ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2023 June 26; 15(6): 284-327

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

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World Journal of Cardiology

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone, Pal Pacher

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
June 26, 2023

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World Journal of Cardiology

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World J Cardiol 2023 June 26; 15(6): 284-292

DOI: 10.4330/wjc.v15.i6.284

ISSN 1949-8462 (online)

MINIREVIEWS

Current role and future perspectives of artificial intelligence in echocardiography

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Morya AK, India; Yang JS, China

Received: April 11, 2023
Peer-review started: April 11, 2023
First decision: April 20, 2023
Revised: May 2, 2023
Accepted: June 21, 2023
Article in press: June 21, 2023
Published online: June 26, 2023

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Abstract

Echocardiography is an essential tool in diagnostic cardiology and is fundamental to clinical care. Artificial intelligence (AI) can help health care providers serving as a valuable diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and interpretation of results. In addition, it can help expand the capabilities of research and discover alternative pathways in medical management specially on prognostication. In this review article, we describe the current role and future perspectives of AI in echocardiography.

Key Words: Echocardiography; Artificial intelligence; Machine learning; Deep learning; Prognosis

Core Tip: Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence (*e.g.,* pattern recognition) by mimicking human thought processes. Echocardiography is an essential tool in diagnostic cardiology and is fundamental to clinical care. AI could help the health care providers by one side serving as a valuable diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and by the other side helping on the interpretation of results. The current role of this technique is described in this review and its future perspectives are covered through the text highlighting the obstacles and advantages expected on this implementation.

Citation: Vidal-Perez R, Grapsa J, Bouzas-Mosquera A, Fontes-Carvalho R, Vazquez-Rodriguez JM. Current role and future perspectives of artificial intelligence in echocardiography. *World J Cardiol* 2023; 15(6): 284-292
URL: https://www.wjgnet.com/1949-8462/full/v15/i6/284.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i6.284

INTRODUCTION

Artificial intelligence (AI) is the process of having a computational program that can perform tasks of human intelligence by mimicking human thought processes[1]. The AI applications in cardiology are showing that not complex devices like electrocardiography (ECG) machine could generate big amounts of potential data transforming the ECG into a powerful tool for prediction[2].

On the same side, the use of AI techniques in cardiovascular imaging into the process of daily decision-making will enhance the delivery of care, and AI has been influencing in the last years every field of cardiac imaging in all phases from the beginning with acquisition to the last step of reporting[3-5]. But for sure it will be basic for the specialty that cardiologists retain the final step in the control of the system, take care of the decisions, and have the authority to amend algorithms in the cases that these get mistaken.

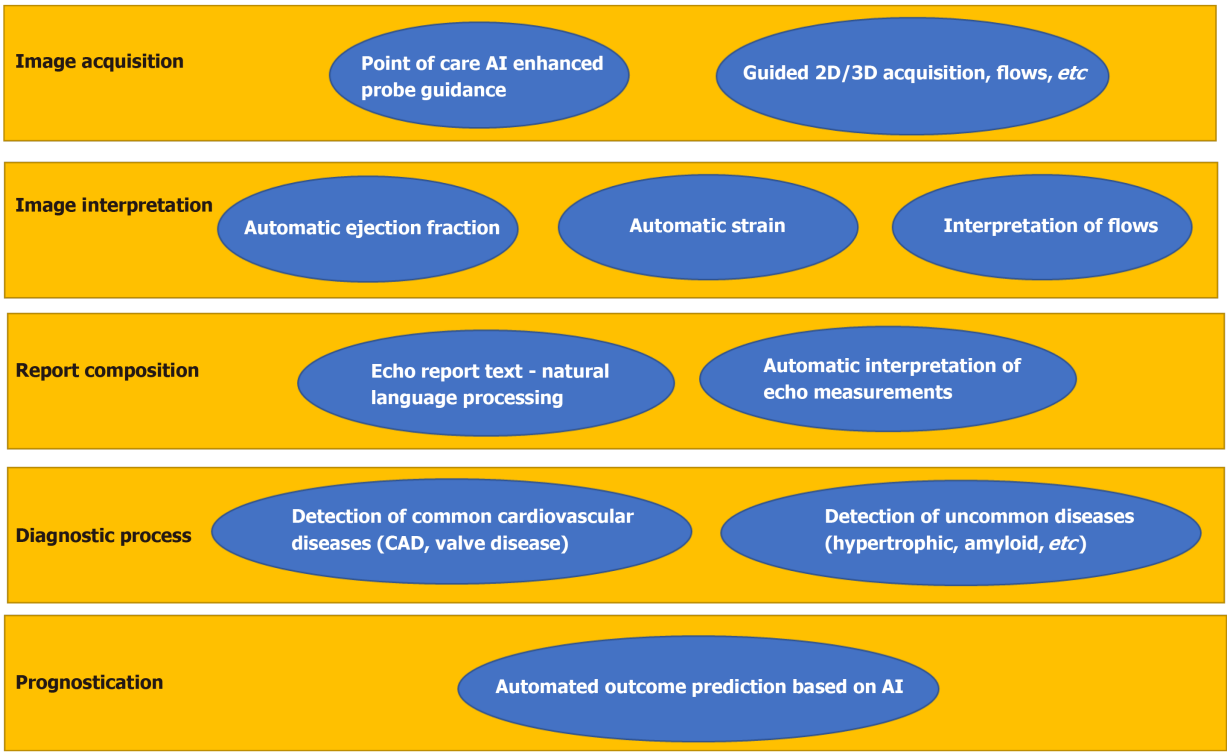
In radiology departments, the likely influence of AI on the imminent advance of this area of medical specialization is crystal clear. The use of computers to assist with radiologic image interpretation tasks is a practice that will endure for a considerable period, one example of this that we could see it on cardiothoracic imaging where the subset most commonly utilized in medical imaging is machine learning (ML) and the more complex deep learning (DL). Much scientific research has been done focusing on the use of ML for pattern recognition to identify and diagnose potentially a great amount of pathologies[6].

ML models based on AI are being applied quickly to the assessment of magnetic resonance or cardiac computed tomography (CT) as it is an independent tool completely different from the manual approach that the echocardiography needs. For echocardiography, the quality of the imaging obtained during the study is the most critical element for a good interpretation; however, for cardiac imaging with magnetic resonance or CT, the obtained imaging quality is seldom an issue as it is not obtained manually. The workforce for performing echocardiography will prevail for a long period of time as is needed to obtain good quality imaging in patients with adequate acoustic windows.

Echocardiography has a critical role in the diagnosis and management of patients that develop a cardiovascular disease. It allows for real-time imaging of the cardiac structures and fast detection of various anomalies[7]. Despite the large amount of echocardiographic interpretation and evaluation guidelines, the quantification and diagnosis are mainly based on a subjective review of the images obtained by 2- and 3-dimensional (3D) echocardiography, and due to this, we could say that echocardiography is still an error-prone and imperfect technique. Another element is that there exists a high level of inter-operator variation in the interpretation of echocardiography findings, which has been for ages a long-standing problem[8]. This inter-operator variation can lead to incorrect interpretations and diagnoses, especially when the poor-quality images obtained previously are interpreted. Furthermore, critical care specialists (cardiologist, intensivists, and anaesthesiologists) frequently have limited time to improve echocardiographic images and measurements in the critical care patients and have to make analyses quickly in unstable patients due to hemodynamic reasons. The need for fast, automated analysis of echocardiography data that are less dependent on operator effort is crucial for critical care scenarios.

Although the application of AI in echocardiography is still in its first steps to greater implementation, the use of this technology in the future has great potential and is presumed to support the improvement of the efficiency and accuracy of the manual tracing. The technology based on AI can help in a more standardized evaluation of echocardiographic images/videos to decrease human errors by producing automated, consistent, and accurate interpretations.

Current and future applications of AI in echocardiography are shown in Figure 1, and these applications of the AI technology in echocardiography go through multiple areas, including the process of image acquisition, the image interpretation tasks, text interpretation, performing diagnosis, and



DOI: 10.4330/wjc.v15.i6.284

Figure 1 Current and future applications of artificial intelligence in echocardiography. AI: Artificial intelligence; CAD: Cardiovascular diseases; 2D/3D: 2 dimensional/3 dimensional.

prognosis evaluation.

CURRENT ROLE OF AI IN ECHOCARDIOGRAPHY

Imaging techniques like echocardiography have many advantages in relation with other techniques, and the main advantages of echocardiography include a wide availability, the potential portability, and nowadays the affordability that was not real before. However, when it comes to interpreting echocardiographic images, there is a notable level of variability among observers compared to other cardiovascular imaging techniques. In this regard, AI has the potential to play a valuable role by not only reducing observer variability but also enhancing diagnostic accuracy[9].

On the other hand, the utilization of AI in this field has been constrained by the intricate multi-view format of echocardiography and the indispensable requirement for human expertise in both image acquisition and interpretation. In daily clinical practice, this is mostly evident, as happened for new multidimensional imaging technologies that are not easily adopted, such as 3D echocardiography and speckle-tracking[1,5,10-17].

Image acquisition

In numerous clinical settings, echocardiography is not available because of an absence of qualified workforce. In these locations, nonexpert operators may perform limited exams [point-of-care ultrasound (POCUS)] using portable or handheld machines, but quality is no homogeneous, with risks for misleading and nondiagnostic imaging[18]. POCUS is commonly utilized in intensive care units; emergency departments; preoperative and outpatient clinics; and areas medically underserved, from rural areas of US to low- and middle-income countries to man operated space flights. POCUS also enabled frontline clinicians to acquire echocardiograms in patients with coronavirus disease 2019 during the pandemic, restricting the exposure of sonographers[19]. During this period, technology based on AI allowed acquisition of diagnostic-quality ultrasonographic studies by users with a minimal training in these locations, and data from one study showed this recently with novice users, demonstrating that they could obtain 10-view transthoracic echocardiographic studies of diagnostic quality using DL-based software[20] approved by the United States Food and Drug Administration[21], that guides the operator on the recording of the right views.

Image interpretation

In comparison with image acquisition technology, echocardiographic interpretation using AI has evolved in recent years based on a correct automated image interpretation and classification[22,23]. Several studies have confirmed and validated the use of AI for automated quantification of left ventricle and right ventricle volumes or ejection fraction, global longitudinal strain, and atrial size or function from both 2D and 3D acquisitions[23-31].

One of the notable applications of AI in the field of echocardiography is the assessment of myocardial thickening and endocardial excursion, which enables the detection of regional wall motion abnormalities (RWMAs). This application holds great significance, particularly in managing ischemic coronary artery disease[9]. The assessment of RWMAs typically relies on the visual interpretation of the operator, which is subjective and experience-dependent. This evaluation holds great importance, especially when assessing patients with chest pain in the emergency room. To mitigate the possibility of incorrect interpretations, AI models have been developed to detect and quantify RWMAs, providing a more objective approach[3]. These ML and DL models exist, designed to evaluate RWMAs and diagnose ischemic cardiomyopathy[32,33]. The sensitivity of RWMAs evaluation models for automated diagnosis of ischemic heart disease is related to the area under the receiver-operating characteristic curve by AI algorithm. It should be remarked that AI algorithm "experience and expertise" are based on the available real-world datasets, that will have the same limits, such as the relatively higher ratios of wrong classification of the left anterior descending coronary artery perfusion territory described in the latest publications[33].

Report composition

The natural language processing algorithms have been created for large-scale extraction of the text data from echocardiographic reports; however, the widespread application has been limited due to the portability of each algorithm, with a potential degradation of algorithm performance when it is applied to an external data set[34,35].

Another step is the automatic interpretation of echo measurements that for sure is the next step for the automation of the echocardiography workflow. One good example of this strategy is the screening for valvular heart diseases (VHDs) using the data obtained through Doppler echocardiography video recordings automatically analyzed; the research of this interesting investigation created a three-step DL framework for the automatic screening of the echocardiographic videos for the detection of mitral regurgitation (MR) and stenosis (MS), and the detection of aortic regurgitation (AR) and stenosis (AS), and this DL algorithm categorizes the echocardiographic views, detects the presence of VHDs, and, when present, measures essential metrics related with the valvular severities. The DL algorithm was trained initially with 1335 exams, then was validated with 311, and finally was tested in 434 individuals using retrospectively selected studies from five hospitals. A prospectively collected set of 1374 consecutive echocardiograms was used later as the real-world data set for testing the algorithm. Disease categorization accuracy obtained was high, showing the following areas under the curve: 0.88 (95% confidence interval: 0.86-0.90) for MR; 0.99 (95% confidence interval: 0.97-0.99) for MS; 0.90 (95% confidence interval: 0.88-0.92) for AR; and 0.97 (95% confidence interval: 0.95-0.99) for AS in the prospective test data set[36].

Diagnostic process

In this aspect, a continuous progress has been made, and one of the first successful approaches was published by Zhang *et al*[23] that used a model based on DL to create a fully automated echocardiogram interpretation program, that included view identification (a kind of chamber view detection), image segmentation (detection of the different parts of the image), quantification of structure and function (automatic measurements), and disease detection (after the integration of prior data). By analyzing over 14000 echocardiographic studies, the algorithm achieved an impressive 96% accuracy in recognizing and distinguishing between various echocardiographic view classifications, such as parasternal long-axis and short-axis views. Furthermore, it demonstrated an accuracy ranging from 72% to 90% in accurately segmenting the image.

Additionally, the authors of the research presented that the algorithm for automated quantification of cardiac structure and function was similar to or even superior to the manual measurements across 11 internal consistency metrics, and that unexpectedly the convolutional neural networks were also successfully trained to detect hypertrophic cardiomyopathy, cardiac amyloidosis, and pulmonary artery hypertension, with a high accuracy. Even though the accuracy has not reached the level of the experts, the potential application of the DL models to echocardiography interpretation is a very promising tool for the detection of uncommon diseases.

Another important research is the one centered on common diseases like the potential automation of the detection of severe coronary artery disease with an echocardiographic system using AI. This innovation demonstrates the potential of validating an AI system for automating the analysis of stress echocardiography, thereby assisting clinicians in their interpretation. To achieve this, an automated image processing pipeline was developed to extract new geometric and kinematic features from a dataset of stress echocardiograms. The dataset was collected as part of a large, prospective, multicenter,

multivendor study conducted in the United Kingdom. Using the extracted features, a ML algorithm was trained to identify patients with severe coronary artery disease based on invasive coronary angiography. Through cross-fold validation, the algorithm achieved a satisfactory classification accuracy in identifying patients with severe coronary artery disease in the training dataset. It utilized 31 unique geometric and kinematic features and demonstrated a sensitivity of 84.4% and specificity of 92.7%. Importantly, this accuracy was also observed in the independent validation dataset from the United States. By providing automated classifications to clinicians during the interpretation of stress echocardiograms, this method has the potential to enhance accuracy, improve inter-reader agreement, and boost reader confidence in the near future[37]. Another area of research of great interest is the VHD for the acceleration of echocardiography workflows[36,38-40].

Prognostication

In the scientific literature, we could find nonrandomized studies on the use of AI in echocardiography to predict outcomes, going from the response to cardiac resynchronization therapy to in-hospital mortality[41-43]. Samad *et al*[44] employed an ML framework for the prediction of all-cause mortality combining the information from echocardiographic measurements and electronic medical information of 171510 patients. A random forest model was compared with a logistic regression model based on a range of analytic approaches employing echocardiographic and clinical variables to predict outcomes. The random forest models had a superior prediction accuracy (all areas under the curve > 0.82) over common clinical risk scores (areas under the curve = 0.69-0.79) and did better than logistic regression models ($P < 0.001$) on all survival durations[44].

FUTURE PERSPECTIVES OF AI IN ECHOCARDIOGRAPHY

For the prediction of the future, probably we must focus on the potential gaps and limitations of AI, knowing that elements will guide us on the new advances that we must expect in the years to come.

The utilization of automated tracing and recognition of structures faces several limitations, as outlined in Table 1. However, ongoing advancements in this technology aim to address these limitations and enhance reproducibility and user experience. It is important to note that most studies have primarily focused on patients in sinus rhythm, with limited knowledge regarding the application of automation in patients with arrhythmia, significant conduction disease, and paced rhythm. Erroneous border tracings by the computer were found to be more prevalent in poor and fair-quality images, and the automated software did not function effectively in numerous cases. This poses a significant obstacle to the further development of this software. On the other hand, contour corrections appear to enhance the accuracy of automated analysis, resulting in a stronger correlation with cardiac MRI. However, this does increase the analysis time and may reduce workflow efficiency. In conclusion, the automation processes have demonstrated a favorable correlation with cardiac MRI volumes, as traditional 2D measurements have been shown to potentially underestimate chamber volumes[13].

Nowadays, most of the studies of AI in echocardiography are constructed with retrospective data and centered largely on the performance of AI in specific diagnostic tasks. These studies cover from small exploratory studies (like the 2017 study made by Sanchez-Martinez *et al*[45] with 55 patients) to larger studies (like the 2018 study created by Madani *et al*[22] evaluating > 200000 images or the 2021 study by Solomon *et al*[46] evaluating > 900000 echocardiography reports). There is a need for prospective studies to show the feasibility of the AI algorithms in the cardiovascular field[47], and the first AI-ECG prospective study based on DL (unsupervised system) has been recently published[48] showing that the study arm had increased diagnostic accuracy.

