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# Bibliometric Analysis and Knowledge Mapping of Research Trends in Brugada Syndrome

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**Abstract:** *Background:* Brugada Syndrome (BrS) has been extensively studied over the last 30 years, warranting a review of its research landscape, including prevalent themes and potential future directions. *Objective:* By employing bibliometric analysis, this work seeks to map the current state and trajectory of BrS research, highlighting key contributors and unexplored areas while suggesting avenues for future studies which could propel the field forward. *Methods:* This paper analyzed BrS-related articles from 1992 to 2023, extracted from the Web of Science core collection, using tools like CiteSpace, VOSviewer, Pajek, and Scimago Graphica to examine research output, geographies, authors, affiliations, keywords, and citation patterns. *Results:* Out of 3,713 BrS publications, the US has been the most prolific, with the Netherlands producing the highest caliber work, and China ranking fourth in output. The University of Amsterdam emerged as the leading institution. Pedro Brugada topped the author list. The journal *Circulation* led in citations, with an impact factor of 37.8, indicative of its JCR Q1 status and elite ranking. Keyword analysis revealed 'Brugada syndrome' (2756), 'Sudden death' (1387), and 'ST-segment elevation' (1200) as common terms, with 'Management,' 'Guidelines,' 'Consensus conference,' and 'Genetics' as up-and-coming topics. *Conclusions:* Stable research funding and publication rates indicate a mature phase for BrS research, with genomics, proteomics, biomarkers, clinical prediction models, and gene therapy poised as future focal points.

**Keywords:** Brugada syndrome; CiteSpace; VOSviewer; Bibliometric

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## 1. Introduction

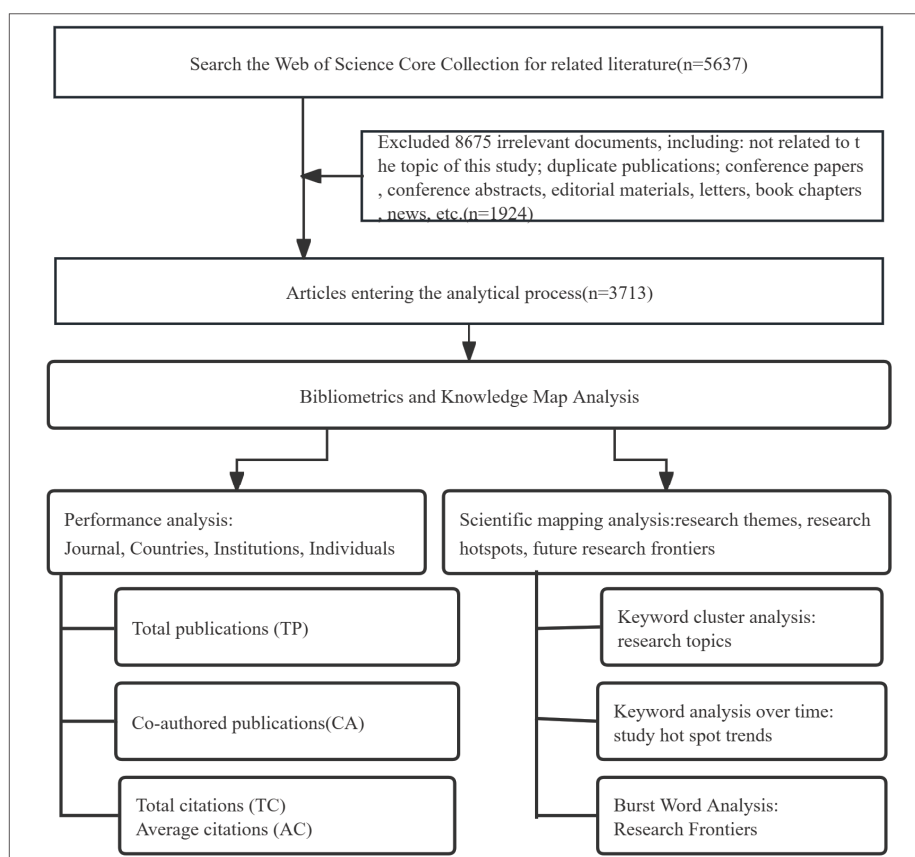
Brugada Syndrome (BrS) is a hereditary cardiac disorder marked by atypical ST-segment elevation, with an increased risk of ventricular tachycardia or fibrillation, potentially causing sudden heart failure. Identified in 1992 by the Brugada brothers, BrS has since garnered considerable attention in electrocardiography and cardiology worldwide <sup>[1]</sup>. Research over the last 30 years has spanned BrS genetics <sup>[2]</sup>, its molecular foundations <sup>[2,3]</sup>, clinical features <sup>[1,4]</sup>, diagnostic techniques, and therapeutic approaches <sup>[5]</sup>. Key advancements include the identification

of a critical genetic mutation, SCN5A<sup>[6,7]</sup>, ongoing enhancement of risk evaluation and treatment protocols<sup>[8–10]</sup>, and improvements in treatment options, including medication and defibrillator implants<sup>[11]</sup>. Nonetheless, debates over BrS diagnostic standards persist, causing diagnosis inconsistencies<sup>[8,12]</sup>, and current risk prediction models lack precision, affecting the management of high-risk individuals<sup>[13]</sup>. Furthermore, incomplete knowledge of BrS’s genetic diversity and complex traits complicates personalized treatment. This study aims to employ bibliometric analysis to thoroughly assess BrS research status and trends, monitor key authors’ contributions, pinpoint research deficiencies, and suggest potential future study avenues, thereby propelling progress in this domain.

## 2. Methods

### 2.1. Data source and retrieval strategy

This study’s statistical data was derived from the Web of Science Core Collection, specifically utilizing the “Science Citation Index Expanded (Sci-Expanded)” citation index. This study constructed a search string to include various terms related to Brugada syndrome and its manifestations, as well as ventricular fibrillation susceptibility syndrome, covering publications from 1992 to December 31, 2023, with the search executed on February 7, 2024. The study confined our document selection to peer-reviewed articles and reviews, deliberately excluding conference papers, early-access content, letters, and commentaries. Two researchers independently screened titles and abstracts, discarding irrelevant studies to maintain data integrity. The final dataset, post-verification and deduplication, comprised 3,713 records, plus the seminal 1992 paper by Brugada P and Brugada J, which was included manually. All selected documents were downloaded in a “tab-delimited file” format, opting for “Full Record and Cited References” as the record content. The overall workflow is shown in **Figure 1**.



**Figure 1.** Literature search process.

## 2.2. Data cleaning strategy

The de-duplication tool in CiteSpace eliminates repeated entries, while VOSviewer’s “replace” function and CiteSpace’s “citespace.alias” file consolidate synonyms. This includes standardizing terms to their singular form (e.g., “cardiomyopathies” to “cardiomyopathy”), unifying variations of expression (e.g., “ventricular-arrhythmias” to “ventricular arrhythmia”), and normalizing geographical names (e.g., “England,” “North Ireland,” “Scotland,” “Wales” to “UK”).

