microcyst can be defined as a round cyst with a diameter up to 5 mm which has no surrounding ducts[4-6]. Parenchymal atrophy can be considered when the largest antero-posterior thickness of the pancreas is less than 20 mm [7]. These Authors demonstrated an increase in microcyst prevalence with advancing PanIN stages, with PanIN-3 showing the highest incidence[2,3]. Moreover, the association of PanIN with adjacent parenchymal fibrosis highlights the interplay between precursor lesions and the pancreatic microenvironment, offering insights into pancreatic cancer pathogenesis.

The case report by Furuya *et al*[1] also underlines the importance of continuous patient monitoring and early intervention. Advanced imaging techniques, such as MRCP, have transformed PanIN diagnosis, allowing precise identification and longitudinal monitoring of patients. MRCP, being non-invasive, facilitates a comprehensive lesion evaluation, guiding the selection of patients for invasive procedures like ERCP. Moreover, identification of PanIN risk factors, including obesity and intrapancreatic fat deposition, is mandatory for an early diagnosis; these risk factors underscore the multifaceted nature of pancreatic carcinogenesis, necessitating a holistic approach to risk assessment[8].

Understanding PanIN pathogenesis and morphological features allows to obtain diagnostic algorithms, risk stratification, and therapeutic decisions. Incorporating imaging-based surveillance into clinical practice aids in early PanIN detection, enabling timely intervention and potentially avoiding disease progression. Additionally, recognizing PanIN manifestations across different pancreatic conditions underscores the need for nuanced differential diagnosis and management approaches.

CONCLUSION

However, despite diagnostic progresses, PanIN diagnosis remains difficult and tricky. Further studies on molecular mechanisms leading to PanIN progression, and exploration of novel biomarkers and radiomics features for early tumor detection are needed. Novel prospective and observational studies on patient follow-up are needed, also in order to refine imaging techniques to grant an early and better identification of PanIN, particularly grade 3.

FOOTNOTES

Author contributions: Posa A and Genco E wrote the preliminary draft of the manuscript and revised it; all authors have read and approved the final manuscript.

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