Nowadays, the utilization of AI in the field of echocardiography is characterized by a scarcity of randomized control trials. The objective of the Prospective Randomized Controlled Trial Evaluating the Use of Artificial Intelligence in Stress Echocardiography (ISRCTN15113915) trial is to evaluate the benefit of using an AI model for a complex modality like stress echocardiography. If we think how the upcoming studies in AI in echocardiography look like, we could affirm that it is likely that AI will be used for the assessment of diagnostic test performance in the field of the automatization of measurements and automatic interpretations of the set of images obtained during the echocardiographic studies. Nevertheless, future studies in the field of echocardiography will explore the capability of AI to identify diagnostic or prognostic insights that may elude human comprehension, as has been done for ECG exams, and AI has the potential to transform ECG into a tool that can accurately detect conditions that were previously undetectable using conventional methods[48].

As fresh data emerges in this field, it becomes crucial, without any hesitation, to establish a comprehensive plan and framework for integrating AI into daily clinical practice, including its incorporation into clinical practice guidelines. These guidelines should encompass various domains, undoubtedly encompassing the utilization of AI for diagnosis assistance as well as clinical management and prognostication. One indispensable aspect of these clinical guidelines is to provide clinicians with a curated body of evidence that they can be relied upon for patient care. This evidence must possess the following attributes: Validity, accuracy, generalizability, safety, and fairness. The initial step involves

Table 1 Current applications, strengths, and limitations of artificial intelligence in echocardiography

Applications of AI in echocardiography	Strengths	Limitations
View interpretation and classification	View identification and classification among thousands of images. Possibility of quantification of both structure and function. Possibility of disease diagnosis	Lack of learning process clarification. Possibility of imperfect classification. Image quality is often suboptimal, and nonstructural echocardiographic data need careful preprocessing by the specialist to build the definitive model. Non-standardized intermediate off-axis and continuously rotational and sweeping views, which can be clinically very helpful, even though of low technical quality, are difficult to be managed by AI models
Measuring anatomy and morphofunctional structure	Building a patient similarity model (*e.g.*, for predicting major cardiac events). Comparing automatic analysis between echocardiography and other imaging modalities	Possibility of suboptimal image quality. Possibility of limited number and representativeness of datasets. Current inferiority of automatic compared to semi-automatic software. Frequently inadequate standardization
Wall motion abnormalities detection	Reducing the potential operator-dependent misreading. Detecting different patterns of responses to stress. Possibility of integration with other technologies (*e.g.*, strain technology)	AI algorithms are based on the existing real world datasets, that bring with them the same limits and misclassification risks. Possibility of suboptimal images quality (which implies the exclusion of some acquisitions, hence limited authenticity). Presence of arrhythmias (difficult to be managed by AI models)

AI: Artificial intelligence.

promoting the standardization of study design and reporting when utilizing AI in conjunction with echocardiography. The CONSORT-AI initiative has already taken a pivotal stride in this direction, and it is recommended that this or similar standardized reporting formats be endorsed in all future studies [49].

ML has given us a greater ability to build predictive models, and now we are facing due to these advances a translational crisis[50]. Two studies found four essential stages in the process of creating a predictive model that could advance to a practical use: Development, validation, association with actual patient outcomes, and knowledge transition to a wide applicability[51,52]. They revised more than 800 predictive models for cardiovascular diseases previously published and found that a great part of them were improperly validated and only 0.1% were widely used finally in clinical practice.

One open question needs to be answered: Will the use of AI replace echocardiographers? Probably we could answer that not anytime soon. When considering the outcomes generated by AI, it is essential to interpret them in conjunction with the additional information obtained from echocardiography and stress testing. Nonetheless, AI holds promising potential for enhancing the reproducibility and efficiency of echocardiography. Cardiologists should make an effort to comprehend the AI tools and be ready to validate their effectiveness. For instance, the integration of AI into stress echocardiography should not be perceived as a threat but rather as an exceptional opportunity to further amplify the advantages of an already highly valuable test[53].

Considering the multitude of encouraging and promising outcomes, it begs the question why we have not implemented them in clinical practice. Should not our ethical obligation be to utilize every available resource to provide the best patient care? Or perhaps we doubt the authenticity of these findings? Alternatively, could it be that we are simply apprehensive about the potential threat to our roles if AI technology starts assuming some of our current tasks? Throughout human history, it has been demonstrated that our opinions hold little significance in the grand scheme of things. We may disagree with or even resist these technological advancements, but ultimately, they will prevail. Why? Because, in the long run, they prove to be beneficial for everyone involved[54].

Another concern that arises is how to address situations when there is a discrepancy between the machine and human opinions. As the accurate validation of algorithms holds immense importance, it is vital to underscore the necessity for it. While utilizing AI to supplement clinical decision-making, it is imperative for the physician to exercise their judgment while maintaining a degree of modesty. Unsupervised ML, specifically the advanced methods used in DL, may have limitations in terms of explanation ability (the ability to clarify how the algorithm produced its results). Despite these challenges, the potential of AI applications in healthcare is promising, and its capacity to enhance medical practices is remarkable.

CONCLUSION

Echocardiography is an essential asset in diagnostic cardiology and is really necessary to clinical care. AI is helping healthcare providers as a worthy diagnostic tool for physicians in the field of echocardiography specially on the automation of measurements and interpretation of results. Furthermore, it will help to expand the abilities of research and find alternative pathways in medical management specially

on prognostication. For sure many obstacles or barriers need to be broken to reach a whole integration of AI in the echocardiography lab workflow.

FOOTNOTES

Author contributions: Vidal-Perez R designed the study, collected the data, and edited and wrote the paper; Grapsa J, Bouzas-Mosquera A, Fontes-Carvalho R, and Vazquez-Rodriguez JM contributed to the critical revision and editing of the paper.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 June 26; 15(6): 293-308

DOI: 10.4330/wjc.v15.i6.293

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Basic Study

Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of *TDO2* as a potential therapeutic target

Ru Wang, Yan-Mei Yang

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Brody AR, United States; Jaing TH, Taiwan

Received: April 14, 2023
Peer-review started: April 14, 2023
First decision: May 17, 2023
Revised: June 1, 2023
Accepted: June 13, 2023
Article in press: June 13, 2023
Published online: June 26, 2023

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Abstract

BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a high mortality rate. On this basis, exploring potential therapeutic targets to meet the unmet needs of IPF patients is important.

AIM

To explore novel hub genes for IPF therapy.

METHODS

Here, we used public datasets to identify differentially expressed genes between IPF patients and healthy donors. Potential targets were considered based on multiple bioinformatics analyses, especially the correlation between hub genes and carbon monoxide diffusing capacity of carbon monoxide, forced vital capacity, and patient survival rate. The mRNA levels of the hub genes were determined through quantitative real-time polymerase chain reaction.

RESULTS

We found that *TDO2* was upregulated in IPF patients and predicted poor prognosis. Surprisingly, single-cell RNA sequencing data analysis revealed significant enrichment of *TDO2* in alveolar fibroblasts, indicating that *TDO2* may participate in the regulation of proliferation and survival. Therefore, we verified the upregulated expression of *TDO2* in an experimental mouse model of transforming growth factor-β (TGF-β)-induced pulmonary fibrosis. Furthermore, the results showed that a *TDO2* inhibitor effectively suppressed TGF-β-induced fibroblast activation. These findings suggest that *TDO2* may be a potential target for IPF treatment. Based on transcription factors-microRNA prediction and scRNA-seq analysis, elevated *TDO2* promoted the IPF proliferation of fibroblasts

and may be involved in the P53 pathway and aggravate ageing and persistent pulmonary fibrosis.

CONCLUSION

We provided new target genes prediction and proposed blocking TGF-β production as a potential treatment for IPF.

Key Words: Idiopathic pulmonary fibrosis; Lung function; Overall survival; Transforming growth factor-β; *TDO2* inhibitor

Core Tip: This study is unique in several aspects: (1) We identified six hub genes for idiopathic pulmonary fibrosis (IPF) and determined through quantitative real-time polymerase chain reaction; (2) Multi-omics analysis proved that *TDO2* was upregulated in IPF patients and promoted the IPF proliferation of fibroblasts; (3) *TDO2* may be involved in P53 pathway and aggravate aging and persistent pulmonary fibrosis; and (4) *TDO2* inhibitor effectively suppressed transforming growth factor-β-induced fibroblast activation.

Citation: Wang R, Yang YM. Identification of potential biomarkers for idiopathic pulmonary fibrosis and validation of *TDO2* as a potential therapeutic target. *World J Cardiol* 2023; 15(6): 293-308
URL: https://www.wjgnet.com/1949-8462/full/v15/i6/293.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i6.293

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease characterized by exertional dyspnoea and diminished lung function. Its progression seriously affects the quality of life of patients, leading to respiratory failure and death in severe cases. In addition, IPF is a fatal disease characterized by abnormal lung epithelial cells and excessive accumulation of lung interstitial matrix [1]. Clinical symptoms are usually progressive and manifest as shortness of breath, dry cough, and dyspnoea. Smoking exacerbates the loss of lung function in patients with IPF[2]. In addition to smoking, other factors, including viral and bacterial infections, genetic factors, age and sex, have different effects on IPF patients[3-7]. IPF mainly occurs in male patients and may develop earlier in men than in women for various biological reasons[8]. In terms of age, IPF predominantly affects elderly individuals, and its prevalence increases with age[9]. These microinjuries induce abnormal epithelial-fibroblast communication[10,11]. Moreover, slight injuries induce matrix-producing myofibroblasts and the accumulation of extensive extracellular matrix (ECM) with remodelling in the lung interstitium[12].

The median annual survival after the diagnosis of IPF is 2 to 3 years[13]. Although two antifibrotic drugs (pirfenidone and nintedanib) are currently available, they can only slow the progression of the disease instead of curing IPF[14]. There is no effective treatment for the illness, and a major need for new therapies has not been satisfied[15]. Therefore, identifying and intervening in key genes of IPF and exploring new therapeutic approaches are essential. The diagnosis of IPF usually requires respiratory physicians, radiologists, and pathologists to review various clinical features, imaging results, and biopsy results of patients in a group discussion to arrive at the final diagnosis. Standard imaging assessment of IPF with high-resolution computed tomography provides diagnostic and predictive information[16]. The degree of fibrosis and cellularity correlated with forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO), as well as predicted mortality, can be observed. The most common indicators of lung function associated with prognosis are total vital capacity, FVC, and DLCO[17,18]. The decreases in FVC and DLCO in IPF patients reflect disease progression and predict mortality[19,20].

Previous studies on IPF still need to be extended, and further identification of additional gene-targeted therapies for IPF remains challenging. In this study, several novel genes were investigated to explore the treatment of IPF. We adopted quantitative real-time polymerase chain reaction (qRT-PCR) to identify common hub genes in multiple sets of IPF data and discussed the correlation between these genes and lung function and the overall survival rate. Afterwards, a hub gene, *TDO2*, was used as an example to demonstrate the expression level. This gene was increased in IPF and validated by western blotting. After inhibitor treatment, transforming growth factor-β (TGF-β)-induced fibroblast activation was effectively inhibited.

MATERIALS AND METHODS

Data collection and preprocessing

All raw data in this study were retrieved from the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). GSE53845 (platform: Agilent microarray GPL6480) consists of lung tissues from 8 healthy subjects and 40 IPF patients[21]. In GSE47460[22], only samples with IPF from the interstitial lung disease population were included. The Agilent GPL14550 platform consists of 91 normal and 122 IPF samples, and the Agilent GPL6480 platform consists of 17 normal and 38 IPF samples. There were 110 men and 50 women with IPF, of whom 58 had never smoked, 96 had smoked, 2 were current smokers and 4 had an unclear smoking status. The age range of individuals with these IPF data was 37 to 82 years. GSE24206 (platform: Affymetrix GPL570) consists of 6 healthy and 17 IPF samples[23]. GSE110147 (platform: Affymetrix GPL6244) consists of 11 normal and 22 IPF samples[24]. The GEOquery package[25] was used to download the series matrix files of the databases above in R (v4.0.2). Soft formatted family files were downloaded to correctly map the probe ID to the gene symbol. GSE136831 contains lung tissue from 32 IPF and 28 control patients.

Differentially expressed gene screening

We screened differentially expressed genes (DEGs) between IPF patients and controls using the R package of the Microarray Data Linear Model (limma, version 3.50.3)[26]. The significant DEGs were identified according to the thresholds of adjusted $P < 0.05$ and fold change (FC) > 1.5. The common DEGs in the datasets were visualized by ggVennDiagram[27].

Functional and pathway enrichment analyses

Gene Ontology (GO) enrichment analyses of hub genes were performed by the clusterProfiler package with a background set of all Entrez IDs mapped to a GO pathway[28]. There are three functional categories, specifically biological processes (BPs), cell components (CCs), and molecular functions (MFs). Because GO is organized in a parent-child structure, a parent term can have a large percentage of overlap with its child terms. Concerning this problem, a simplified approach in the clusterProfiler implements was used. The organism reference was set as "org.Hs.eg.db". The terms meeting $P < 0.05$, p AdjustMethod = "BH" and P adjust < 0.05 were selected. Enrichment analyses of the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome were performed using Database for Annotation, Visualization and Integrated Discovery (DAVID)[29]. After Benjamini-Hochberg adjustment, terms meeting $P < 0.01$ were selected.

Protein-protein interaction network establishment and hub gene exploration

The protein-protein interaction (PPI) network of identified DEGs was built using the Search Tool for the Retrieval of Interacting Genes (STRING, https://string-db.org, v11.5) to determine the functional interactions between the products of the key genes. The condition for constructing the PPI network was an interaction combined score > 0.4. The interaction information network was downloaded and visualized through Cytoscape software (v3.9.1). The Molecular Complex Detection (MCODE) plugin was applied to select the significant subnetworks from the PPI network (degree cut-off ≥ 2, node score cut-off ≥ 0.2, K-core ≥ 2, and max depth = 100, score ≥ 3)[30]. The hub genes were identified through a plugin from Cytoscape named cytoHubba[31]. The cytoHubba plugin quantifies the importance of nodes in biological interaction networks through 11 node ranking methods. Five of these methods were adopted in this study: Degree, maximum neighbourhood component (MNC), density of maximum neighbourhood component (DMNC), maximal clique centrality (MCC), and edge percolated component (EPC). The top 30 Hubba nodes were ranked by these methods, and common hub genes were taken as the true final hub genes.

Overall survival analyses

Disease status, survival days, age, and survival status were extracted from GSE70866[32]. Clinical data from 176 IPF-diagnosed cases were used to analyse survival changes in specific genes in IPF. According to the mRNA expression from one of the hub genes, IPF patients were divided into high-expression (upper tertile) and low-expression (lower tertile) groups. The survival analysis of hub genes was performed in R using the functions "survfit" and "coxph" of the "survival" package. Survival curves were generated using the "ggsurvplot" function of the "survminer" package. The final results were visualized by ggplot2[33].

Clinical correlation

Several factors, including age, sex, smoking history, carbon monoxide diffusion capacity (DLCO), and FVC, have been identified as predictors of poor survival in IPF patients[34]. Varying degrees of decline in FVC and DLCO predict higher mortality in patients with IPF[35]. In this study, clinical metadata were analysed using clinical datasets of GEO accession No. GSE47460[22]. Linear models were created for selected gene expression and clinical variables such as DLCO and FVC percentage using the lm function in the R stats package. Scatterplots were made using the ggscatter function in the ggpubr package. The

Pearson correlation coefficient and significance were calculated in R using the stat_cor function in the ggpubr package.

Prediction of target microRNAs

We used three online microRNA (miRNA) databases (miRWalk, DIANATools, and miRDB) to predict miRNAs of hub genes with the default parameters. The miRNA was selected if it targeted a gene in all three databases. Subsequently, Cytoscape was used to construct the mRNA-miRNA coexpression network.

Transcription factors-miRNA prediction

Both miRNAs and transcription factors (TFs) are important in gene transcription and expression. Thus, clarifying the regulatory relationship between miRNAs and mRNAs and discovering key TFs can provide more insight into the pathological mechanisms of IPF. The "Enrichment analysis" module in TransmiR v2.0[36] was used to identify significant TFs that may regulate the list of miRNAs targeting TDO2.

Mouse model of Bleomycin-induced pulmonary fibrosis

SPF C57/6J mice were purchased from Beijing Weitonglihua Experimental Animal Co., Ltd. This experiment was approved by the Experimental Animal Welfare Ethics Review Committee of Henan University of Traditional Chinese Medicine (Review No. DWLL202110014). Mice were fed for one week in an SPF barrier environment in the Animal Experimental Center of Henan University of Chinese Medicine. Mice were randomly divided into two groups. For the phosphate-buffered saline (PBS) group, mice were intratracheally administered 50 μL of saline at Day 0. All mice were subjected to an anaesthesia experiment with a small animal anaesthesia machine (Ruiwode Life Technology Co., Ltd., Shenzhen, China). The light source was fixed at the pharyngeal skin, and the surgical instrument was fully exposed to the pharynx. At this time, a bright spot could be observed to open and close continuously with the spontaneous respiration of mice, and a tracheal intubation was inserted into the bright spot. For the Bleo group, mice were given intratracheal instillation of 50 μL of bleomycin (5 mg/kg). On Day 21, mice were euthanized by intraperitoneal injection of excessive pentobarbital sodium. Lung tissue was homogenized in TRIzol (Invitrogen) and stored at -80 °C for subsequent RNA isolation.