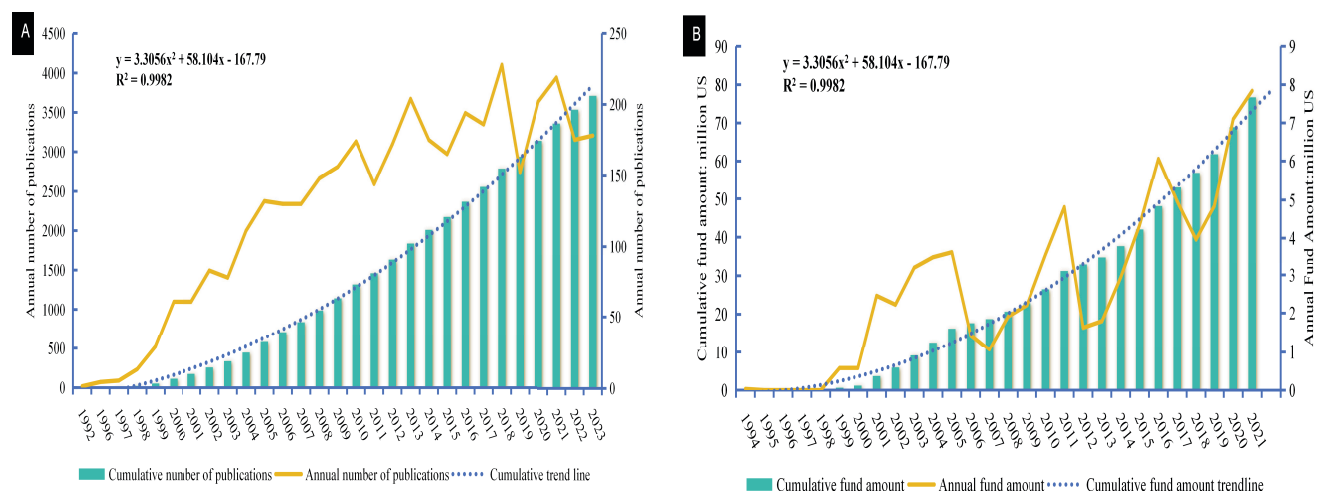
## 2.3. Data analysis tools

Bibliometric analysis of publication volume, countries, authors, institutions, keywords, and co-citation networks is conducted using bibliometric analysis software such as CiteSpace<sup>[14]</sup> and VOSviewer<sup>[15]</sup>. Map drawing is carried out using software like Pajek, Scimago Graphica, and WPS. Zotero and Notepad++ are used for organizing references and documents.

## 3. Results

### 3.1. Annual publication trends and fund volume analysis

By December 2023, 3,713 studies had been disseminated, averaging 128 studies per year. In 2018, a record high of 228 studies was published. Publication growth exceeded 20% annually during 1998–2000, 2003–2005, and 2011–2013, signifying rapid progression in the field. In the last ten years, the field has seen a steady output of 187 studies annually, reflecting consistent research activity but a lack of emerging focal points. Financially, an initial \$ 34,000 was allocated to this domain in 1994, with ongoing investment since 1999 reaching \$ 76.7 million by 2021, though this figure is not exhaustive.

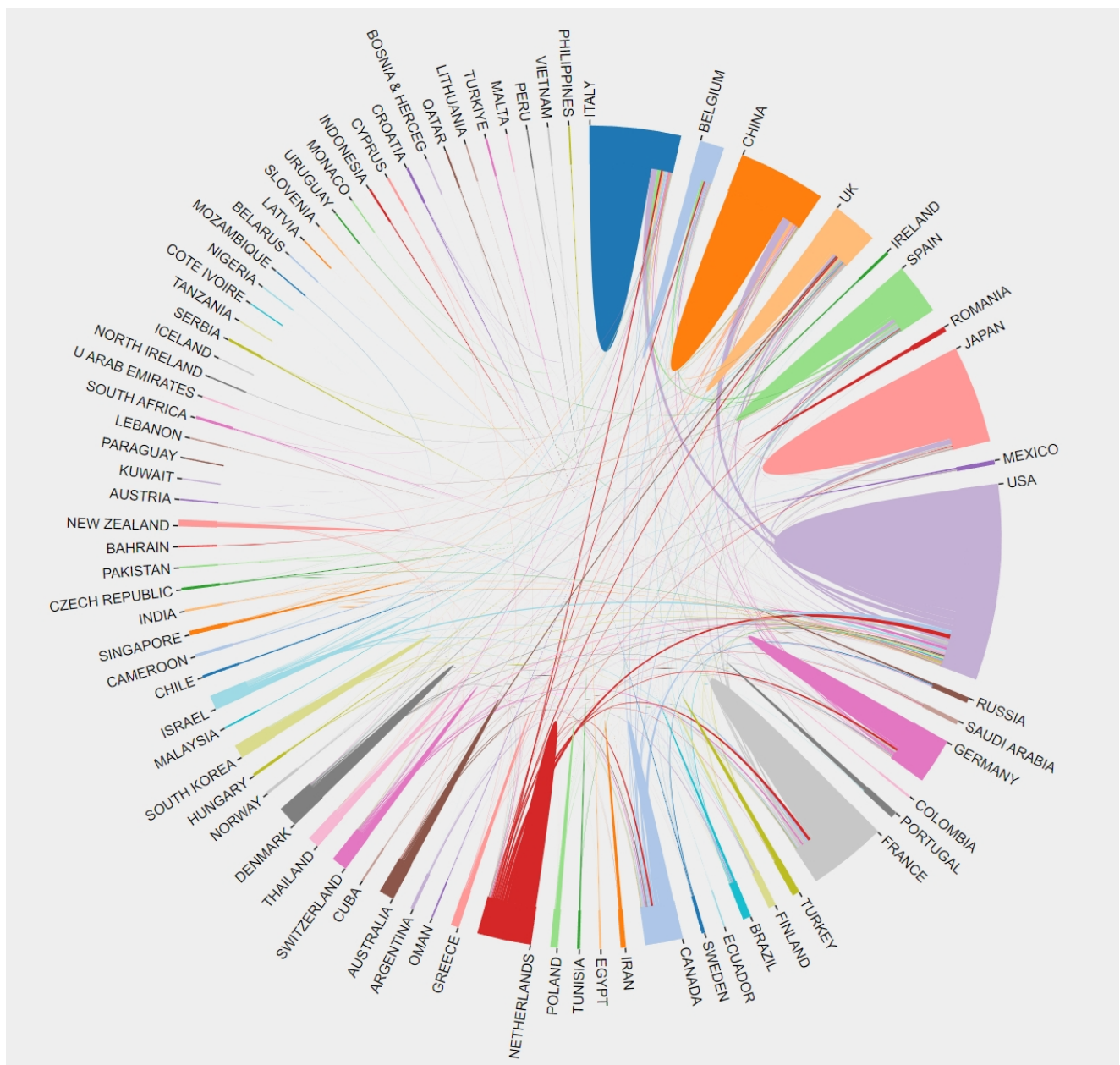


**Figure 2.** Trend chart of annual issuance and fund amount. The grant data comes from the public data of the National Science Foundation (NSF), National Institute of Health (NIH), EUROPA, PubMed Europe (PMC), Wellcome Trust, Research Councils UK, GRB (Taiwan Government Research Bulletin), Canadian Institutes of Health Research (CIHR), Natural Sciences and Engineering Research Council (NSERC), Social Sciences and Humanities Research Council (SSHRC), excluding other grant data. The data is only queried to 2021.

### 3.2. National co-occurrence and citation analysis

Research on BrS has seen participation from 83 countries, with 78 forming collaborative ties. The United States leads in partnerships, boasting 1,208. It notably collaborates with Canada, European nations, Japan, and China,

as shown in **Figure 2A**. The United States, Japan, and Italy rank as the top three publishers, with 1078, 597, and 428 papers respectively, while the United States, Japan, and the Netherlands have the most citations, as per **Figure 2B**, with 57072, 23354, and 22743 citations respectively. The Netherlands, France, and Germany have the highest citations per publication, with averages of 69.13, 57.44, and 56.81, indicating the Netherlands' high-impact research. China is fourth in publication count, showing growth since 2012, but with an average citation of 19.31, suggesting a need for higher quality work and more academic interaction. Domestically, collaboration prevails, and strong international partnerships are lacking. The United States has the greatest centrality, with a value of 0.21. The summary is shown in **Figure 3**. **Table 1** indicates that America, Japan, Italy and other countries ranked as the Top 10 countries in terms of publications, with **Figure 4** supports the ranking with respective annual trend chart.