Cell culture and treatment

The A549 cell line and IMR-90 cell line were purchased from ATCC. A549 cells were cultured in F-12K medium (Boster Biological Technology) containing 10% foetal bovine serum (FBS), 100 U/mL penicillin, and 100 μg/mL streptomycin. IMR-90 cells were cultured in DMEM (Biological Industries) containing 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin. The MLE-12 cell line was purchased from the Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). MLE-12 cells were cultured in DMEM/F-12 medium (Corning) containing 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin. A549, MLE-12, and IMR-90 cells were incubated in a humidified incubator with 95% air and 5% CO_2 at 37 °C. A549 cells, MLE-12 cells, and IMR-90 cells were seeded in six-well plates and cultured overnight. Cells were treated with TGF-β (10 ng/mL) for 24 h[37] and then exposed to 680C91 (20 μm) for 24 h.

Quantitative real-time polymerase chain reaction assay

Primers were designed using PrimerBank (https://pga.mgh.harvard.edu/primerbank/index.html) and synthesized by Sangon Biotech Co., Ltd. (Shanghai, China). Total RNA was extracted using RNAiso Plus (TaKaRa) according to the manufacturer's instructions. Reverse transcription (RT) was performed using HiScript® II Q RT SuperMix for qPCR (Vazyme, Nanjing, China). The reactions were performed using a QuantStudio 6 real-time fluorescence quantitative PCR System (Life Technologies, Singapore). The procedure was detailed as follows: Lung tissue was homogenized on ice with TRIzol. After complete homogenization, the homogenized solution was allowed to settle at room temperature for 5 min. The homogenate was then mixed with 200 μl/mL chloroform, allowed to stand at room temperature for 3 min and then centrifuged at 12000 × *g* for 15 min at 4 °C to separate the phases. The aqueous RNA phase was removed and dispensed into a new 2 mL microcentrifuge tube. The upper aqueous phase (RNA solution) was transferred to a new EP tube, mixed with isopropyl alcohol equal to the supernatant, and placed at 12000 × *g* for 10 min at 4 °C, and the supernatant was discarded. Then, 75% ethanol was added to 1 mL/mL TRIzol and gently shocked at 4 °C and 12000 × *g* for 10 min, and the supernatant was discarded. The pellets were allowed to air dry for approximately 5 min and then dissolved in DEPC water to measure the RNA concentration. The TOYOBO ReverTra Ace qPCR RT Kit was used for RT. RNA was incubated for 10 min at 65 °C and immediately placed on ice. The RT reaction contained 1 μg of RNA, 2 μL of 5 × RT Buffer, 0.5 μL of RT Enzyme Mix, 0.5 μL of Primer Mix, and up to 10 μL of DEPC water and was subsequently incubated at 37 °C for 15 min and 98 °C for 5 min. The values of the target genes were normalized using the $2^{-\Delta\Delta CT}$ method with the values of the housekeeping gene 18S. Technical repeats were performed three times. Notably, all mRNA levels are expressed as the mean ± SD.

Western blot assay

After treatment with TGF-β and 680C91, cells were lysed with RIPA buffer in ice. Protein samples of equal concentrations were separated using a 10% SDS-PAGE gel and electrotransferred onto PVDF membranes. Membranes with proteins were blocked with 5% skim milk, followed by incubation with primary and secondary antibodies. *TDO2* (Cat No.:15880-1-AP), α-smooth muscle actin (α-SMA) (Cat No.:14395-1-AP), COL-I (Cat No.:14695-1-AP), and GAPDH (Cat No.:10494-1-AP) were detected using the Bio-Rad Imaging System. These antibodies were purchased from Proteintech Group, Inc.

Statistical analysis

Independent-samples t tests were performed using SPSS 22.0 (IBM Corporation, Armonk, NY, United States), and $P < 0.05$ was considered significant. Pearson's correlation coefficient r was calculated using the R function stat_cor.

RESULTS

Identification and enrichment analysis of DEGs

Four sets of raw GEO data (GSE53845, GSE47460, GSE24206, and GSE110147) from five platforms were used to analyze the DEGs between the normal and IPF groups. Data sources are summarized in Supplementary Table 1. After background correction and data standardization, DEGs were determined between IPF and normal lung tissues. DEG analysis was performed by the R package "limma". Based on the threshold of adjusted $P < 0.05$ and FC > 1.5, 2157 DEGs were identified in GSE53845, 2861 DEGs were screened out from GSE47460 under the GPL6480 platform, 2113 DEGs were obtained in GSE47460 under the GPL14550 platform, 2525 DEGs were detected in GSE24206, and 7146 DEGs were selected in GSE110147. Venn analysis showed that the DEGs of GSE110147 had less than 50% consistency with other datasets (Supplementary Figure 1). Therefore, GSE110147 was discarded in subsequent analyses. A total of 254 common genes were screened by intersecting the remaining four DEG datasets (Figure 1A).

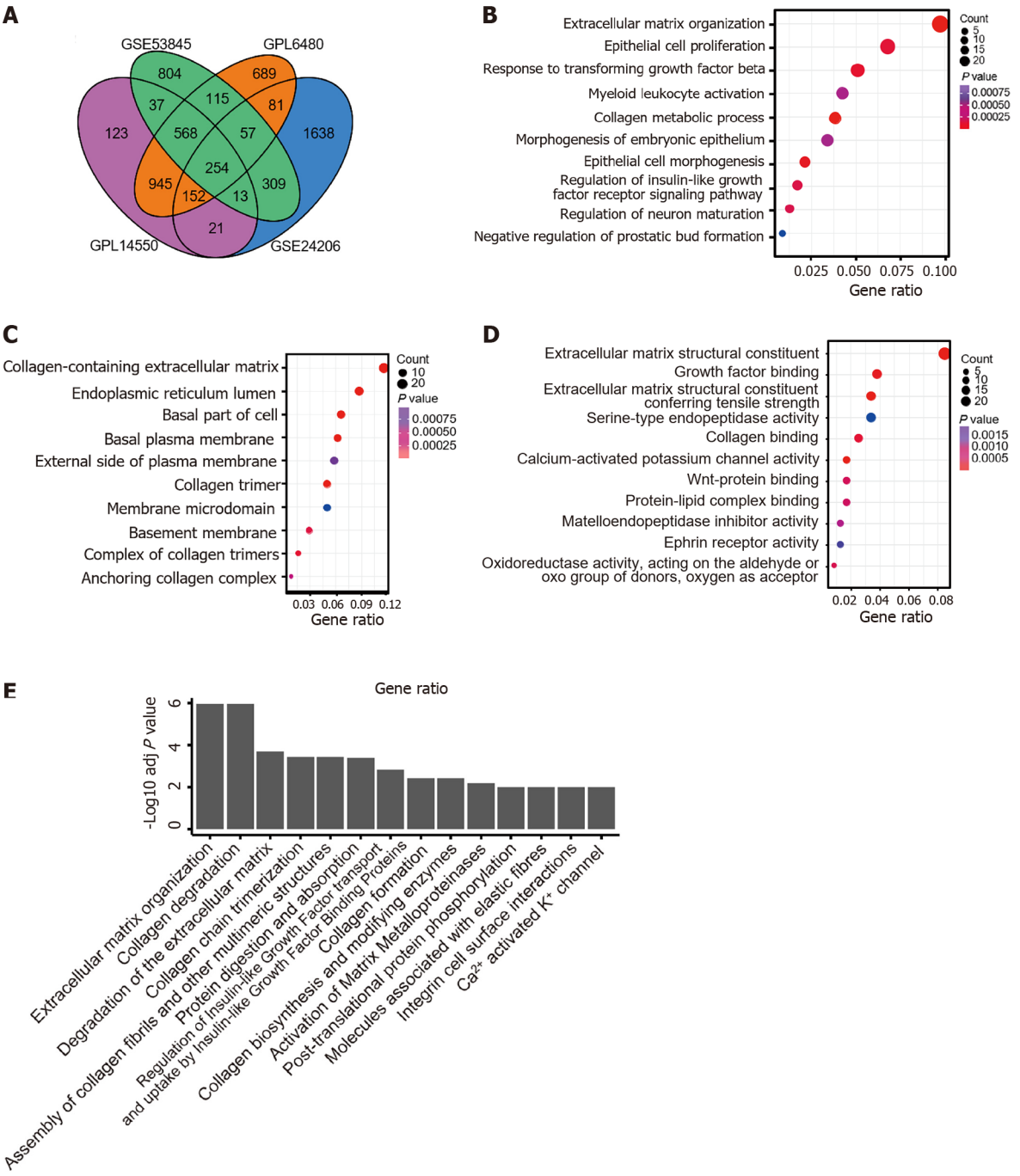
The biological roles and functional pathways of the 254 DEGs were revealed by GO enrichment analysis. The three functional categories were BPs (Figure 1B), CCs (Figure 1C), and MFs (Figure 1D). The results showed that DEGs were significantly involved in "extracellular matrix organization", "response to transforming growth factor beta", "regulation of insulin-like growth factor receptor signalling pathway", "regulation of neuron maturation", "collagen-containing extracellular matrix", "extracellular matrix structural constituent", "serine-type endopeptidase activity", "calcium-activated potassium channel activity", and "Wnt-protein binding". The results of the KEGG and Reactome pathway analyses (Figure 1E) identified by DAVID showed that the DEGs were significantly correlated with "extracellular matrix organization", "collagen degradation", "regulation of insulin-like growth factor transport and uptake by insulin-like growth factor proteins", and "molecules associated with elastic fibres".

PPI network analysis and identified hub genes

For further elucidation of the interaction of common DEGs, interaction networks were constructed using STRING (STRING v11.5, https://string-db.org/). The TSV file containing information on PPI network interactions was downloaded and visualized by Cytoscape (V3.9.1). The network included 69 nodes and 59 edges, with an average number of neighbours of 2.0. The MCODE plugin in Cytoscape was used to detect the most significant hub gene modules and cluster scores under the default parameters. Three modules were identified with the MCODE plugin (Supplementary Figure 2) according to the following filter criteria: Cluster 1 (score: 4.000, 4 nodes and 6 edges), Cluster 2 (score: 4.000, 4 nodes and 6 edges), and Cluster 3 (score: 3.000, 3 nodes, and 3 edges). Afterwards, five algorithms (MCC, DMNC, MNC, Degree, and EPC) were used to identify hub genes in the cytoHubba plugin (Figure 2A-E). The top 30 genes in each algorithm were considered hub genes (Supplementary Tables 2-6). Finally, 15 genes were detected in all five algorithms: *RET*, *TGFB3*, *HSD17B6*, *SULF1*, *ASPN*, *SDR16C5*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNMB4*, *AOX1*, *KCNN3*, and *KCNN4* (Figure 2F).

Correlation between gene expression and lung functions

The above analysis showed significant enrichment of genes in epithelial cell proliferation. We expect a variety of candidate targets that can be used to treat IPF. Combined with the results of GO molecular functional enrichment analysis, these findings showed that tryptophan 2,3-dioxygenase activity and amino acid binding were significantly enriched ($P < 0.05$), and TDO2 was involved in these pathways. Figure 1D does not show this pathway because it was not ranked high enough. Moreover, in conjunction with the query results from DGIdb (https://dgidb.org/search_categories), which indicated that *TDO2* has a potential drug effect, these data were added to the downstream analysis. Moreover, *TDO2* has been confirmed to promote tumour cell proliferation and differentiation in the progression of oesophageal squamous cell carcinoma[38]. No relevant studies have been reported on the role of *TDO2*



DOI: 10.4330/wjc.v15.i6.293

Figure 1 Identification and enrichment analysis of differentially expressed genes in idiopathic pulmonary fibrosis data compared with control data. A: Analysis of common differentially expressed genes was performed between idiopathic pulmonary fibrosis and normal lung tissues with thresholds of $P < 0.05$ and fold change > 1.5 based on GSE53845, GSE47460 (GPL14550 and GPL6480), and GSE24206; B-D: Three categories of Gene Ontology analysis: Biological processes, cell components, and molecular functions; E: Kyoto Encyclopedia of Genes and Genomes and Reactome pathway analysis.

in IPF. Therefore, 15 genes identified by PPI and *TDO2* were included in the subsequent analysis.

The potential role of these genes in IPF development was examined by tracking expression changes in public datasets. We used linear models to assess changes in gene expression and lung function. The results showed that changes in 16 genes were directly associated with lung function. Twelve (*TDO2*, *RET*, *TGFB3*, *SULF1*, *ASPN*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNN3*, *KCNN4*) of the 16 genes were upregulated in IPF patients in all datasets. Additionally, these 12 genes significantly decreased in terms of lung function (decrease in DLCO and FVC, as shown in Figure 3A-L and Supplementary Figure 3A-L respectively). The changes in *AOX1* expression were conflicting. We observed a downregulation in IPF in the GSE53845 and GSE24206 data (logFC of -0.94 and logFC of -1.27, respectively) and an upregulation in IPF in the GSE47460 data (logFC of 0.9). Therefore, although *AOX1* is negatively correlated with DLCO and FVC (Figure 3M and Supplementary Figure 3M), we

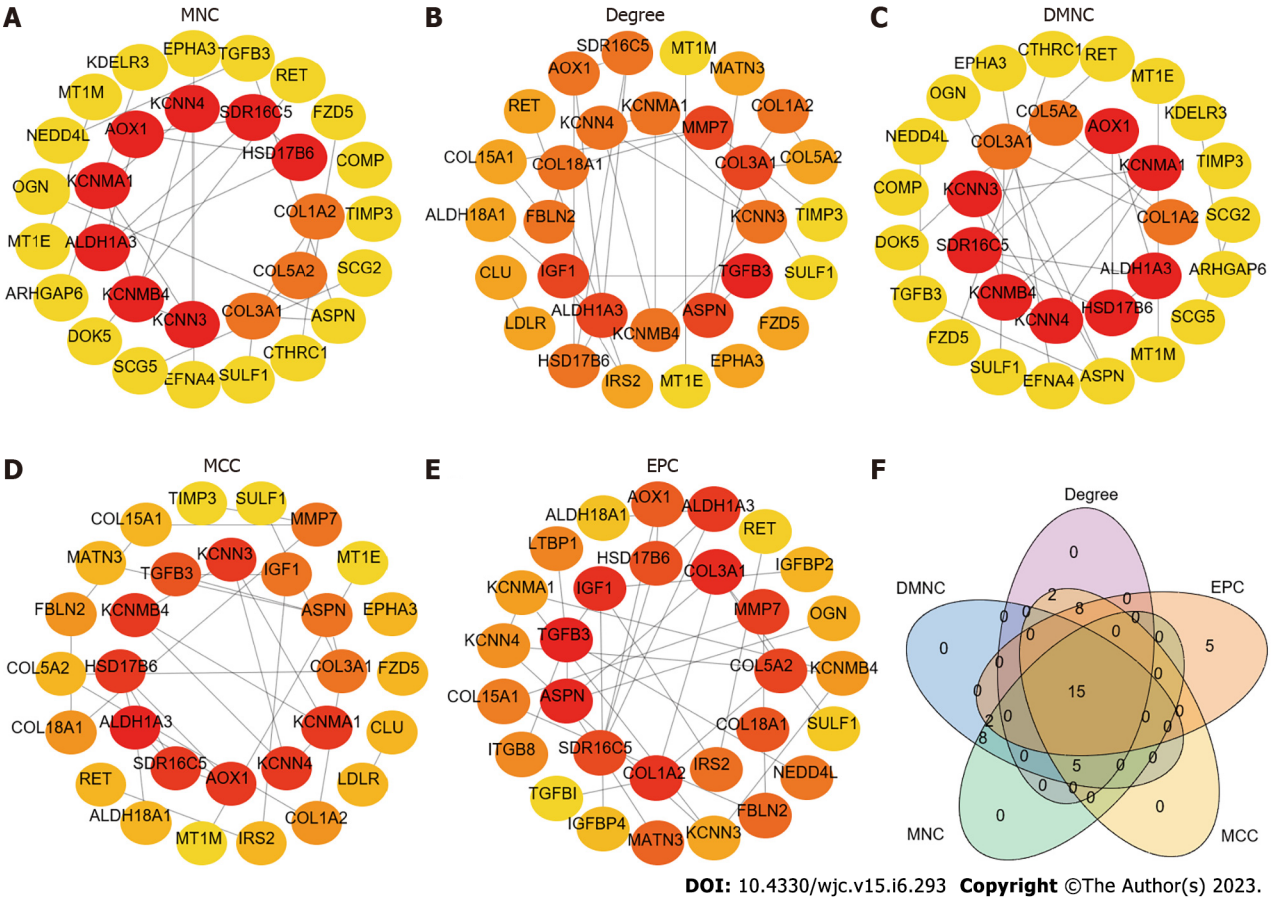


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Figure 2 Hub genes identified by maximum neighbourhood component, Degree, density of maximum neighbourhood component, maximal clique centrality, edge percolated component, venn diagram of hub genes. A: Maximum neighbourhood component; B: Degree; C: Density of maximum neighbourhood component; D: Maximal clique centrality; E: Edge percolated component; F: Venn diagram. The 15 hub genes were *RET*, *TGFB3*, *HSD17B6*, *SULF1*, *ASPN*, *SDR16C5*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNMB4*, *AOX1*, *KCNN3*, and *KCNN4*.

have excluded this gene from the subsequent analysis. Three (*HSD17B6*, *SDR16C5*, *KCNMB4*) of 16 genes were downregulated in IPF patients in all datasets, revealing a decrease in lung function (decreased DLCO and FVC, as shown in Figure 3N-P and Supplementary Figure 3N-P respectively).

Survival analysis

To explore the prognostic value of hub genes in IPF, we performed a survival analysis by Cox models. The data were from GSE70866[32]. Sample grouping information and the average expression and difference statistics of hub genes in each group are shown in Table 1. Survival analysis showed that *TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4*, and *ALDH1A3* were independent prognostic factors for poor survival in IPF (Figure 4). Patients with high expression of these genes are likely to suffer unfavourable outcomes. There was no significant difference between the expression of other hub genes and survival in IPF patients.

Validation of hub gene expression by qRT-PCR

The mRNA expression levels of the hub genes associated with low survival rates were detected through qRT-PCR. The sequences of the primers are shown in Table 1. The results showed that the mRNA expression levels of six genes (*TDO2*, *COL3A1*, *KCNN4*, *SULF1*, *KCNMA1*, *ALDH1A3*) were significantly increased in the bleomycin-induced pulmonary fibrosis group compared with the control group ($P < 0.01$, Figure 5). The direction of gene dysregulation was consistent with the test data analysis. These results demonstrate the validity of these genes for further analysis.

Prediction of target miRNAs and identifying genes of interest

Previous studies have shown that miRNAs are widely involved in disease regulation by targeting key genes[39]. The typical function of miRNAs is to bind to their 3′ untranslated regions to regulate various target genes. TFs can upregulate or downregulate miRNAs, corresponding to positive and negative feedback phenomena. Identification of the TF-miRNA-mRNA coregulatory network can help determine which miRNAs play a crucial role in the pathogenesis of hub genes involved in IPF and how they interact with TFs to regulate IPF-related genes. We used three online miRNA databases (miRWalk,

Table 1 Primer sequences

Gene name	Forward	Reverse
TDO2	AACATGCTCAAGGTGATAGCTC	GAACCGAGAACTGCTGTACCA
SULF1	TGTGTTCCACCGTTCGGTC	CACATCCTGGTCGTCAGTGAG
KCNN4	GCTCAACCAAGTCCGCTTC	GTGATCGGAATCAGCCACAGT
COL3A1	CTGTAACATGGAAACTGGGGAAA	CCATAGCTGAACTGAAAACCACC
HSD17B6	GGAGCGTGTTGGAGACAGAG	GAGGTTCACTTGAAAGATAGGCA
KCNMA1	TCACGGAACTCGCTAAGCC	AATGTGCGTCCCACTGTTTTT
KCNMB4	ACCAACCCCAAGTGCTCCTAT	GAATGGCTGGGAACCGATCTC
ALDH1A3	ATCAACAACGACTGGCACGAA	CACATCGGGCTTATCTCCTTC
SDR16C5	TTGAGTGTTTTGGAGGCCCTA	AACTGCAATGCTAAGAGCCTT
18S	GTAACCCGTTGAACCCCATT	CCATCCAATCGGTAGTAGCG

DIANATools, and miRDB) to predict miRNAs targeting the above nine hub genes. The targeted miRNA was selected when it targeted a gene in all three databases. Finally, 367 miRNAs were selected, and 401 mRNA-miRNA pairs were obtained (Supplementary Table 7). The interaction network of mRNAs and miRNAs, comprising 376 nodes and 401 edges, was constructed by Cytoscape (Supplementary Figure 4). Finally, TDO2 was selected to further explore the regulatory network.

TFs and miRNAs regulate each other to form feed-forward loops or feedback loops, where a TF regulates a miRNA or a miRNA inhibits a TF[40,41]. In this study, TransmiR was adopted to predict a list of significant TFs that may regulate miRNAs, and it provided 3730 highly reliable TF-miRNA regulations[36]. TDO2 was regulated by seven miRNAs (hsa-let-7g, hsa-mir-6878, hsa-mir-4270, hsa-mir-4441, hsa-mir-7974, hsa-let-7a-2, hsa-mir-6754). Based on the TFs in TransmiR prediction with a threshold of $P < 0.05$, the number of targeted miRNAs for regulation was 7. Nine molecules corresponding to this condition were *TCF12*, *SPI1*, *HIF1A*, *RUNX1*, ETS-related gene (ERG), *MYC*, *EP300*, *RELA*, and *STAT1*. On this basis, the TF-miRNA-mRNA network of *TDO2* was constructed by Cytoscape (Figure 6).

TDO2 in IPF and alveolar fibroblasts

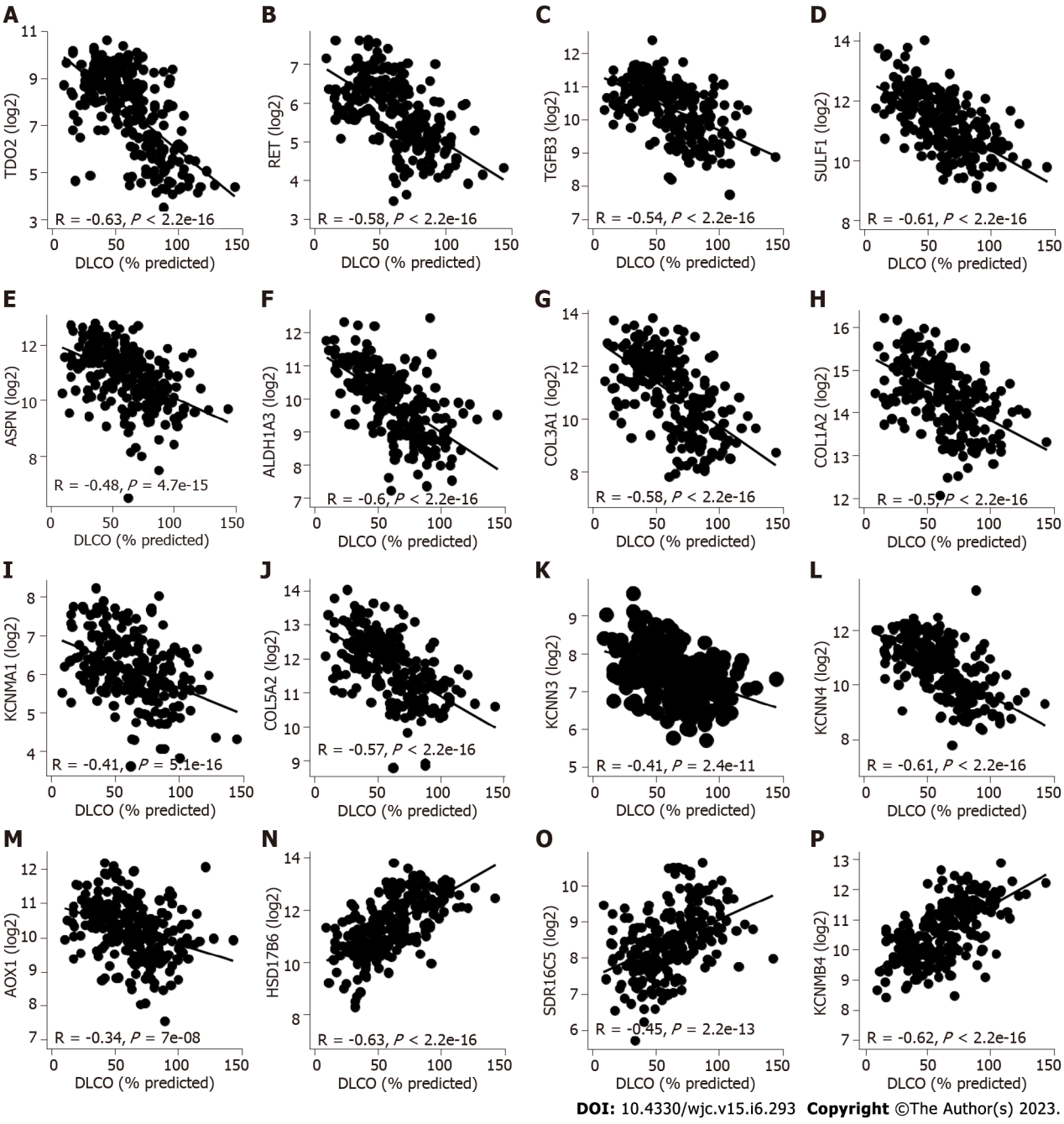
TDO2 was upregulated in IPF in all trained datasets, as shown in Figure 7A. *TDO2* expression was upregulated in IPF, while lung function was decreased (decreased DLCO and FVC, Figure 7B and C and Supplementary Figure 5A). In addition, single-cell RNA-seq data containing 32 IPF and 28 control lung tissues (GSE136831)[42] were used to validate *TDO2* expression between IPF and normal lung tissues of patients. The parameters and cell type identification in UMAP were consistent with those in a study of CD38-mediated pulmonary fibrosis[42]. In addition, *TDO2* expression was significantly enriched in alveolar fibroblasts (Figure 7D-F). This result is consistent with the proliferation of fibroblasts and myofibroblast accumulation in IPF. The above results were also supported by GSE135893 and GSE122960 (Supplementary Figure 5B-E). A UMAP plot with cells labeled by disease identity in GSE136831 has been added to Supplementary Figure 5F.

Reduction of TGF-β-induced fibrosis by TDO2 deficiency

To identify the effect of altered *TDO2* gene expression on fibrosis, we treated cells with *TDO2* inhibitors. Cells treated with TGF-β were the pulmonary fibrosis model group. After 24 h of TGF-β treatment, cells were treated with the *TDO2* inhibitor 680c91 to explore fibrotic changes. The same experiments were performed in three cell lines, including fibroblasts (IMR-90) and epithelial cells (A549 and MLE-12). The attenuated fibrosis was supported by the decrease in α-SMA and COL-I expression (Figure 8). These *in vitro* data reveal that decreased *TDO2* expression inhibited TGF-β-induced fibroblast activation, indicating that *TDO2* is a potential therapeutic target for fibrosis.

DISCUSSION

The progression of IPF seriously affects the lives of patients, while effective treatments are limited. To address the shortage of IPF-targeted therapeutic candidate genes, this study collected four sets of GEO public data to find common DEGs between IPF and normal lung tissues. Information on the common DEGs has been added to Supplementary Table 8. Since screening large public data ensures more accurate and generally applicable hub genes, data containing extensive IPF and control samples were selected for screening. For more robust data results, further screening was performed with clinical lung



DOI: 10.4330/wjc.v15.i6.293

Figure 3 Correlations between lung gene expression and forced vital capacity and diffusing capacity. A-M: *TDO2*, *RET*, *TGFB3*, *SULF1*, *ASPN*, *ALDH1A3*, *COL3A1*, *COL1A2*, *KCNMA1*, *COL5A2*, *KCNN3*, *KCNN4* and *AOX1* expression was negatively correlated with diffusing capacity of carbon monoxide (DLCO); N-P: *HSD17B6*, *SDR16C5*, and *KCNMB4* were significantly positively correlated with DLCO. The Pearson correlation metric was computed by using the 'stat_cor' function in R. DLCO: Diffusing capacity of carbon monoxide.

function indicators and survival analyses. Based on the PPI network and five cytoHubba algorithms, 15 hub genes were identified for the analysis. The relationship of these genes with lung function (such as DLCO and FVC) and overall survival was examined. Nine genes (*TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4*, and *ALDH1A3*) significantly decreased lung function in IPF and caused poor survival. The selected genes were validated by scRNA-seq data, qRT-PCR and western blotting in three cell lines, indicating these results are consistent with the actual situation. Compared with the validation in a single cell line, the results in multiple cell lines provide better support for the therapeutic function of *TDO2* inhibitors.

GO analysis showed that the common DEGs were primarily enriched in extracellular matrix organization (BP), collagen-containing extracellular matrix (CC), and extracellular structure constituent (MF). These biological pathways are involved in the degradation, regeneration, and remodelling of fibrosis[43]. IPF is the most common idiopathic interstitial pneumonia. However, nothing, other than a lung transplant, has thus far increased survival[44]. The antifibrotic drugs on the market are pirfenidone and nintedanib, which are used to slow the progression of the disease. Thus, further exploration of other

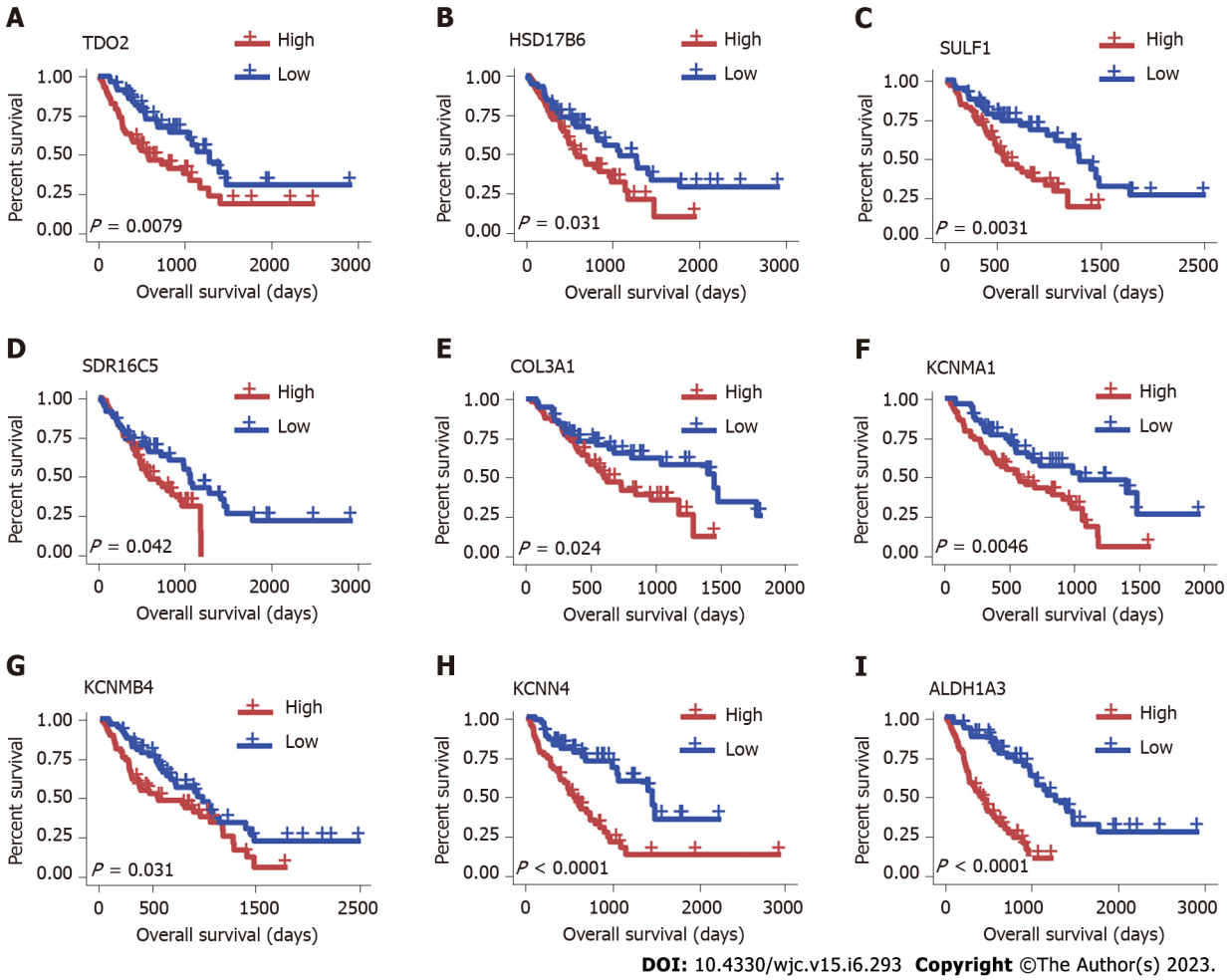


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Figure 4 Survival analysis of overlapping hub genes. Overall survival curves show that higher expression of *TDO2*, *HSD17B6*, *SULF1*, *SDR16C5*, *COL3A1*, *KCNMA1*, *KCNMB4*, *KCNN4* and *ALADH1A3* is associated with a worse survival rate. A: *TDO2*; B: *HSD17B6*; C: *SULF1*; D: *SDR16C5*; E: *COL3A1*; F: *KCNMA1*; G: *KCNMB4*; H: *KCNN4*; I: *ALADH1A3*.

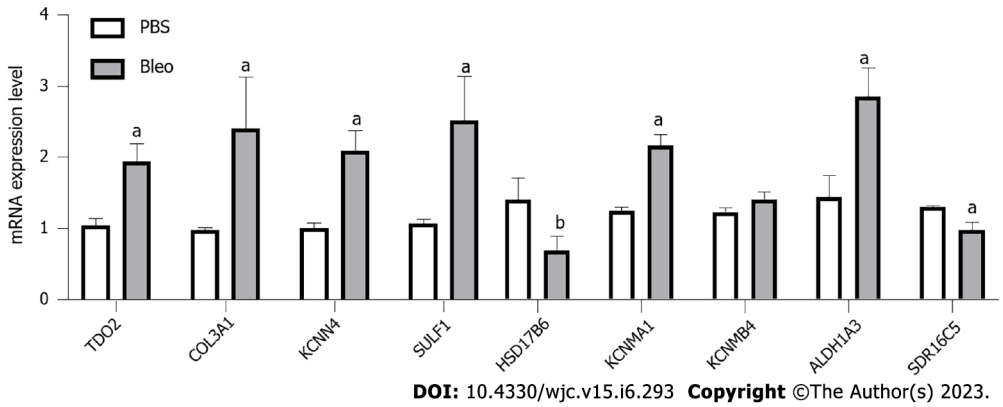

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Figure 5 mRNA expression levels of *TDO2*, *COL3A1*, *KCNN4*, *SULF1*, *HSD17B6*, *KCNMA1*, *KCNMB4*, *ALDH1A3*, and *SDR16C5* in the lung tissue *vs* PBS (*n* = 5 for PBS group, *n* = 5 for Bleo group). The statistical test used was the t test. Data are expressed as the mean with SD. [a]*P* < 0.01, [b]*P* < 0.05.

therapeutic drugs is warranted. Among the screened genes, *SULF1* promotes histone H4 acetylation, enhances the effects of HDAC inhibitors, and inhibits tumorigenesis in hepatocellular carcinoma[45]. HDAC inhibitors can downregulate *COL3A1* expression in primary IPF lung fibroblasts[46]. Therefore, targeting histone deacetylases in IPF may also be a future therapeutic approach[15].