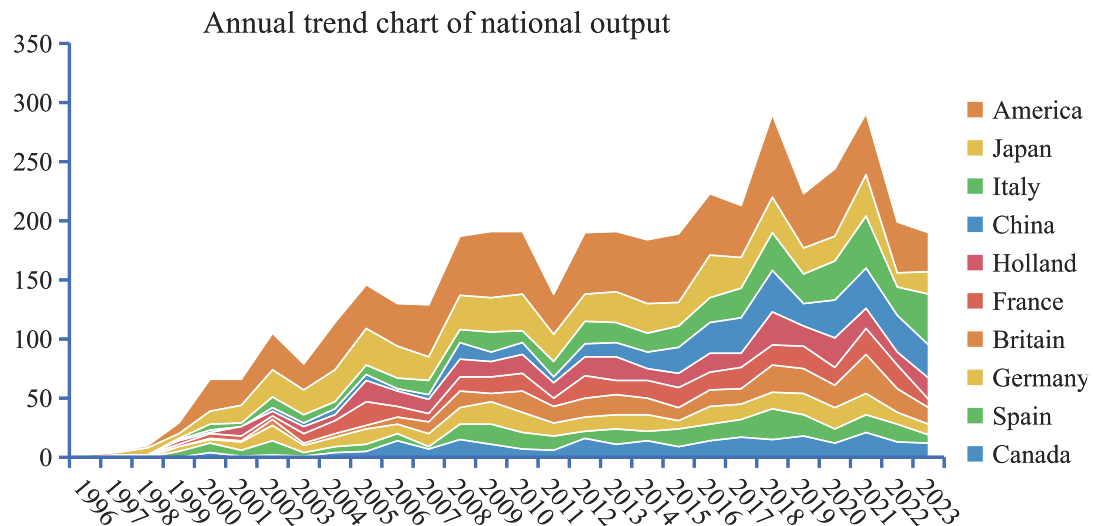


**Figure 3.** Geographic distribution of country cooperation.



**Table 1** Top 10 countries in terms of publications

Country	Volume	Total number of citations	Average number of citations	Centrality	Strength of connections
America	1078	57072	52.94	0.21	1208
Japan	597	23354	39.12	0.07	515
Italy	428	20560	48.04	0.07	703
China	358	6913	19.31	0.09	459
Holland	329	22743	69.13	0.1	645
France	315	18094	57.44	0.17	641
Britain	302	10671	35.33	0.16	654
Germany	297	16873	56.81	0.05	629
Spain	273	13892	50.89	0.17	528
Canada	250	9336	37.34	0.06	563

**Figure 4.** Annual trends in the volume of national communications.

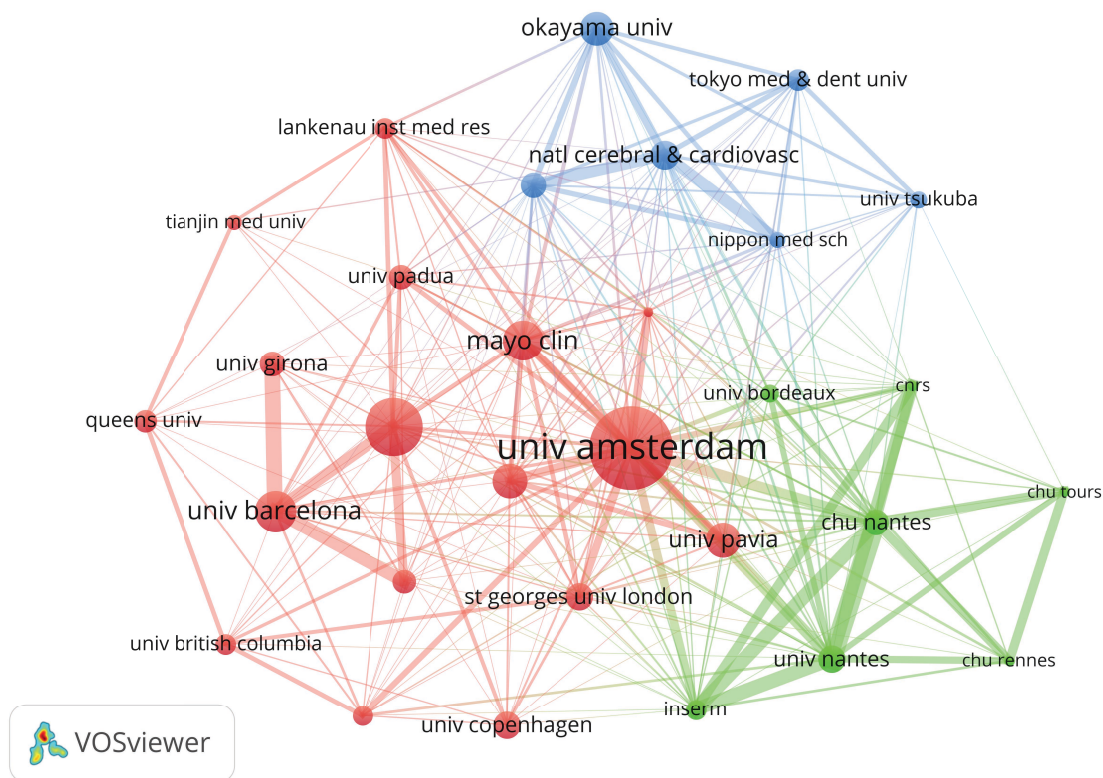
### 3.3. Research institutions and author co-occurrence and citation analysis

The research involved 3,744 entities, with the top 10 publishers listed in **Table 2**. Leading the pack, the University of Amsterdam, Mayo Clinic, and Masonic Medical Research Institute published 321, 316, and 135 papers, respectively. The Masonic Institute stood out with the highest average citation of 61.28, suggesting its research holds superior quality and influence. Based on **Table 3**, a total of 14,221 authors contributed to the research, yet only 277 authored over 10 papers each. Brugada P was the most prolific, with 166 publications, followed by Antzelevitch C and Wilde AAM with 151 and 149. Antzelevitch C also had the top citation count and average amongst the top 10 authors, scoring 8,625 and 57.12 respectively. The most cited paper, “Brugada Syndrome Report of the Second Consensus Conference,” provided comprehensive insights into BrS diagnosis, risk assessment, management, and genetics, offering clinicians a crucial reference for improving patient care<sup>[16]</sup>. **Figure 5** and **Figure 6** show the collaboration network map of the institution and author, respectively.