MiRNAs are endogenous noncoding RNAs with regulatory functions and a length of approximately 22 nt[47]. These molecules play important roles in regulating the expression of genes related to the

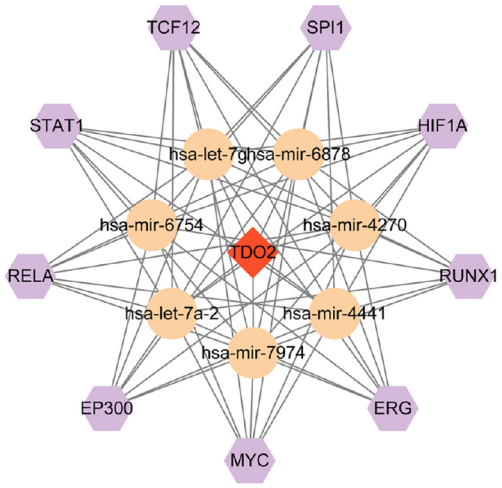

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Figure 6 Transcription factors-miRNA-mRNA regulatory network. Transcription factors, miRNA, and mRNA are represented by hexagons, circles, and diamonds, respectively.

growth and development of organisms and the occurrence of diseases. Studies have shown that each miRNA may have dozens or hundreds of target genes[48]. With the continuous discovery of specific miRNAs, the study of target genes in some disease pathways may lead to the discovery of new therapeutic methods. In this study, a regulatory pathway that may have the potential to regulate the expression of *TDO2* was identified through the TF-miRNA-mRNA network. In this way, the underlying molecular mechanisms of IPF were revealed, providing potential targets for developing new therapeutic agents to treat IPF patients. The results showed nine TFs targeting seven miRNAs to coregulate *TDO2*. Among them, HIF1A induced overexpression of the p53/hypoxia pathway in the tissues of IPF patients [49]; EP300 was highly enriched at enhancers of several genes in multiple profibrotic pathways[50]; immunostaining of RELA (v-rel reticuloendotheliosis viral oncogene homologue A) was increased in type 2 alveolar epithelial cells of mice treated with bleomycin[51]. The function of the TF ERG is dysregulated in ageing. A previous study showed that ERG dysfunction exacerbated pulmonary vascular ageing and persistent fibrosis[52]. We speculated that the disorder of ERG caused positive feedback, such as mechanisms involving miR-4270 and miR-4441 to regulate the expression of *TDO2*, so specific inhibition of ERG could be assessed in follow-up research, and combined treatment may be the future direction of pulmonary fibrosis treatment.

This study also has some limitations. We used five common sets from IPF data, but the intersection of common DEGs between one group of datasets (GSE110147) and the other groups was less than 50%. This group was removed in subsequent analysis, and the DEGs in the remaining groups were screened using thresholds of adjusted $P < 0.05$ and FC > 1.5. The selected common DEGs had identical direction of dysregulation, indicating that the validity of the thresholds and the data are reasonable. With the progress of scientific research, more IPF-related data can be generated, and additional datasets or novel computing methods can be adopted to find relevant genes affecting IPF. In addition to human lung tissue data, mouse data can be analysed and verified. With the diversification of sequencing technologies, multiomics data analysis can be adopted to validate genes. For example, single-cell RNA sequencing technology can examine the expression of specific genes in different cell populations and the existence of tissue preferences. Some genes were differentially expressed in at least one cell type, while some genes related to ECM were largely expressed in fibroblast subpopulations[53]. By investigating the expression of *TDO2* in each cell cluster in scRNA-seq data (GEO series accession No. GSE135893 and GSE122960[54]), we found higher expression in fibroblasts than in other cell clusters. The specific mechanism of *TDO2* in fibroblasts should be further investigated.

Moreover, when using STRING to construct PPI networks, we used different interaction score thresholds to obtain different network structures. Important candidate genes in common DEGs might be missed, and these genes would not appear in the network due to insufficient research. We reviewed these genes again and found that *TDO2* has potential drug effects. Previous research has shown that *TDO2* knockdown inhibits colorectal cancer progression[55]. In vitro experiments have shown that knocking down or blocking *TDO2* expression in myofibroblast subsets can effectively reverse T-cell immunosuppression in oral squamous cell carcinoma[56]. No relevant studies have been reported on the role of *TDO2* in IPF. Therefore, we included *TDO2* for follow-up analysis. Fortunately, the results of the network analysis in this study validated independent data from public databases and qRT-PCR data from our laboratory. However, the disadvantage is that we performed the experiment once, and there is a lack of repeated experiments to prove the repeatability of these findings. Additionally, it is important to explore whether the other group receiving more or less bleomycin has any effect on the reprodu-

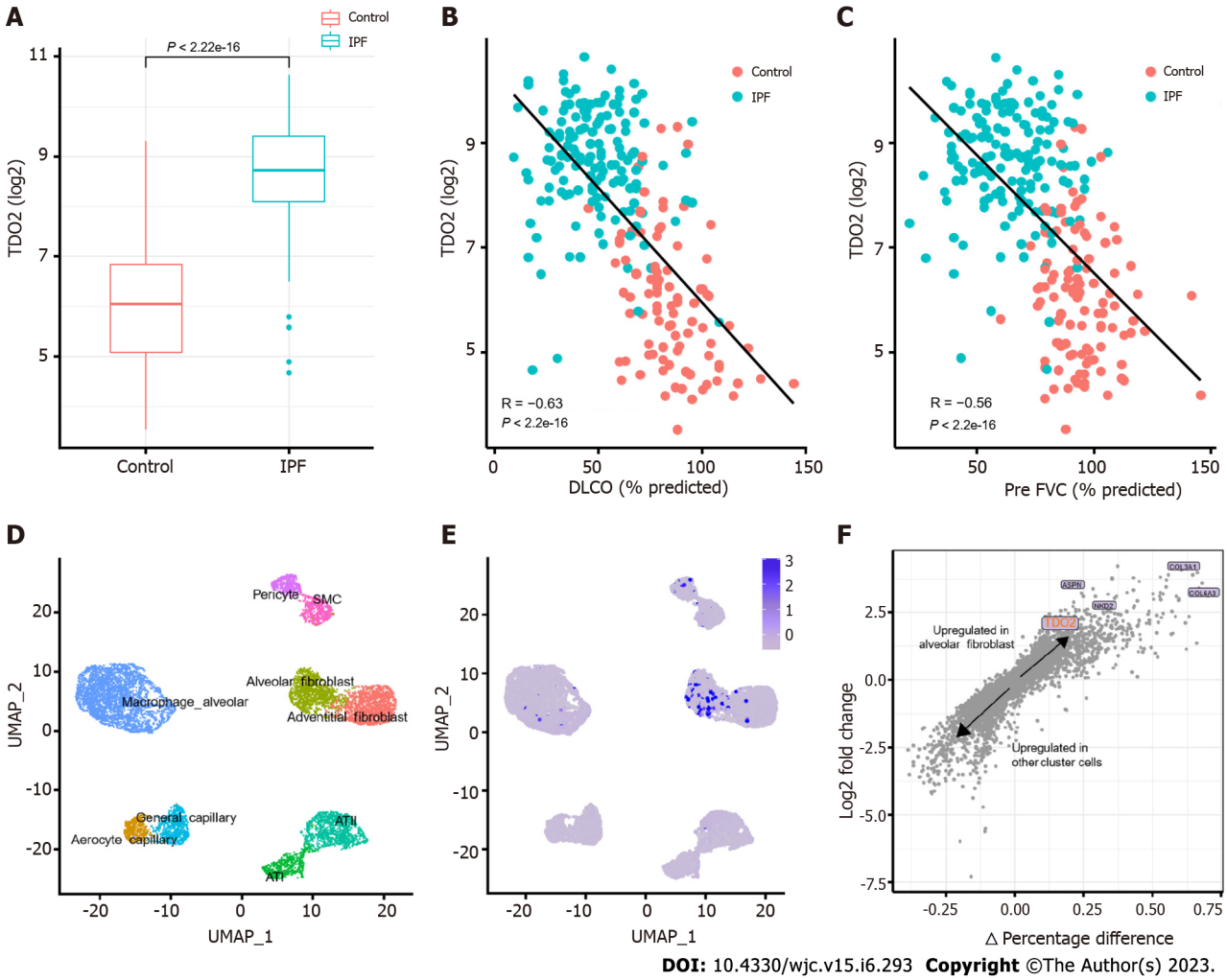

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Figure 7 *TDO2* increased in Idiopathic pulmonary fibrosis and was validated in scRNA-seq data. A: Upregulation of *TDO2* in Idiopathic pulmonary fibrosis of trained data (*e.g.*, in GSE47460). The statistical test used was the t test; B and C: Correlations between lung *TDO2* expression and diffusing capacity of carbon monoxide (B) and forced vital capacity (C) in GSE47460. The Pearson correlation metric was computed by using the 'stat_cor' function in R; D: UMAP of 8,942 randomly selected resident lung parenchymal cells from GSE136831; E: UMAP with cells labelled by normalized *TDO2* expression; F: Differential gene expression analysis using the log-fold change expression *vs* the difference in the percentage of cells expressing the gene comparing alveolar fibroblast cluster *vs* other cluster cells (Δ Percentage Difference). Labelled genes have a log2-fold change > 1, Δ Percentage Difference > 20% and adjusted *P* value from Wilcoxon rank sum test < 0.05. DLCO: Diffusing capacity of carbon monoxide; IPF: Idiopathic pulmonary fibrosis; FVC: Forced vital capacity.

cibility of the results. Representative images of rat body weight, survival rate, lung wet-to-dry weight ratio, lung hydroxyproline content, mouse hematoxylin and eosin staining and Masson's trichrome staining of lung sections are more conducive to increasing the persuasiveness of our results, which will be further studied in the future. In summary, we demonstrated that the *TDO2* gene is significantly upregulated after bleomycin treatment and proposed blocking TGF-β production as a potential treatment for IPF. A more comprehensive study of *TDO2* in animal models would be worthwhile.

CONCLUSION

This study identified novel hub genes to explore the treatment of IPF, examined the upregulated expression of *TDO2*, and investigated the TF-miRNA-gene regulatory network of *TDO2*. After inhibitor treatment, TGF-β-induced fibroblast activation was effectively inhibited. *TDO2* appears to be an effective treatment for IPF. Therefore, the molecular mechanisms of these TFs and *TDO2* deserve further exploration. The findings provide new target gene prediction, and we propose blocking TGF-β production as a potential treatment for IPF.

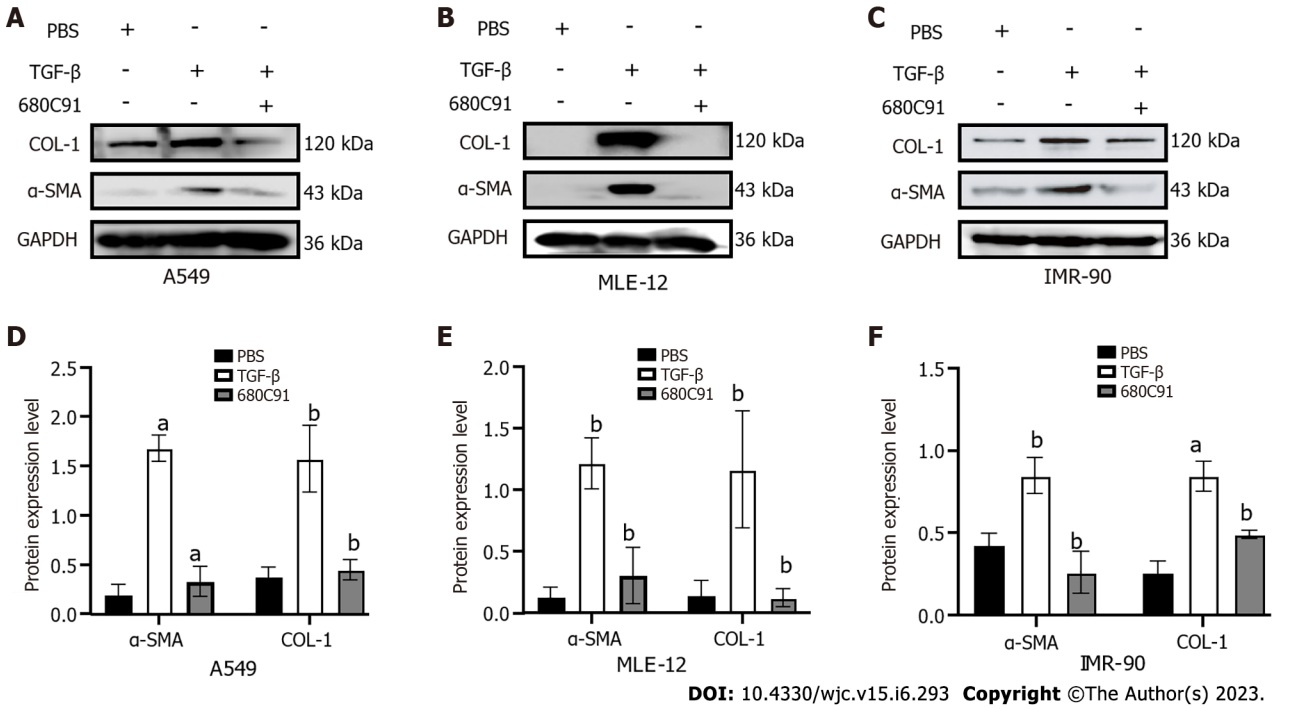

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Figure 8 Western blot analysis of α-smooth muscle actin and COL-1 in A549, MLE-12, and IMR-90 cells. Western blot quantification results in A549, MLE-12 and IMR-90 cells. A and D: A549; B and E: MLE-12; C and F: IMR-90. In line with the homogeneity of variance, the least significance difference method was used when assuming homogeneity of variance. [a]*P* < 0.01 *vs* phosphate-buffered saline; [b]*P* < 0.05 *vs* transforming growth factor-β. PBS: Phosphate-buffered saline; α-SMA: α-smooth muscle actin; TGF-β: Transforming growth factor-β.

ARTICLE HIGHLIGHTS

Research background

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with high mortality rate. Therefore, exploring potential therapeutic targets to meet the unmet needs of IPF patients is of great significance.

Research motivation

To explore potential targets for IPF treatment, as well as potential pathways and therapeutic methods.

Research objectives

Explore novel hub genes for IPF therapy. Whether *TDO2* can be a therapeutic target for IPF.

Research methods

We used public datasets (GSE53845, GSE47460, GSE24206, and GSE110147) to identify differentially expressed genes between IPF patients and healthy donors. Potential targets were considered based on multiple bioinformatics conditions, especially the correlation between hub genes and carbon monoxide diffusing capacity, forced vital capacity, and patient survival rate. The mRNA levels of the hub genes were determined through quantitative real-time polymerase chain reaction. Transforming growth factor-β (TGF-β) induced pulmonary fibrosis mouse model and the expression of *TDO2* was observed before and after the addition of inhibitor.

Research results

This study identifies novel hub genes to explore for IPF treatment. *TDO2* was upregulated in an experimental mouse model of TGF-β-induced pulmonary fibrosis and a *TDO2* inhibitor effectively suppressed TGF-β-induced fibroblast activation.

Research conclusions

TDO2 could be a potential target for treatment of IPF.

Research perspectives

More complete work with animal models is needed, as the *TDO2* gene is apparently upregulated by bleomycin treatment.

FOOTNOTES

Author contributions: Yang YM designed the research study; Wang R and Yang YM performed the research; Yang YM analysed the data and wrote the manuscript; Wang R performed the experiment research; all authors have read and approved the final manuscript.

Institutional review board statement: Our manuscript involves experiments on mice, as well as the A549 and IMR-90 cell lines, but does not involve any human experimentation.

Institutional animal care and use committee statement: The study was reviewed and approved by the Experimental Animal Ethics Committee of Henan University of Chinese Medicine, No. DWLLGZR202202036.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The authors confirm that the data supporting the findings of this study are available.

ARRIVE guidelines statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

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S-Editor: Fan JR
L-Editor: A
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 June 26; 15(6): 309-323

DOI: 10.4330/wjc.v15.i6.309

ISSN 1949-8462 (online)

SYSTEMATIC REVIEWS

Effect of fibrinolytic therapy on ST-elevation myocardial infarction clinical outcomes during the COVID-19 pandemic: A systematic review and meta-analysis

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Tan X, China; Tumminello G, Italy; Yu F, China

Received: December 9, 2022
Peer-review started: December 9, 2022
First decision: March 15, 2023
Revised: March 30, 2023
Accepted: May 19, 2023
Article in press: May 19, 2023
Published online: June 26, 2023

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Abstract

BACKGROUND

ST-elevation myocardial infarction (STEMI) is the result of transmural ischemia of the myocardium and is associated with a high mortality rate. Primary percutaneous coronary intervention (PPCI) is the recommended first-line treatment strategy for patients with STEMI. The timely delivery of PPCI became extremely challenging for STEMI patients during the coronavirus disease 2019 (COVID-19) pandemic, leading to a projected steep rise in mortality. These delays were overcome by the shift from first-line therapy and the development of modern fibrinolytic-based reperfusion. It is unclear whether fibrinolytic-based reperfusion therapy is effective in improving STEMI endpoints.