**Table 2** Top 10 organizations in terms of publications

Organization	Publications	Total citations	Average citations	Publications of the first author	Citations of the first author	Average citations of the first author
University of Amsterdam	321	12522	39.01	117	3700	31.62
Mayo Clinic	316	9664	30.58	44	1195	27.16
Masonic Medical Research Institute	135	8273	61.28	70	4205	60.07
University of Barcelona	121	5801	47.94	21	1485	70.71
Vanderbilt University	188	5103	27.14	49	1447	29.53
Baylor College of Medicine	84	5082	60.5	14	226	16.14
National Cardiovascular Center	71	4816	67.83	29	1686	58.14
Nantes University Hospital	76	4269	56.17	11	371	33.73
University of Pavia	98	3794	38.71	15	891	59.4
University of Munster	46	2997	65.15	11	78	7.09

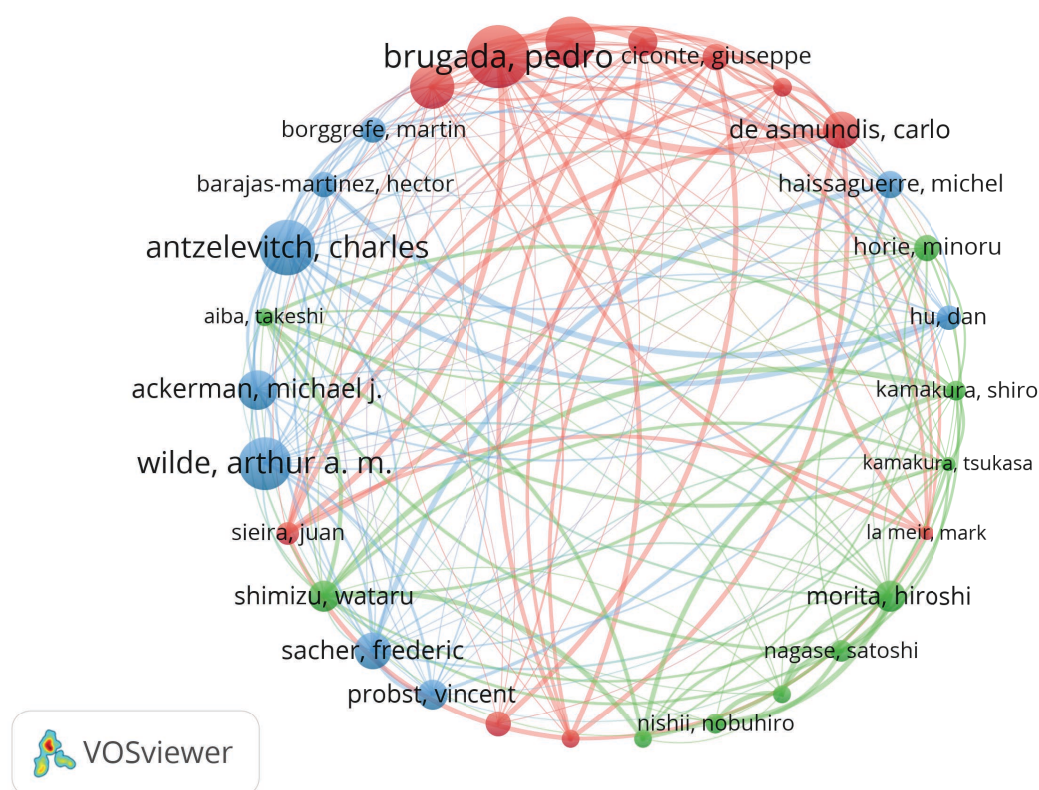
Note: All literature only takes the top 25 institutions or authors; First author refers to the first author, excluding co-authors (the same below). Only the top 30 institutions in terms of the number of publications are shown in the collaborative network map.

**Figure 5.** Institutional collaboration network map.



**Table 3** Top 10 authors in terms of publications

Author	Publications	Total citations	Average citations	Publications of the first author	Citations of the first author	Average citations of the first author	Publications of the corresponding author	Citations of the corresponding author
Brugada P	166	6703	40.38	15	402	26.8	22	516
Antzelevitch C	151	8625	57.12	33	2576	78.06	68	4593
Wilde AAM	149	6951	46.65	15	900	60	31	1696
Brugada R	132	6006	45.5	3	381	127	28	559
Brugada J	124	6348	51.19	11	999	90.82	12	1311
Shimizu W	88	4661	52.97	16	514	32.13	31	1193
ProBrSt V	87	4305	49.48	11	733	66.64	12	720
Sacher F	86	2719	31.62	8	318	39.75	9	318
Ackerman MJ	78	2623	33.63	5	131	26.2	31	1174
Bezzina CR	74	2782	37.59	4	357	89.25	13	703



**Figure 6.** Author's collaborative web chart.

### 3.4. Publication journal analysis

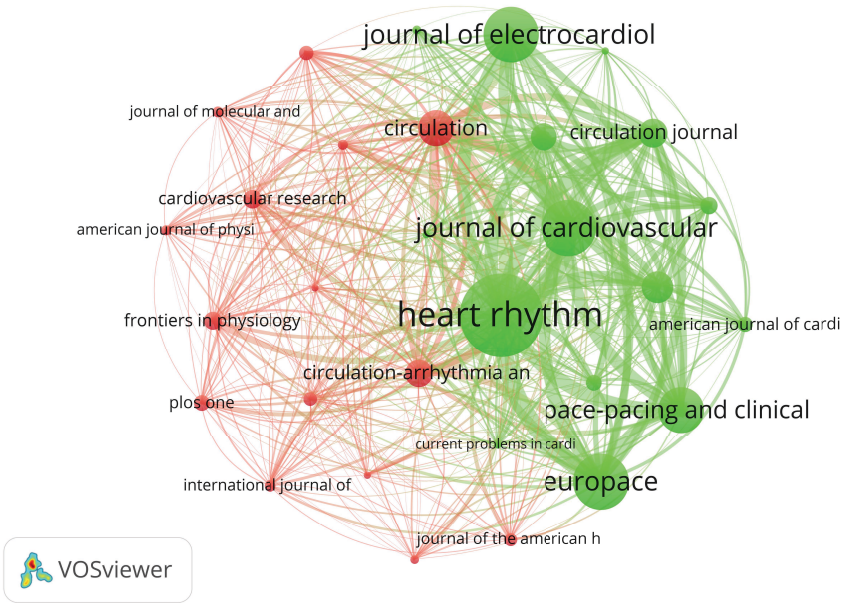
Research on Brugada Syndrome (BrS) was published across 616 journals, with the leading 10 featured in **Table 4**. The journals *Heart Rhythm*, *Journal of Cardiovascular Electrophysiology*, and *Europace* topped the publication count, delivering 245, 166, and 166 papers, respectively. *Circulation* led in total and mean citations with an impact factor of 37.8, marking its status as a JCR1 zone TOP journal, and highlighting its prominence in the field. *Journal of The American College of Cardiology* and *Circulation-Arrhythmia and Electrophysiology* followed as the second

and third for average citations in the top 10, scoring 122.04 and 49.89, respectively, both also classified as JCR1 zone TOP journals. **Figure 7** supports the above statement with the web chart of issuing journals.