AIM

To determine the incidence of fibrinolytic therapy during the COVID-19 pandemic and its effects on STEMI clinical outcomes.

METHODS

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were queried from January 2020 up to February 2022 to identify studies investigating the effect of fibrinolytic therapy on the prognostic outcome of STEMI patients during the pandemic. Primary outcomes were the incidence of fibrinolysis and the risk of all-cause mortality. Data were meta-analyzed using the random effects model to derive odds ratios (OR) and 95% confidence intervals. Quality assessment was carried out using the Newcastle-Ottawa scale.

RESULTS

Fourteen studies including 50136 STEMI patients (n = 15142 in the pandemic arm; n = 34994 in the pre-pandemic arm) were included. The mean age was 61 years; 79% were male, 27% had type 2 diabetes, and 47% were smokers. Compared with the pre-pandemic period, there was a significantly increased overall incidence of fibrinolysis during the pandemic period [OR: 1.80 (1.18 to 2.75); I^2= 78%; P = 0.00; GRADE: Very low]. The incidence of fibrinolysis was not associated with the risk of all-cause mortality in any setting. The countries with a low-and middle-income status reported a higher incidence of fibrinolysis [OR: 5.16 (2.18 to 12.22); I^2 = 81%; P = 0.00; GRADE: Very low] and an increased risk of all-cause mortality in STEMI patients [OR: 1.16 (1.03 to 1.30); I^2 = 0%; P = 0.01; GRADE: Very low]. Meta-regression analysis showed a positive correlation of hyperlipidemia (P = 0.001) and hypertension (P < 0.001) with all-cause mortality.

CONCLUSION

There is an increased incidence of fibrinolysis during the pandemic period, but it has no effect on the risk of all-cause mortality. The low- and middle-income status has a significant impact on the all-cause mortality rate and the incidence of fibrinolysis.

Key Words: ST-elevation myocardial infarction; Myocardial infarction; Thrombolytic therapy; Fibrinolysis; COVID-19; Pandemics

Core Tip: The guideline-recommended time goals for primary percutaneous coronary intervention (PPCI) could not be met during the coronavirus disease 2019 (COVID-19) pandemic for the treatment of ST-elevation myocardial infarction (STEMI) patients. Leading cardiology societies recommended considering a new fibrinolytic-based reperfusion strategy during the time of the COVID-19 pandemic; however, previous large-scale studies have indicated that fibrinolytic therapy may offer a reduced prognostic value and poor survival outcomes in patients with STEMI compared to PPCI. We investigated the differential prevalence of the use of fibrinolytic therapy by healthcare systems belonging to countries with distinct income status, and its effect on the risk of all-cause mortality in STEMI patients.

Citation: Khedr A, Hennawi HA, Khan MK, Elbanna M, Jama AB, Proskuriakova E, Mushtaq H, Mir M, Boike S, Rauf I, Eissa A, Urtecho M, Koritala T, Jain N, Goyal L, Surani S, Khan SA. Effect of fibrinolytic therapy on ST-elevation myocardial infarction clinical outcomes during the COVID-19 pandemic: A systematic review and meta-analysis. *World J Cardiol* 2023; 15(6): 309-323
URL: https://www.wjgnet.com/1949-8462/full/v15/i6/309.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i6.309

INTRODUCTION

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease caused by transmural ischemia that affects the entire thickness of the myocardium. This condition is associated with high morbidity and mortality rates, making it a significant public health concern[1]. According to the Global Registry of Acute Coronary Syndrome Events (GRACE), STEMI accounts for approximately 30% of all acute coronary syndrome events[2].

The preferred treatment for STEMI is primary percutaneous coronary intervention (PPCI)[3]. However, the coronavirus disease 2019 (COVID-19) pandemic placed a significant strain on healthcare resources and providers, leading some experts to recommend changes in STEMI management. Fibrinolytic therapy was suggested as an alternative treatment for patients with severe resource limitations, a shortage of personal protective equipment, low-risk STEMI, systems of care delays, and the inability to provide PPCI in a timely fashion[4-8]. In a recent systematic review and meta-analysis conducted by Kamarullah and colleagues, it was found that the performance of STEMI care declined and clinical outcomes deteriorated in STEMI patients during the COVID-19 pandemic[9]. Despite this, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

Therefore, the aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era, and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

MATERIALS AND METHODS

Protocol and registration

To ensure transparent reporting, this systematic review and meta-analysis follow the PRISMA guidelines[10] and the MOOSE group's reporting guidelines[11] for observational studies in epidemiology. The research protocol has been registered with PROSPERO, the international prospective register of systematic reviews, under registration number CRD42022300242.

Literature search

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched systematically for articles in the English language between the time when severe acute respiratory syndrome coronavirus 2 was declared a Public Health emergency of international concern-PHIEC (January 2020) up until February 2022. We used the following keywords: STEMI, fibrinolysis, and COVID-19. We utilized minimum keywords to maximize the initial scope of research in order to ensure the largest number of articles recorded. Complete search strategies used for all electronic databases were developed by an experienced librarian and are reported in the Supplementary material. Reference mining included scanning reference lists of relevant papers, included studies, and systematic reviews published during the analysis of literature.

Eligibility criteria and study selection

Our study population consisted of patients with confirmed STEMI. We included studies that reported the impact of the COVID-19 pandemic on STEMI care. We searched for clinical trials, cohort studies, case-control studies, and case series. Animal studies, expert opinions, literature reviews, news articles, letters, editorials, case reports, guidelines, and any studies that did not mention the timing, population, intervention, and outcomes of interest were excluded.

We imported articles retrieved from the systematic search and exported them to EndNote reference library software (Thomson Reuters), where duplicates were identified and removed. Initially, articles were screened based on titles and abstracts by two independent reviewers (H.A.H. and E.P), then filtered relevant articles underwent full-text screening by another two reviewers working independently (H.A.M. and A.B.J). Another reviewer (A.K.) was consulted for decisions regarding any discrepancies during screening.

Data extraction

Data were extracted in a standardized data extraction form. We extracted data related to the following: (1) Summary of the included studies: Authors, year, timing, country, study design, sample size, inclusion criteria, duration of symptoms to intervention, study arms, and duration of follow up; (2) baseline characteristics of the included patients for regression purpose: Age, gender, race, body mass index, comorbidities, smoking status, and type of STEMI; and (3) the study outcomes as stated below. Any disagreements during data extraction were discussed to reach a consensus.

Risk of bias and quality assessment

The Newcastle–Ottawa Scale for observational studies was used by two independent reviewers (M.E. and M.K.K.) to evaluate quality on three diverse characteristics: Selection of study groups, comparability of groups, and ascertainment of the outcome of interest[12]. Each article was given a score that indicated how biased it was. Studies with a total score of seven or above were regarded to have a minimal probability of bias. If a study had a total score of six or less, it was determined to have a significant risk of bias. Disagreements in quality ratings were solved by a third reviewer (A.K.).

Study outcomes

We included studies that reported the incidence of the use of fibrinolytic therapy for STEMI patients during the pandemic compared to the timeline before the pandemic. The primary outcomes were the incidence of fibrinolysis and all-cause mortality.

Data synthesis and analysis

The analysis was performed in a sequence of calculations; the odds ratio (OR) of the incidence of fibrinolysis was calculated, followed by the subgrouping of studies based on significant increase in the incidence of fibrinolysis, no change in the incidence of fibrinolysis, and economic status of the countries where the studies were carried out, respecting the World Bank's classification of developed and developing countries into high-income and low- and middle-income countries (HICs and LMICs), respectively[13]. The effect sizes and the corresponding 95% confidence intervals (CIs) were calculated from raw data and variability measures or extracted directly from the studies. The outcomes were calculated using the DerSimonian and Laird random-effects model. The Higgin I^2 test was used to evaluate the heterogeneity between studies, and higher percentages indicated higher heterogeneity. The summation effect measures were calculated as OR with 95%CIs. Statistical significance was set at < 0.05 for all calculations.

Publication bias was assessed using the Begg funnel plot test[14]. Sensitivity analysis was performed by adding and removing studies one after another. Meta-regression analysis was executed for all-cause mortality. Two covariates having significant correlation among all the tested ones were displayed in the results. MetaXL version 5.3 (Epigear) add-on for Microsoft Excel 365 and Review Manager 5.4 was used to perform all analyzes. The statistical methods of the study were reviewed by a biomedical statistician.

Evaluating certainty of evidence

A summary of estimated effects and the certainty of each piece of evidence was produced using the GRADE approach (Supplementary Table 1). The GRADE criteria categorize the certainty of evidence as High, Moderate, Low, and Very low. The rating process followed the GRADE manual. GRADEpro GDT was used to construct the certainty of evidence and the summary of findings table.

RESULTS

Search results

The process of study selection and the characteristics of the included studies are summarized in Figure 1 and Tables 1 and 2, respectively. A total of 2938 studies were initially identified through database

Table 1 Characteristics of included studies

Ref.	Country	Study design/Sa	Study group/time period of study / sample size
Daoulah *et al*[15]	Saudi Arabia	Retrospective Cohort/500	Pandemic period STEMI/01/01/2020–30/04/2020/500
			Pre-pandemic period STEMI/2018–2019/1285
Leng *et al*[16]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–30/04/2020/164
			Pre-pandemic period STEMI/Equivalent period in 2019/240
Song *et al*[17]	China	Retrospective Cohort	Pandemic period STEMI/24/01/2020–31/03/2020/73
			Pre-pandemic period STEMI/24/01/2019–31/03/2019/95
Wang *et al*[18]	China	Retrospective Cohort	Pandemic period STEMI/23/01/2020–20/03/2020/37
			Pre-pandemic period STEMI/01/09/2019–02/12/2019/41
Wu *et al*[19]	England	Retrospective Cohort	Pandemic period STEMI/01/01/2019/1600
			Pre-pandemic period STEMI/22/05/2020/15646
Xiang *et al*[20]	China	Retrospective Cohort	Pandemic period STEMI/20/02/2020/10516
			Pre-pandemic period STEMI/27/12/2019/14634
Zhang *et al*[21]	China	Retrospective Cohort	Pandemic period STEMI/01/01/2020–31/03/2020/119
			Pre-pandemic period STEMI/2018 and 2019/276
Huang *et al*[22]	China	Retrospective Cohort	Pandemic period STEMI/01/02/2020–15/04/2020/31
			Pre-pandemic period STEMI/01/01/2019–31/12/2019/31
Erol *et al*[23]	Turkey	Retrospective Cohort	Pandemic period STEMI/2020/485
			Pre-pandemic period STEMI/2018/711
Mesnier *et al*[24]	France	Retrospective Cohort	Pandemic period STEMI/16/03/2020–12/02/2020/252
			Pre-pandemic period STEMI/17/02/2020–15/03/2020/331
Balghith[25]	Saudi Arabia	Retrospective Cohort	Pandemic period STEMI/01/2020–05/2020/81
			Pre-pandemic period STEMI/08/2019-12/2019/92
Clifford *et al*[26]	Canada	Retrospective Cohort	Pandemic period STEMI/17/03/2020–16/07/2020/193
			Pre-pandemic period STEMI/15/11/2019–16/03/2020/238
Rodríguez-Leor *et al*[27]	Spain	Retrospective Cohort	Pandemic period STEMI/16/03/2020–14/04/2020/1009
			Pre-pandemic period STEMI/01/04/2019–30/04/2019/1305
Calvão *et al*[28]	Portugal	Retrospective Cohort	Pandemic period STEMI/03/2020–04/2020/71
			Pre-pandemic period STEMI/03/2020–04/2020/80

STEMI: ST-elevation myocardial infarction.

searches, and after removing duplicates, 14 studies were found to be eligible for inclusion in this meta-analysis[15-28]. These studies involved 50136 adult STEMI patients, with 15142 patients receiving fibrinolytic therapy during the pandemic era and 34994 patients receiving standard of care before or during the pre-pandemic era. Our meta-analysis assessed the impact of fibrinolytic therapy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to standard-care before or during the pandemic.

Quality assessment

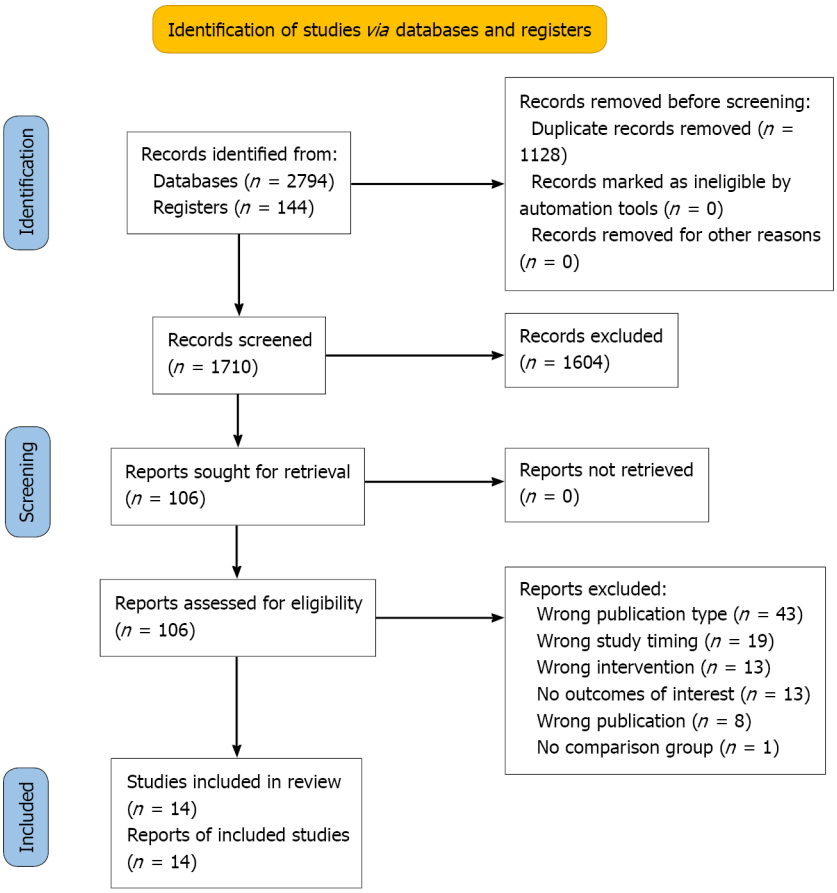
To assess the quality of the included studies, we used the Newcastle-Ottawa Scale for observational studies. Out of the 14 included studies, two were cohort studies, while the remaining 12 were case-control studies. Five studies had a low risk of bias (total score: 7-9), while the remaining studies were found to have a moderate risk of bias (total score: 4-6). None of the included studies had a high risk of bias (total score: 0-3). The detailed quality assessment of each study is provided in the (Supplementary Figure 1). The symmetrical funnel plot (Figure 2) indicated no small study or publication bias.