**Table 4** Top 10 journals in terms of publications

Journal	Publications	Total citations	Average citations	IF	JCR	TOP Journal
Heart Rhythm	245	11458	46.77	5.5	2	No
Journal of Cardiovascular Electrophysiology	166	6033	36.34	2.7	3	No
Europace	166	3493	21.04	6.1	2	No
Journal of Electrocardiology	164	2913	17.76	1.3	4	No
Pace-Pacing and Clinical Electrophysiology	135	2561	18.97	1.8	4	No
Circulation	107	20863	194.98	37.8	1	Yes
Annals of Noninvasive Electrocardiology	94	1168	12.43	1.9	4	No
Circulation Journal	85	1909	22.46	3.3	3	No
Journal of the American College of Cardiology	82	10007	122.04	24	1	Yes
Circulation-Arrhythmia and Electrophysiology	81	4041	49.89	8.4	1	Yes

Note: Impact factors and JCR partitions are for 2023 data; only the top 30 journals in terms of publications are shown coupled network diagrams



**Figure 7.** Analysis of issuing journals.

### 3.5. Keyword co-occurrence and burst change analysis

Keywords summarize research themes, and examining them can reveal the progression and focal points in an academic area over time. Using VOSviewer, we analyzed 7,055 keywords from 3,713 studies (refer to **Figure 8**). A cluster analysis on the 200 most common keywords yielded five categories: epidemiology and genetics, clinical features, risk evaluation, treatment strategies, and fundamental molecular studies. Notable terms included ‘Brugada syndrome,’ ‘Sudden death,’ ‘St-segment elevation,’ and others such as ‘Arrhythmia’ and ‘Mutation.’ Based on **Figure 9**, burst terms, indicating a sharp rise in usage within a certain timeframe, signal new shifts and important findings. Our research identified such burst terms, pointing to early clinical signs,





## 4. Discussion

In 1992, Brugada siblings initially documented a syndrome with specific clinical and EKG patterns, including right bundle branch block, ST-segment elevation without heart abnormalities, and life-threatening arrhythmias <sup>[1]</sup>. Four years later, Miyazaki T defined Brugada syndrome (BrS) and its electrocardiographic modulation through autonomic influences and drug interactions, noting that certain drugs could worsen or mitigate ST elevation <sup>[17]</sup>. Building on this, Dumaine R discovered a gene mutation (SCN5A) in 1999, connecting it to BrS's EKG traits and its heightened risks during fever <sup>[18]</sup>. Further research identified over 90 additional mutations <sup>[2,3,6,7]</sup>. In 2002, Wilde *et al.* set diagnostic benchmarks for BrS, integrating EKG, family history, and other tests <sup>[19]</sup>. The consensus on BrS was refined in 2005 by Antzelevitch and colleagues, expanding its diagnosis, management, and genetic understanding <sup>[16]</sup>. ICD therapy emerged as a go-to for BrS, but a 2015 study by Conte *et al.* revealed its limitations, including preventive success, unintended shocks in asymptomatic patients, and device complications <sup>[11]</sup>. That year, Brugada J showcased epicardial ablation as a potential cure by eliminating Brugada patterns <sup>[13]</sup>. A 2023 study confirmed ablation's efficacy in preventing ventricular fibrillation, suggesting it could supplant ICDs <sup>[10]</sup>. Barc J and a large team in 2022 exposed 21 genetic markers for BrS, revealing the role of genetic variation and identifying new mechanisms like microtubule-related transport affecting Nav1.5 <sup>[3]</sup>. Pattarapong M's team found BrS-linked variants in the Thai population <sup>[20]</sup>, and Giuseppe C *et al.* linked genetic makeup to BrS severity <sup>[21]</sup>. Shohreh H developed a model to predict arrhythmic risks in BrS <sup>[3]</sup>. Recent trends point to genome-wide studies, cross-population genetics, risk models, and novel treatments as burgeoning areas of BrS research, poised for significant advancements.

While considerable progress has been made in understanding Brugada Syndrome (BrS), many mysteries persist, pointing to areas needing further investigation. These include:

- (1) Genetics and molecular mechanisms: The connection between gene mutations, such as those in the SCN5A gene, and the array of clinical presentations needs clarification, as does the molecular basis for related arrhythmias <sup>[5,22]</sup>.
- (2) Physiological mechanisms: The precise ways in which gene mutations affect ion channels and how these perturbations cause electrocardiographic changes and arrhythmias, remain to be uncovered <sup>[2,3]</sup>.
- (3) Clinical diagnosis: Diagnosis is currently based on electrocardiographic patterns and family history, yet these indicators can be indistinct. Future research could leverage big data and various omics technologies to refine diagnostic criteria and discover new biomarkers <sup>[5,12]</sup>.
- (4) Risk stratification: There is a need for more accurate methods to identify patients at high risk. Big data and AI could help develop predictive models for risk assessment <sup>[9,23–25]</sup>.
- (5) Therapeutic strategies: ICDs prevent sudden cardiac death but raise issues for young patients. Investigating the long-term impact of treatments like quinidine and exploring gene editing and stem cell technologies as treatment options are critical <sup>[9,10,26,27]</sup>.
- (6) Epidemiological studies: More studies are needed to understand the interplay between BrS, genetics, environmental factors, and lifestyle <sup>[9]</sup>.
- (7) Early screening and prevention: Effective strategies are urgently required for high-risk groups to prevent sudden cardiac death, which may include genetic research and exploration of ion channel dysfunction <sup>[28,29]</sup>.

Combining various scientific fields, interdisciplinary research is imperative to address these challenges in BrS. This study proposes that research will likely concentrate on genomics, proteomics, biomarkers, clinical prediction models, and gene therapy, informed by the latest advancements in big data, bioinformatics, and AI.

## Author contributions

Conceptualization: Yanli Yang

Investigation: Shiliang Xi

Analysis: Yanli Yang, Shiliang Xi

Writing – draft: Yanli Yang

Writing – review & editing: Ying Li, Yanli Yang

## Disclosure statement

The authors declare no conflict of interest.

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# Retrospective Analysis of Coagulation Abnormalities in Patients with Different Types of M-proteinemia

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**Abstract:** M protein (MP) is an abnormal monoclonal immunoglobulin produced by the abnormal proliferation of plasma cells or B lymphocytes which is very homogeneous in amino acid composition and sequence. Clinically, it can be seen in a variety of haematological diseases. This paper compares the coagulation indexes of patients with different types of M-proteinemia and patients with different levels of M proteins and observe the effects of different types and levels of M-proteinemia on the coagulation results. Different types of M-proteinemia were classified in 103 patients and the coagulation indexes of the patients were analyzed. *Aim:* To analyze the correlation between M proteins and coagulation function by analyzing the effects of different M-proteinemia patients' serum globulin types and contents on their indicators reflecting different coagulation functions. *Methods:* 103 patients with an initial diagnosis of M protein abnormality were selected from the Affiliated Hospital of Hebei University, and the results of their coagulation, liver function, and serum protein electrophoresis were collected to compare the coagulation function between patients with different types of M-proteinemia and between patients with the same type of M-proteinemia with different levels of M proteins and to analyze the correlation between them and the content of M proteins. *Results:* The differences in prothrombin time (PT) and fibrinogen (FIB) between the heavy-chain group (including IgG, IgA and IgM groups) and the light-chain group were statistically significant ( $P < 0.05$ ), and PT in the heavy-chain group were higher than those in the light-chain group. The difference of PT, TT and FIB between the M proteins  $> 30\text{g/L}$  group and M protein  $\leq 30\text{g/L}$  group was statistically significant ( $P < 0.05$ ), and the high M protein group PT and TT were higher than the other group while FIB was lower than the other group as there was no statistically significant difference of APTT comparing between the two groups ( $P > 0.05$ ). In the M protein  $> 30$  group, the mean values of PT and TT exceeded the upper limit of the reference interval, which had some clinical significance. *Conclusion:* There are some differences in the effect of different M protein types on PT and FIB results in patients with M-proteinemia, and the amount of serum M protein in patients has an effect on coagulation results.