Table 2 Baseline characteristics of the included subjects

Ref.	Study group	Age, years (SD)	Male, *n* (%)	Hypertension, *n* (%)	Diabetes mellitus, *n* (%)	Hyperlipidemia, *n* (%)	Smoking, *n* (%)
Daoulah *et al*[15]	Pandemic period STEMI	55.4 (11.8)	454 (90.8)	229 (46.7)	257 (52.1)	190 (38.9)	213 (43)
	Pre-pandemic period STEMI	56.5 (12.8)	1123 (87.5)	599 (47.6)	632 (50.4)	450 (35.8)	318 (41.6)
Leng *et al*[16]	Pandemic period STEMI	63.13 (13.6)	131 (79.9)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.21 (13.14)	178 (73.9)	N/A	N/A	N/A	N/A
Song *et al*[17]	Pandemic period STEMI	61.6 (13.1)	59 (80.82)	43 (58.9)	16 (21.9)	39 (53.4)	36 (49.3)
	Pre-pandemic period STEMI	60.6 (13.9)	68 (71.57)	56 (59)	22 (23.2)	51 (53.7)	55 (57.9)
Wang *et al*[18]	Pandemic period STEMI	59.29 (11.46)	33 (89.18)	20 (54.05)	6 (16.21)	13 (35.13)	37 (100)
	Pre-pandemic period STEMI	55.49 (11.89)	35 (85.36)	18 (43.90)	5 (12.19)	15 (36.58)	31 (75.60)
Wu *et al*[19]	Pandemic period STEMI	65.1 (13.6)	1181 (73.81)	581 (36.31)	309 (19.31)	368 (23)	450 (28.12)
	Pre-pandemic period STEMI	65.76 (13.44)	11263 (71.98)	6060 (38.73)	3005 (19.20)	3645 (23.29)	4704 (30.06)
Xiang *et al*[20]	Pandemic period STEMI	61.59 (13.10)	7986 (75.94)	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	62.86 (12.33)	11019 (75.29)	N/A	N/A	N/A	N/A
Zhang *et al*[21]	Pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
	Pre-pandemic period STEMI	N/A	N/A	N/A	N/A	N/A	N/A
Huang *et al*[22]	Pandemic period STEMI	61	25 (80.6)	16 (51.6)	8 (25.8)	7 (22.6)	18 (58.1)
	Pre-pandemic period STEMI	60	25 (80.6)	18 (58.1)	6 (19.4)	8 (25.8)	20 (64.5)
Erol *et al*[23]	Pandemic period STEMI	59 (13)	552 (77.63)	221 (45.56)	151 (31.13)	108 (22.26)	248 (50.30)
	Pre-pandemic period STEMI	60 (14)	387 (79.79)	273 (38.39)	201 (28.27)	67 (9.4)	401 (56.39)
Mesnier *et al*[24]	Pandemic period STEMI	63.4 (12.5)	357 (74)	116 (24.11)	35 (7.27)	N/A	96 (19.95)
	Pre-pandemic period STEMI	64.4 (13.6)	509 (74)	139 (20.26)	55 (8.01)	N/A	131 (19.09)
Balghith[25]	Pandemic period STEMI	57.2 (12.6)	83 (90.21)	44 (54.32)	45 (48.91)	36 (39.13)	41 (44.56)
	Pre-pandemic period STEMI	51.3 (11.5)	81 (100)	38 (41.3)	41 (44.56)	31 (33.69)	35 (38.04)
Clifford *et al*[26]	Pandemic period STEMI	65 (12)	169 (71)	99 (51.29)	55 (28.49)	86 (44.55)	53 (27.46)
	Pre-pandemic period STEMI	64 (13)	135 (70)	123 (51.68)	54 (22.68)	99 (41.5)	93 (39.07)
Rodríguez-Leor *et al*[27]	Pandemic period STEMI	63.1 (12.5)	786 (78.4)	520 (51.9)	226 (22.6)	466 (46.7)	442 (44.6)
	Pre-pandemic period STEMI	63.7 (13.2)	1023 (78.4)	647 (50)	224 (25.2)	592 (45.8)	581 (45.7)

Calvão *et al*[28]	Pandemic period STEMI	63.3 (12.7)	56 (78.9)	49 (69.01)	23 (32.39)	38 (53.52)	40 (56.33)
	Pre-pandemic period STEMI	65.7 (12.8)	60 (75)	48 (60)	26 (32.5)	49 (57.5)	39 (48.75)

N/A: Not available; STEMI: ST-elevation myocardial infarction.



DOI: 10.4330/wjc.v15.i6.309

Figure 1 PRISMA chart displaying the process of search to study selection.

Frequency of fibrinolytic therapy

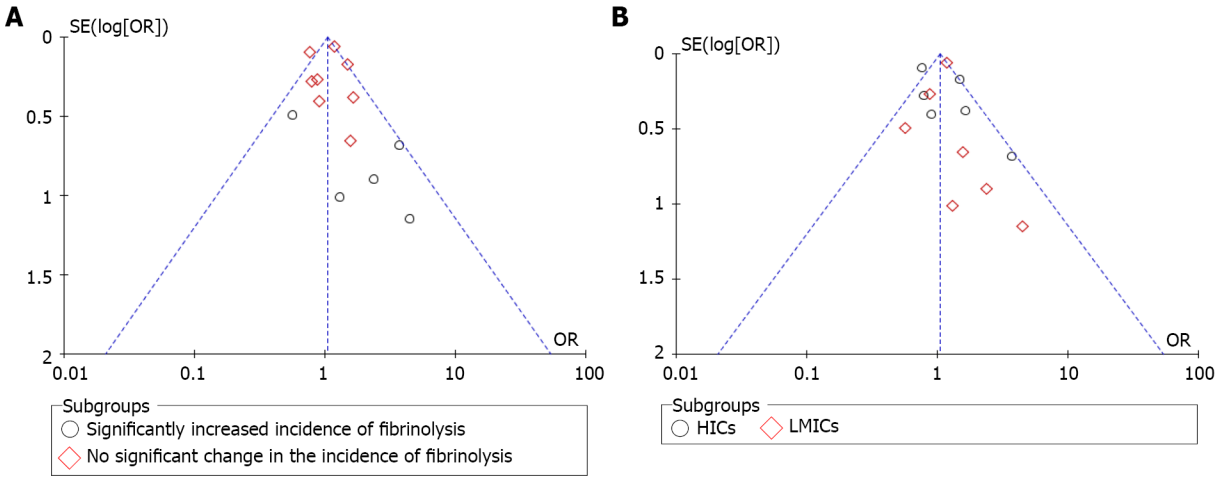
All 14 studies included in this meta-analysis investigated the frequency of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Our analysis revealed a significantly higher incidence of fibrinolytic therapy during the pandemic [OR: 1.80 (95%CI: 1.18-2.75); I^2 = 78%; P = 0.00; GRADE: Very low] (Figure 3A). Moreover, we observed that patients treated in LMICs had a higher probability of receiving fibrinolytic therapy [OR: 5.16 (95%CI: 2.18-12.22); I^2 = 81%; P = 0.00; GRADE: Very low] (Figure 3B).

All-cause mortality

We evaluated all-cause mortality in 13 of the included studies. The increased incidence of fibrinolytic therapy was not found to be associated with an increased risk of all-cause mortality [OR: 1.65 (95%CI: 0.67-4.06); I^2 = 40%; P = 0.27; GRADE: Very low] (Figure 4). However, patients who received fibrinolytic therapy in LMICs were at a higher risk of all-cause mortality [OR: 1.16 (95%CI: 1.03-1.30); I^2 = 0%; P = 0.01; GRADE: Very low]. Overall, we found no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy [OR: 1.09 (95%CI: 0.87-1.37); I^2 = 58%; P = 0.47; GRADE: Very low] (Figure 5).

Meta-regression for exploring specific covariates

Meta-regression of heterogeneity was performed for the outcome of all-cause mortality, as it is one of our primary outcomes and more clinically relevant. Hyperlipidemia (reported in 9 studies[15,17-19,22,23,24-28]) and hypertension (reported in 10 studies[15,17-19,22-28]) were tested as covariates. The meta-



DOI: 10.4330/wjc.v15.i6.309

Figure 2 No evidence of publication bias. A: When studies have been divided based on the incidence of fibrinolysis; B: When studies have been divided based on the income status of countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

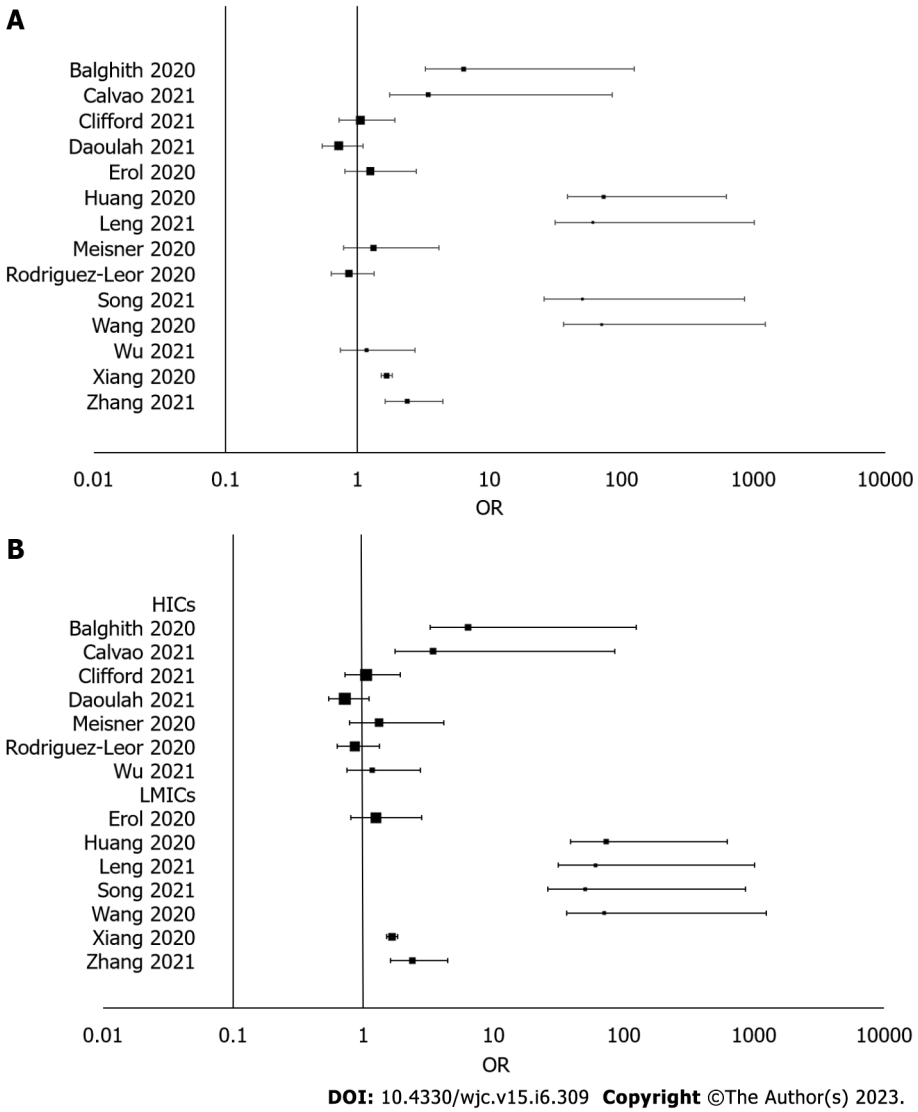
regression analysis provide evidence that hyperlipidemia is associated with an increased risk of all-cause mortality (P = 0.001) (Figure 6A). The meta-regression analysis further revealed that hypertension is also a significant predictor of all-cause mortality (P < 0.001) (Figure 6B). These findings suggest that managing hyperlipidemia and hypertension may be crucial for reducing the risk of all-cause mortality.

DISCUSSION

After conducting a thorough meta-analysis, we observed a significant increase in the use of fibrinolytic reperfusion in STEMI cases during the COVID-19 pandemic. Interestingly, we found no significant association between fibrinolysis and all-cause mortality rates. However, our analysis revealed that countries with lower-middle-income and low-income status reported a higher incidence of fibrinolysis, which in turn was associated with an elevated risk of all-cause mortality for STEMI patients.

In our meta-regression analysis, we found out that patients having hyperlipidemia and hypertension tend have an increased risk of all-cause mortality. Hyperlipidemia decreases the stability of plaques that are most likely to rupture and decreases endothelial function[29]. It also promotes the formation of platelet thromboses at the site of the injury[30]. LIPID trial also showed a decrease in the risk of mortality for those patients who were treated for hypercholesteremia with the help of Statins therapy [31]. hypertension is also a crucial prognostic factor for STEMI. Hypertension reduces the elastic ability of blood vessels and causes atherosclerosis[32].

The COVID-19 pandemic has added to the already existing challenges of chronically strained healthcare systems worldwide. Among the many areas of healthcare that have been impacted, primary cardiac interventions for STEMI patients have also faced significant obstacles[33]. In high-income countries, meeting the recommended time goals for such interventions was difficult even before the pandemic, with only 25%-50% of patients receiving PPCI within the recommended time frame of 120 minutes from first medical contact (FMC) to balloon[34]. Unfortunately, the pandemic has further exacerbated delays in symptoms-to-FMC and door-to-balloon time, creating an additional challenge for healthcare systems to provide timely and effective care to STEMI patients. A study reported that the mean time from symptoms to intervention was longer during the COVID-19 pandemic compared to the previous year[35]. The need to screen for COVID-19, which includes procedures such as chest radiographs, epidemiological screening, polymerase chain reaction swab tests, and other laboratory tests, has potentially contributed to delays in providing PPCI for STEMI patients. The goal of these screening measures is to prevent the spread of COVID-19 within healthcare settings. However, delays in PPCI have been linked to a significant increase in mortality rates for STEMI patients[36]. Moreover, the incidence of STEMI has been reported to decrease during the COVID-19 pandemic. A study by Furnica *et al*[37] found that the incidence of STEMI decreased by 48.8% during the COVID-19 pandemic compared to the same time in the previous year[37]. Another study by Oettinger *et al*[38] reported a similar increase in STEMI incidence of 22.9% during the COVID-19 pandemic[38]. These findings suggest that there may be an association between the declining incidence of STEMI and the COVID-19 pandemic. The use of fibrinolysis and PCI in the management of STEMI has been reported to differ before and during the COVID-19 pandemic. A study found that the use of fibrinolysis increased by 20.2% during the COVID-19 pandemic, while the use of PCI decreased by 74.6%[16]. While the use of



DOI: 10.4330/wjc.v15.i6.309

Figure 3 Increased incidence. A: Fibrinolysis during the pandemic period; B: Fibrinolysis in low-and middle-income countries as compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

PPCI has become the standard of care for STEMI patients, fibrinolytic therapy may still be considered in situations where delays in PPCI are expected[39]. In light of major unexpected events like the COVID-19 pandemic, it is important to establish the effectiveness of fibrinolytic reperfusion therapy based on available evidence. Thus, the objective of this review is to critically evaluate the efficacy of fibrinolytic therapy in the context of such unprecedented and unpredictable events, like the COVID-19 pandemic.

The response to the COVID-19 pandemic has been rapidly evolving and may differ between countries based on their ability to adapt to the situation[40]. While previous studies have shown relatively consistent outcomes during the pandemic compared to the pre-pandemic period, our latest meta-analysis suggests a potential increase in the use of fibrinolytic therapy among countries with lower economic status, particularly in the eastern regions. Our subgroup analyses, which adjusted for income status, revealed that LMICs faced a higher incidence of fibrinolytic therapy and increased mortality rates for STEMI during the pandemic. Even before the pandemic, nearly three-quarters of myocardial infarction patients in such countries were treated with fibrinolytic therapy[41]. These findings raise concerns about the challenges faced by LMICs during the pandemic, as their lack of modern infrastructure may hinder their ability to provide timely reperfusion and cope with the pandemic's impact on STEMI care. Conversely, countries with high-income status and well-organized emergency systems have been able to continue using PPCI as the preferred treatment for patients requiring urgent intervention[42].

The fundamental principle of STEMI therapy is to achieve immediate, complete, and microvascular reperfusion to limit the extent of myocardial damage. Although PPCI remains the recommended reperfusion therapy by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, it must be performed by an experienced team within a specific time frame to achieve the best outcomes. Compared to fibrinolytic therapy, PPCI significantly improves

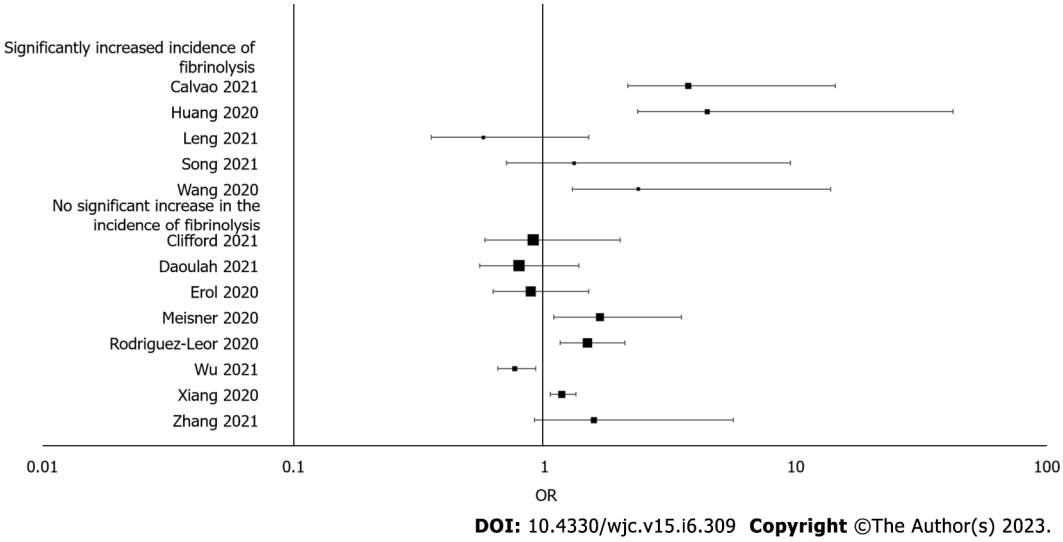


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Figure 4 No association between all-cause mortality rate and the incidence of fibrinolysis.

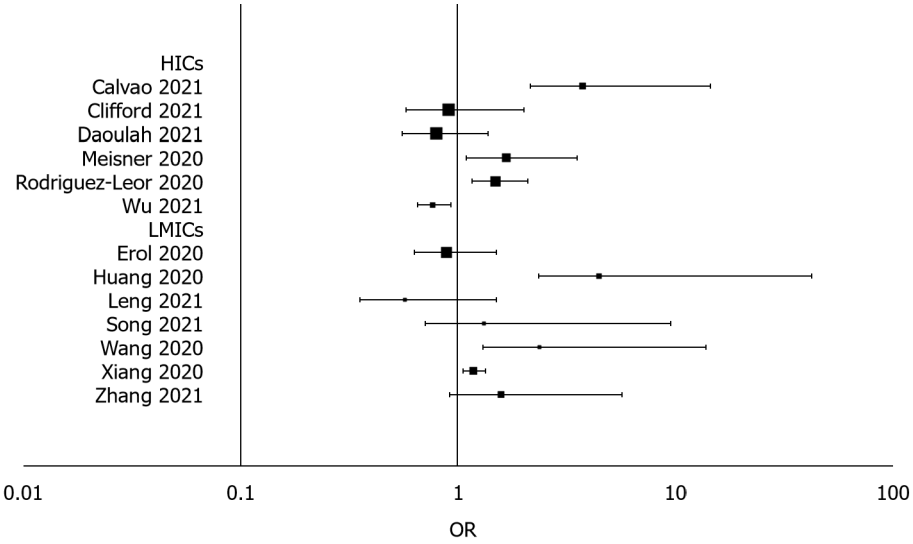

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Figure 5 Increased all cause-mortality rate in low-and middle-income countries compared to high-income countries. HIC: High-income countries; LMIC: Low- and middle-income countries.

survival and reduces the risk of major adverse cardiovascular events, reinfarction, and intracranial hemorrhage[43]. However, if PPCI cannot be delivered promptly, there is a sharp increase in mortality rates. In response to the pandemic, an interim guideline from China suggested the use of fibrinolytic therapy for STEMI patients presenting to healthcare facilities within 12 h of symptom onset[44]. As the saying goes, 'Time is muscle', emphasizing the importance of prompt treatment to preserve viable myocardium.

Regarding the clinical relevance of our findings, our results suggest that there may have been a decrease in the use of PCI during the COVID-19 pandemic, which could have important implications for patient outcomes. PCI is generally considered the preferred treatment for STEMI, as it has been shown to reduce mortality and the risk of complications compared to fibrinolysis. Therefore, any reduction in the use of PCI should be carefully evaluated to ensure that patient care is not compromised. Overall, the results of our study highlight the impact of the COVID-19 pandemic on the incidence, treatment, and outcomes of STEMI. These findings have important implications for clinical practice, as they underscore the need for continued efforts to promote timely recognition and treatment of STEMI, even in the midst of a pandemic. Strategies such as public education campaigns, telemedicine, and streamlined healthcare delivery systems may help to mitigate the impact of the pandemic on the management of STEMI and improve patient outcomes.

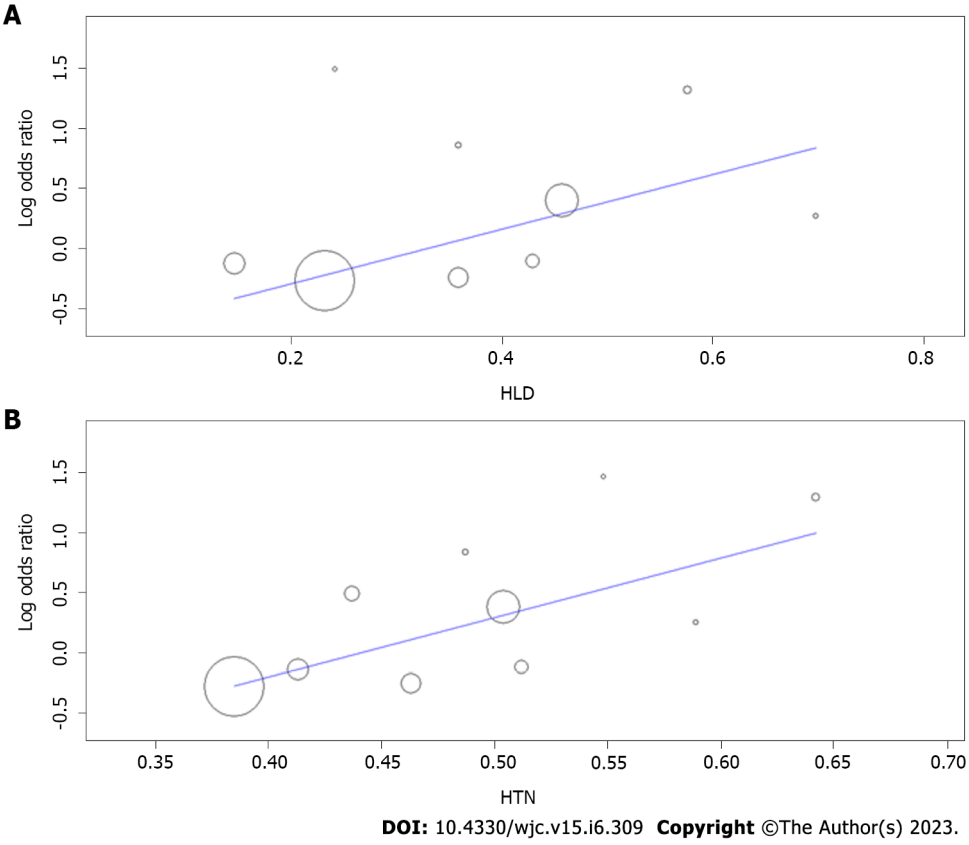

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Figure 6 Meta-regression plot. A: The significant direct relationship between hyperlipidemia and the risk for all-cause of mortality; B: Meta-regression plot displaying the direct relationship between hypertension and the risk for all-cause of mortality. HLD: Hyperlipidemia; HTN: Hypertension.

Limitations

This meta-analysis has some limitations that warrant consideration. Firstly, it is possible that the use of diverse fibrinolytic agents might have had an impact on our findings, thus confounding the results. Secondly, some of the outcomes in our study displayed high heterogeneity and wide confidence intervals, indicating low certainty. This could be due to the fact that the results were based on small sample sizes with varied outcomes. Additionally, the restriction of the review to English-language studies might have resulted in the exclusion of data published in other languages, which could have affected the findings.

CONCLUSION

Fibrinolysis-based reperfusion was found to be a major reperfusion strategy during the pandemic period, but the hypothesis of an association between overall all-cause mortality and the incidence of fibrinolysis was nullified. The present analysis of non-randomized studies was suggestive of a high casual association in populations living in LMICs. These results should remain an important focus of public health initiatives. The non-randomized selection process in individual studies could have contributed bias to the current meta-analysis.

ARTICLE HIGHLIGHTS

Research background

ST-elevation myocardial infarction (STEMI) is a severe form of coronary artery disease with high morbidity and mortality rates. The preferred treatment is primary percutaneous coronary intervention, but the coronavirus disease 2019 (COVID-19) pandemic led to changes in STEMI management, including the use of fibrinolytic therapy as an alternative treatment.

Research motivation

The COVID-19 pandemic placed a significant strain on healthcare resources and providers, leading to changes in STEMI management. However, the impact of fibrinolytic therapy on clinical outcomes during the pandemic remains largely unknown.

Research objectives

The aim of this systematic review is to examine the significance of the increase in fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-COVID-19 era and to assess the impact of this treatment strategy on clinical outcomes, particularly the risk of all-cause mortality, in comparison to patients who received standard-care before or during the pandemic.

Research methods

This study analyzed the incidence of fibrinolytic therapy and all-cause mortality for STEMI patients during the COVID-19 pandemic compared to the pre-pandemic period. Data synthesis and analysis were performed using the DerSimonian and Laird random-effects model, subgrouping studies based on changes in fibrinolysis incidence and economic status of countries. The study used sensitivity analysis, meta-regression analysis, and Begg's funnel plot test to assess publication bias and heterogeneity. Statistical significance was set at < 0.05.

Research results

This meta-analysis of 14 studies revealed a significantly higher incidence of fibrinolytic therapy in adult STEMI patients during the COVID-19 pandemic compared to the pre-pandemic era. Patients in low- and middle-income countries (LMICs) were more likely to receive fibrinolytic therapy, and those who received it in LMICs had a higher risk of all-cause mortality. However, overall, there was no significant association between the all-cause mortality rate and the incidence of fibrinolytic therapy. Meta-regression analysis showed that hyperlipidemia and hypertension were significant predictors of all-cause mortality, indicating that managing these conditions may be crucial in reducing mortality risk.

Research conclusions

The incidence of fibrinolytic therapy for STEMI patients increased during the COVID-19 pandemic, particularly in LMICs. However, there was no significant association between fibrinolysis and all-cause mortality. The findings of this study have important implications for public health initiatives.

Research perspectives

Fibrinolytic therapy was more frequently used during the COVID-19 pandemic, particularly in LMICs, but no significant association was found between the incidence of fibrinolysis and overall all-cause mortality.

FOOTNOTES

Author contributions: Khedr A substantial contributions to conception and design of the study, drafting the article, final approval; Hennawi HA acquisition of data, or analysis and interpretation of data, drafting the article, final approval; Khan MK analysis of data, revising and drafting the article, final approval; Elbanna M performed the data analysis, drafting the article, final approval; Jama AB and Proskuriakova E interpretation of data, drafting the article, final approval; Mushtaq H and Jain N contributed to the acquisition of data, revising the article, final approval; Mir M, Boike S, Rauf I, Eissa A, Koritala T, and Khan SA contributed to the interpretation of data, revising the article, final approval; Urtecho M contributed to the interpretation of data, making critical revisions, final approval; Surani S contributed to the acquisition of data, making critical revisions, final approval.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Fan JR
L-Editor: A
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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 June 26; 15(6): 324-327

DOI: 10.4330/wjc.v15.i6.324

ISSN 1949-8462 (online)

LETTER TO THE EDITOR

Virtual patient education for hypertension: The truth about behavioral change

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Freund O, Israel; Tostes RC, Brazil

Received: March 19, 2023
Peer-review started: March 19, 2023
First decision: April 28, 2023
Revised: May 11, 2023
Accepted: May 22, 2023
Article in press: May 22, 2023
Published online: June 26, 2023

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Abstract

Anti-hypertensive education is an important public health intervention to decrease the mortality and burden of the disease. Using digital technologies for education as a part of preventive measures for hypertension is a cost-effective approach and helps low-income communities and vulnerable populations overcome barriers to healthcare access. The coronavirus disease 19 pandemic further highlighted the need of new health interventions to address health inequalities. Virtual education is helpful to improve awareness, knowledge, and attitude toward hypertension. However, given the complexity of behavioral change, educational approaches do not always provide a change in behavior. Some of the obstacles in online hypertensive education could be time limitations, not being tailored to individual needs and not including the different elements of behavioral models to enhance behavior change. Studies regarding virtual education should be encouraged and involve lifestyle modifications emphasizing the importance of Dietary Approaches to Stop Hypertension diet, salt restriction, and exercise and should be used adjunct to in-person visits for the management of hypertension. Additionally, to stratify patients according to hypertension type (essential or secondary) would be useful to create specific educational materials. Virtual hypertension education is promising to increase awareness regarding risk factors and most importantly motivate patients to be more compliant with management helping to decrease hypertension related complications and hospitalizations.

Key Words: Hypertension; Virtual education; Health promotion; Public health; Patient education; Patient adherence; Dietary approaches to stop hypertension diet

Core Tip: Online anti-hypertensive education can play an important role in preventing and managing hypertension by providing individuals with the knowledge and resources they need to make lifestyle changes. Hypertensive management and education can be difficult in certain populations due to lack of access to healthcare, lack of information, and social determinants of health. Virtual education would promote health in those vulnerable populations.

Citation: Yukselen Z, Singh Y, Malempati S, Dasari M, Arun Kumar P, Ramsaran E. Virtual patient education for hypertension: The truth about behavioral change. *World J Cardiol* 2023; 15(6): 324-327
URL: https://www.wjgnet.com/1949-8462/full/v15/i6/324.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i6.324

TO THE EDITOR

In a recent article titled "Impact of the virtual anti-hypertensive educational campaign towards knowledge, attitude, and practice of hypertension management during the COVID-19 pandemic", Andrianto *et al*[1] emphasized the importance of online education in patients with hypertension[1]. Given the burden of hypertension, we found this article very interesting and promising for health promotion. Hypertension has been described as the "largest epidemic ever known to mankind"[2]. In the United States, nearly half of the adults have hypertension, and only 25% are under control[3]. Being an epidemic globally, it's not surprising that the economic burden of hypertension is enormous. In the United States itself, hypertension costs about $131 billion each year[4]. From the public health intervention perspective, Andrianto *et al*'s study is brilliant as we believe that one of the ways to cut the cost of hypertension is community-based interventions, such as health education and support groups, which can help reduce the cost of hypertension by providing individuals with the information and resources they need to manage their condition effectively[1].

As highlighted by the authors, overall, the coronavirus disease 19 (COVID-19) pandemic has had a significant impact on health disparities and healthcare access[5]. Even in the non-COVID era, patients with low economic status have been disproportionately affected by hypertension. The Prospective Urban Rural Epidemiology study, including patients from 17 countries on five continents, showed that awareness, diagnosis, and control of hypertension were lower in low-income countries compared with other countries and in rural settings compared with urban areas[6]. Considering the disadvantages of the vulnerable population, the COVID-19 pandemic highlighted the importance of addressing health disparities to ensure that all individuals have access to the care they need. Some of the difficulties in the population-level management of hypertension for minorities are barriers to healthcare, awareness, and understanding of the importance of monitoring, which is often linked to social determinants of health such as poverty, cultural beliefs, illiteracy, discrimination, and language barriers[7].

In the current era, the increasing use of mobile applications and telemedicine for communication has the potential to bridge disparities and play a significant role in managing hypertension in outpatient settings. A study by Freund *et al*[8] suggests that even elderly patients can effectively use online interventions as an inexpensive way to find answers to their health-related questions and improve their medical knowledge[8]. To address the global burden of hypertension, the Lancet commission encourages governments, pharmaceutical companies, healthcare professionals, and professional societies to develop simple mobile apps and online education programs to provide equal basic health access to people in low-income and middle-income countries[9]. In sync with this concept, the study conducted by Andrianto *et al*[1] reveals the importance of anti-hypertensive education in lower-middle-income countries. They found that virtual anti-hypertensive educational campaign implementation led to a significant improvement in the knowledge and attitude of patients with hypertension; however, it did not reflect a change in patient practice in taking measures against hypertension[1].

We are curious as to why a prospective study such as this with robust methodology could detect an improvement in facets of hypertension management but could not alter patient behavior. The education provided by Andrianto *et al*[1] was mainly directed toward the Dietary Approaches to Stop Hypertension (DASH), which is known as one of the most effective dietary interventions to lower blood pressure (BP)[1,10]. While dietary changes constitute a part of the non-pharmacologic therapy of hypertension, trials have shown that DASH dietary pattern reduced BP by 6/4 mmHg compared to a typical American-style diet[11]. Interestingly, and contrary to popular belief, dietary salt restriction is not a constituent of the original DASH dietary approach. In a systematic review of well-controlled randomized control trials, sodium restriction was associated with a reduction of BP by 4.8/2.5 mmHg in hypertensive and 1.9/1.1 mmHg in normotensive patients, respectively[12]. The benefits of dietary

sodium restriction coupled with the DASH approach were only later studied[10]. Given the heterogeneity in the approach, we would like to know how much emphasis was placed on salt restriction education in the population. Further, the authors set the level of significance for practice-changing reduction of systolic BP at 10 mmHg. It is possible that since the primary education was directed at dietary changes amongst the non-pharmacologic measures, this reduction was not detected due to a higher set threshold. Upon reviewing Table 1 of the study, it appears that the intervention did not educate heavily on the importance of physical activity and weight loss. Multiple studies have shown that weight loss effectively reduces systolic blood pressure (SBP) and diastolic BP, and 10 kg of weight loss may lower SBP by 5 to 20 mmHg[13,14]. Integrating this could have potentially led to detecting a significant change in behavior. This is important, especially since a sedentary lifestyle is a well-known contributor to hypertension, accelerated due to the restrictions and lockdown measures during the COVID-19 pandemic.

The other reason could be a limited time of education and a lack of other intervention components. According to the behavior change wheel model, ten different intervention functions have been suggested, some of them being education, incentivization, persuasion, training, and enablement[15]. Given the complexity of behavior change required in hypertension; applying those intervention elements, such as providing patient-centered, tailored information and feedback by the healthcare professionals, would be required. Virtual education can also be tailored to an individual's specific needs and preferences. For example, some virtual programs may offer personalized meal and exercise plans, while others may provide resources and support for stress management or medication management. Although the study by Andrianto *et al*[1] did not show a major behavior change, it greatly impacted the patient's perception towards not stopping medications when the BP is under control. This is another achievement of this study, as patients obtained that awareness after education.

Lastly, we noticed that the inclusion criteria were all patients with a diagnosis of hypertension. Did the authors sub-stratify their findings for the etiology of hypertension (essential *vs* secondary)? It would be valuable to learn how many patients amongst the included 110 participants had secondary/renovascular etiology of hypertension, especially since Table 2 indicates that 30 participants were < 40 years, which is when secondary hypertension is more prevalent. Both pharmacologic and non-pharmacologic measures differ for secondary hypertension and could be a reason for not reflecting in the behavioral change of patients.

To conclude, this randomized clinical trial has nicely addressed the importance of virtual hypertension education in the current pandemic, showing an impact on knowledge and attitude specifically. Future studies could focus on the effect of behavior coaching and personalized interventions such as texting patients or following up *via* telemedicine by healthcare providers to change behavior on medication adherence, lifestyle, and BP monitoring. These interventions would make an impactful effect on health promotion when used as an adjunct to management of hypertension and reduce the risk of complications and hospitalizations.

FOOTNOTES

Author contributions: Yukselen Z and Singh Y conceived the idea for the study; Yukselen Z, Singh Y, Malempati S, Dasari M and Arun Kumar P undertook the literature review; Yukselen Z and Singh Y wrote the first draft of the manuscript; Yukselen Z, Malempati S, Singh Y, Dasari M, Arun Kumar P and Ramsaran E revised the subsequent drafts of the manuscript; All authors reviewed and agreed on the final draft of the manuscript.

Conflict-of-interest statement: The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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