**Keywords:** M-proteinemia; Coagulation indices; Serum globulin; Retrospective analysis

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## 1. Background

The main role of the immune system is to protect the body from foreign pathogenic bacteria and kill tumour cells, which is commonly known as “resistance.” It consists of a variety of immune cells and the proteins they secrete. Among them, the immunoglobulins secreted by B-lymphocytes and plasma cells, namely antibodies, can help the body fight against pathogens, such as antibodies against the hepatitis B virus. The body’s immunoglobulins are diverse, targeting a wide range of pathogens and forming a strong defence system. However, when B lymphocytes or plasma cells are abnormally stimulated, or when mutation occurs, abnormal immunoglobulins with identical structure, i.e. monoclonal immunoglobulins, or M proteins for short, are produced, and this condition is called M-proteinemia. Non-haematopoietic system diseases include prolonged chronic liver disease, nephrotic syndrome, viral infections, colon cancer and other malignant tumours, rheumatoid arthritis and other autoimmune diseases that stimulate the body’s immune cells. Lymphohaematopoietic system tumours are mainly multiple myeloma, macroglobulinemia, monoclonal gammaglobulinemia of undetermined significance (MGUS), lymphoma and so on. The onset of the disease is insidious, and in the early stage, there may only be M-proteinemia without clinical manifestations, and the symptoms of abnormal immune cells and M-protein harming the human body will appear in gradual progress. The most common plasma cell malignant tumour is multiple myeloma (MM). Due to the malignant transformation of plasma cells, a high concentration of monoclonal immunoglobulin is secreted, which leads to an abnormally high concentration of M-protein in the blood and a series of symptoms such as bone damage, kidney damage, and haematological damage. In the case of Wahl’s macroglobulinemia, the concentration of monoclonal IgM antibodies in the body is abnormally high, and the patient develops hyperviscosity, as well as a series of symptoms such as thrombosis, embolism, and splenomegaly <sup>[1]</sup>. The prevalence of M-proteinemia is as high as 6% in people over 50 years of age and increases progressively with age. Both morbidity and mortality have been on the rise in recent years <sup>[2]</sup>.

## 2. Methods

103 patients with abnormal M protein levels at the initial diagnosis of Hebei University Hospital from January 2021 to January 2022 were selected. Among them, 65 cases were male and 38 cases were female; their ages ranged from 38–88 years old, with an average age of 67 years old; they were outpatients and inpatients of various departments; the first symptoms of patients were different, but M protein was abnormal in all of them, and all of them had been tested by blood routine examination, coagulation function examination, liver function examination, immuno-serum protein level and typing test.

According to the different serum M protein components, they were divided into 54 cases of IgG, 18 cases of IgA group, 11 cases of IgM group, and 20 cases of light-chain group; according to the different serum M protein contents of the patients, they were divided into 16 cases of M protein > 30g/L group and 87 cases of M protein ≤ 30g/L group.

### 2.1. Research methodology

#### 2.1.1. Instruments and reagents

- (1) Experimental instruments: Coagulation function instrument (Werfen ACLTOP750 automatic coagulation analyzer, Werfen Instrumentation Laboratory MA, USA), serum electrophoresis instrument (Sebia Capillarys2 Flex Piercing automatic capillary electrophoresis), immunofixation electrophoresis instrument (Sebia HYDRASYS2).
- (2) Experimental reagents: Fibrinogen-CXL, RecombiPlasTin 2G, SynthASil, Thrombin time, D-Dimer



test (Werfen, Instrumentation Laboratory Company reagents); Immunofixation electrophoresis and serum electrophoresis (Sebia reagents).

### 2.1.2. Statistical methods

Data were analyzed using IBM SPSS Statistics 21.0 statistical software to process the data, and the paired-sample *t*-test was used for comparison between groups, with a test level of  $\alpha = 0.05$ , and a difference of  $P < 0.05$  was considered statistically significant.

### 2.1.3. Evaluation criteria

Clinically, the PT reference interval was 9.4–12.5 s; the APTT reference interval was 28.0–42.0 s; the FIB reference interval was 2.00–4.00 g/L; and the TT reference interval was 10.3–16.6 s.

## 3. Results

### 3.1. Comparison of coagulation indices between the heavy-chain group and the light-chain group

Comparison between the heavy-chain group and light-chain group, the PT and FIB values were statistically different by independent samples *t*-test ( $P < 0.05$ ). In the heavy-chain group, PT was higher than the other group and FIB was lower than the light-chain group, while there was no statistically significant difference in APTT and TT compared between the two groups ( $P > 0.05$ ). In the IgA group and IgM group, the mean values of PT exceeded the upper limit of the reference interval, which had some clinical significance. Refer to **Table 1**.

A comparison of the groups from the perspective of PT prolongation rate revealed that the PT prolongation rate was 35.2% in the IgG group, 33.3% in the IgA group, 45.5% in the IgM group and 10% in the light-chain group.

**Table 1.** Comparison of coagulation indices in the groups (Mean  $\pm$  Standard Deviation, SD)

Groups	PT (s)	APTT (s)	FIB (g/L)	TT (s)
Light-chain group ( $n = 20$ )	11.77 $\pm$ 1.00 <sup>[2,3,4,5]</sup>	31.88 $\pm$ 2.83 <sup>[2,4,5]</sup>	3.98 $\pm$ 1.20	14.66 $\pm$ 2.36
Heavy-chain group ( $n = 83$ )	12.29 $\pm$ 1.82 <sup>[1]</sup>	33.19 $\pm$ 5.27 <sup>[1]</sup>	3.32 $\pm$ 1.08	15.39 $\pm$ 3.01
IgA group ( $n = 18$ )	12.56 $\pm$ 2.00 <sup>[1]</sup>	34.81 $\pm$ 3.78	3.47 $\pm$ 1.12	14.54 $\pm$ 3.69
IgG group ( $n = 54$ )	12.10 $\pm$ 1.51 <sup>[1]</sup>	31.96 $\pm$ 5.24 <sup>[1]</sup>	3.34 $\pm$ 1.12	15.85 $\pm$ 2.63
IgM group ( $n = 11$ )	12.76 $\pm$ 2.76 <sup>[1]</sup>	36.52 $\pm$ 5.84 <sup>[1]</sup>	2.97 $\pm$ 0.69	14.57 $\pm$ 3.33
<i>P</i> -value	0.087	0.132	0.034	0.242

Significance level = 0.05

### 3.2. Comparison of coagulation indices by grouping according to serum M protein levels

All patients were divided into two groups M protein  $\leq 30$ g/L and M protein  $> 30$ g/L and the values of PT, APTT, FIB and TT were compared between the two groups. The difference of PT, TT and FIB between the two groups was statistically significant ( $P < 0.05$ ), and the high M protein group PT and TT were higher than the other group and FIB was lower than the other group, while there was no statistically significant difference of APTT comparing between the two groups ( $P > 0.05$ ). In the M protein  $> 30$  group, the mean values of PT and TT exceeded the upper limit of the reference interval, which had some clinical significance. Refer **Table 2**.

**Table 2** Comparison of coagulation indices between M protein  $\leq 30$  g/L and M protein  $> 30$  g/L groups (Mean  $\pm$  SD)

Groups	PT (s)	APTT (s)	TT (s)	FIB (g/L)
M protein $\leq 30$ g/L ( $n = 87$ )	11.76 $\pm$ 1.26	32.63 $\pm$ 4.17	14.64 $\pm$ 2.13	3.63 $\pm$ 1.113
M protein $> 30$ g/L ( $n = 16$ )	14.56 $\pm$ 2.09	34.08 $\pm$ 6.48	17.14 $\pm$ 4.83	2.85 $\pm$ 0.93
<i>P</i> -value	0.000	0.375	0.045	0.004

## 4. Conclusions

M protein is an abnormal monoclonal immunoglobulin produced by monoclonal aberrant proliferation of B lymphocytes or plasma cells that is very homogeneous in amino acid composition and sequence [6]. M protein is clinically seen in multiple myeloma, hypergammaglobulinemia, malignant lymphoma, heavy-chain disease, light-chain disease, etc.

Abnormalities of coagulation and fibrinolytic system in patients with malignant haematological diseases [7]. In recent years, there have been remarkable results in the study of multiple myeloma (MM) [4]. For example, MM is a malignant proliferative tumour of B-lymphocytes characterized by the secretion of large amounts of monoclonal immunoglobulin, which is the most common and typical disease in M-proteinemia [8]. In the report of Zhang et al. (2018), reported that the prolongation of PT in MM patients was due to the combination of elevated serum globulin and coagulation factors in patients [5]. However, there are not many studies on the analysis of coagulation function in patients with different types of M-proteinemia.

In this study, the correlation between the abnormal changes in coagulation function of 103 patients with M-proteinemia and the correlation between the patients' M-protein types and serum M-protein levels are analyzed retrospectively. In the comparison of the coagulation function of 20 patients in the light-chain type, 54 in the IgG, 18 in the IgA group, and 11 in the IgM group, it was found that patients in the heavy-chain type were more likely to have abnormal PT results than patients in the light-chain type. In the comparison of the coagulation function of 16 patients in the M protein  $> 30$  g/L group and 87 patients in the M protein  $\leq 30$  g/L group, it was shown that patients in the M protein  $> 30$  g/L group were more likely to have abnormalities in coagulation function, and such results indicate that the amount of M protein affects coagulation results.

The reason for the altered coagulation function in the heavy-chain type may be that: (1) IgG immunoglobulin can lead to abnormal coagulation, which covers platelets and hinders the normal platelet aggregation process [5]; (2) IgG and IgA can easily combine with themselves to form polymers or with other plasma proteins in the plasma or with coagulation factors in the plasma to make the blood turns viscous so that the patient's tendency to bleed increases. In patients with light-chain type [6], the risk of infection is greatly increased in light-chain patients compared to heavy-chain patients because of the reduced level of intact immunoglobulins in their serum.

The mechanism of coagulation abnormality caused by M protein is complicated. These reasons together led to the prolongation of PT and TT in patients in the hyper M-proteinemia group, which was consistent with the collected results.

- (1) M protein inhibits the binding site of negatively charged thrombin, and the binding of IgG to thrombin accelerates the antithrombin-thrombin reaction, thus prolonging the prothrombin time. Moreover, IgG inhibits thrombin-activating factor VIII and may prolong APTT by interfering with the formation of factor IXa-VIIIa complex, which is consistent with the prolongation of APTT in the high M protein group.

- (2) M protein may interfere with the normal coagulation process by encapsulating platelets to seal off their receptors, affecting fibrin polymerization.
- (3) Heparin-like substances are increased in patients with M-proteinemia, and the anticoagulant effect is strengthened *in vivo*.
- (4) Plasma cell bone marrow infiltration, so that the haematopoietic function is inhibited, causing thrombocytopenia.
- (5) Vascular wall damage caused by hyperimmunoglobulinemia and amyloidosis.

Patients with M-proteinemia produce large amounts of M-protein due to abnormal proliferation of immune cells <sup>[3]</sup>. Not only can they induce bleeding tendency by inhibiting the activity of antithrombin or coagulation factors, affecting platelet adhesion by covering the platelet surface, and selectively inhibiting the polymerization of fibrinogen, but globulin is closely related to the body's immune function and plasma viscosity <sup>[9]</sup>. At the same time, globulins are closely related to immune function and plasma viscosity <sup>[4]</sup>. The increase of M-protein will reduce the repulsive force between charges on the surface of erythrocytes so that the M protein content is positively correlated with the blood viscosity. The increase of abnormal M protein can increase the blood viscosity, which will lead to the occurrence of poor blood flow and thromboembolism, and eventually the clinical manifestations of hyperviscosity, such as haemorrhage and blurring of vision, will appear.

In this study, IgG type accounted for the largest number of cases, followed by light-chain type, IgA type, and IgM type, and according to a database on monoclonal immunoglobulin cases <sup>[10]</sup>. According to a database of monoclonal immunoglobulin cases, IgG, IgM, and IgA types ranked the top three in the number of cases, respectively, and cases of each type were collected more comprehensively in this study, especially the addition of the understudied IgM type. However, as the number of IgM cases was still small, there may be other mechanisms of IgM's influence on the coagulation function of patients with M-proteinemia that were not found in the present study, and there was no statistically significant difference between the results of the  $\kappa$ -type and  $\lambda$ -type groupings. There were fewer domestic and international studies on the comparison of the light-chain subtypes, so it is necessary to further study and explore the differences in coagulation function of the different light-chain types and the related mechanisms.

Plasma prothrombin time (PT) is the most sensitive and commonly used screening test in the exogenous coagulation system <sup>[11]</sup>. The activated partial thromboplastin time (APTT) is the most sensitive and commonly used screening test in the endogenous coagulation system, and has been used as a routine coagulation programme for the prediction of hypercoagulability and coagulation-fibrinolytic function, but it is poor in sensitivity and specificity. In Zhou et al. (2018)'s study, it was mentioned that TAT, as a complex generated by the 1:1 binding of thrombin and antithrombin, has the advantages of long half-life, irreversibility, inactivity, easy to be detected, etc., thus it is recommended to be used as a sensitive marker for coagulation abnormality <sup>[12]</sup>. However, this marker is still not popularized in daily testing and is not as commonly used as coagulation indexes such as PT, APTT, etc.

Proteinemia is common in a variety of primary and secondary diseases <sup>[13]</sup>. The presence of one or more abnormal coagulation indexes in patients with M-proteinemia is related to the type and level of abnormal immunoglobulins in their bodies. The effect of M protein level on the coagulation function of patients with M-proteinemia is more obvious, which can provide a simple and quick basis for the clinical consideration of M proteinemia earlier through the abnormality of coagulation indexes of the patients, and guide the clinic to make the next step in the examination. However, there is still a need for further research on the difference in serum globulin type on the coagulation function of patients with different types of M-proteinemia. However, the differences in the effects of serum globulin types on the coagulation function of patients with M-proteinemia need to be studied in depth.

## Disclosure statement

The authors declare no conflict of interest.

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# Analysis of Clinical Teaching Difficulties and Countermeasures in Vascular Interventional Surgery

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**Abstract:** Vascular interventional surgery, as a key branch in the continuous progress of modern medicine, mainly carries out the diagnosis and treatment of related vascular diseases through minimally invasive surgical methods and thus puts forward higher requirements for clinical teaching in this field. Combined with the actual situation of clinical teaching of Vascular interventional surgery at the present stage, it faces various challenges and difficulties, and the effect of knowledge teaching is unsatisfactory. Based on the analysis of the main difficulties in the teaching of Vascular interventional surgery are technical complexity, practical difficulty and equipment dependence. This study proposes targeted innovative countermeasures, aiming to provide a reference for improving the clinical teaching of Vascular interventional surgery.

**Keywords:** Vascular interventional surgery; Clinical teaching; Teaching difficulties; Innovation

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## 1. Introduction

With the rapid development of medical technology, the application of vascular interventional surgery has become more and more extensive, and its therapeutic effects in cardiovascular and cerebrovascular diseases, peripheral vascular diseases and many other vascular-related diseases have been significantly recognized. However, interventional surgery usually requires advanced surgical equipment and highly refined operating skills, which makes it more difficult for clinical teaching in this field. First, surgical operations require not only profound theoretical knowledge, but also exquisite operating skills and clinical judgment, but for beginners, it is more difficult to learn this highly specialized and technical field, and they need to receive more guidance and practice opportunities during the learning process. Secondly, vascular interventional surgery often relies on angiography and other specialized interventional tools, the purchase cost and maintenance requirements of these advanced medical equipment limit their popularity in clinical teaching, coupled with patient safety considerations, making it difficult for students to obtain sufficient hands-on opportunities in the initial learning stage, increasing the difficulty of the teaching process. For this reason, it is necessary to implement targeted



teaching countermeasures to overcome the difficulties in clinical teaching of vascular interventional surgery and ensure the effective improvement of students' specialized knowledge and practical ability in vascular interventional surgery.

## **2. Current status of clinical teaching in vascular interventional surgery**

As an important branch of the medical education system, clinical teaching of vascular interventional surgery is mainly divided into two major parts: theoretical teaching and practical operation. Among them, theoretical teaching, as the foundation of teaching, provides students with the necessary basic medical knowledge and professional theory support. The theoretical teaching content often centers on the basic knowledge of vascular interventional surgery, surgical techniques, pathology, pharmacology and the latest research progress. During the teaching process, traditional classroom lectures are usually used, i.e., textbooks, medical literature and case studies are used as the main teaching tools to ensure that students can master the basic concepts and operating principles of vascular interventional surgery by imparting a large amount of theoretical knowledge<sup>[1]</sup>. However, relying solely on the transfer of book knowledge has certain limitations. Firstly, the knowledge and technology in the field of vascular interventional surgery are updating rapidly, and it may be difficult to cover the latest medical techniques and treatments by only relying on traditional textbooks. Secondly, the theoretical teaching is too abstract, for beginners, it is difficult to understand the complex surgical techniques and clinical operation essentials only through the book knowledge, obviously cannot meet the requirements of the development of clinical education in the context of the new curriculum reform, and it is necessary to implement a large number of practical teachings to enhance the students' job competence.

Practical teaching in vascular interventional surgery mainly includes clinical internship, apprenticeship and situational simulation, etc. These practical activities make up for the inadequacy of theoretical teaching. Through direct participation in clinical work, students can gain valuable practical experience. In the clinical internship stage, students have the opportunity to directly observe and participate in the diagnosis and treatment process of patients, and learn how to analyze medical records, formulate treatment plans, and perform some basic medical operations under the supervision of the teaching staff, which helps them to apply their theoretical knowledge to practice and cultivate their clinical thinking and decision-making ability. Apprenticeship is a more in-depth form of practical learning and is usually arranged in students' senior years. During the apprenticeship, students have more opportunities to participate in interventional surgical work, through direct observation and learning the operation skills of advanced vascular interventional surgery, so as to obtain the development of clinical professional skills. Contextual simulation is a teaching method that has received more and more attention in the field of clinical education in recent years. Through the implementation of experiential teaching by using advanced simulators and virtual reality technology, students are allowed to practice operations in simulated surgical environments to familiarize themselves with a variety of surgical procedures and techniques, which not only helps students apply their theoretical knowledge to practice but also better cultivates their clinical thinking and decision-making abilities.

## **3. Analysis of clinical teaching difficulties in vascular interventional surgery**

### **3.1. Technical and operational complexity**

Vascular interventional surgery is an extremely demanding medical operation that requires not only highly refined operating skills, but also an in-depth understanding of the complex vascular system of the human body, making it a great challenge for beginners to master these skills. Interventional procedures often require the use

of minimally invasive devices such as catheters, stents, and balloons to perform precise operations within the blood vessels, especially when a limited field of view and relying only on image guidance, the doctor must be required to have a very high degree of operational precision and hand coordination to complete the surgical operation. Thus, students are required to have to learn how to navigate the complex vascular network and to maintain precise control over the instruments. This also requires students to learn how to navigate through complex vascular networks and maintain precise control of the instruments, which not only poses a technical challenge to students, but also tests their spatial perception and mental ability. The learning curve in vascular interventional surgery is steep, in part, because it involves not only extensive theoretical knowledge but also complex surgical techniques <sup>[2]</sup>. The acquisition of theoretical knowledge provides students with the necessary background knowledge, but to truly master practical skills requires gradual accumulation in practice. Therefore, for beginners, every step from basic vascular operations to complex interventional procedures requires a lot of practice. Not only do they have to face the challenges of operating skills, but also learn how to make fast and accurate decisions in complex or emergencies, because any small mistake in interventional procedures may lead to serious consequences, and all students need to remain calm and focused under high-pressure environments. They are required to be not only skillful but also have good psychological quality and emergency handling ability. With the continuous development of modern medical technology, new surgical techniques and methods are constantly emerging, which requires students to constantly learn and adapt to keep up to date with the latest medical technology, thus making it doubly difficult to master all the practical knowledge within the limited study time.

### **3.2. Equipment and resource constraints**

Imaging equipment, specialty catheters, stents, balloons, and other specialized surgical tools and materials required for high-end interventional procedures are often expensive. All teaching hospitals can afford the high cost of such equipment, especially in resource-limited regions or small healthcare organizations, and the lack of such critical equipment not only limits students' opportunities for high-quality hands-on teaching but also limits their ability to access and learn the latest medical technologies and methods. In addition, the inability of students to gain sufficient hands-on experience in resource-limited teaching environments not only limits their mastery of interventional surgical techniques, but also affect their performance in their future careers, or even lead to a disconnect between theoretical knowledge and practical skills <sup>[3]</sup>. In conclusion, equipment and resource constraints are a major challenge to clinical teaching in vascular interventional surgery, and the solution to this problem requires more financial resources and innovative teaching strategies to ensure that students can gain the necessary hands-on experience and understanding of advanced medical technologies.

### **3.3. Difficulty in acquiring practical experience**

The inherently high-risk nature of interventional procedures and the extremely high priority towards the patient's safety make the opportunity for students to be directly involved in procedures in a clinical setting very limited. The operating room is an environment that requires a high degree of precision and control, and any minor errors in surgical procedures can have serious consequences. As a result, there are significant limitations for beginners to participate directly in complex interventional procedures, with few opportunities to improve surgical skills and clinical judgment through direct practice. Although theoretical teaching can provide the necessary medical knowledge, the lack of hands-on experience poses an obstacle to students' understanding of the entire interventional procedure and clinical decision-making process, thus preventing them from effectively translating academic knowledge into practical operative skills, with the direct consequence that after completing

their studies and entering their professional careers, it takes them longer to adapt to the real-world clinical environment and to obtain additional guidance and support before they can operate at a fully independent level.

#### **4. Analysis of countermeasures to improve the quality of clinical teaching in vascular interventional surgery**

In response to the above problems, this paper proposes the following countermeasures:

##### **4.1. Innovative teaching models**

###### **4.1.1. PBL teaching model application**

Problem-Based Learning (PBL) is a modern teaching model that is student-oriented and teacher-oriented. The PBL teaching model guides students to actively participate in the learning process by taking the overall case diagnosis and treatment process as a precursor to the specific problem. Under this teaching framework, the whole process of teaching through questioning, hypothesizing, collecting information, arguing hypotheses, and summarizing is aimed at developing the students' comprehensive abilities and improving them. In the PBL model, the teacher is no longer the knowledge transmitter in the traditional sense but changes his role to a guide and facilitator, while the student becomes the leader of the learning process, prompting students to learn in an interactive and collaborative environment through exploration and discussion, which not only effectively enhances the interest and participation in learning, but also allows for a more in-depth understanding of the course content. Especially in the vascular interventional surgery clinical teaching education, PBL teaching method can make students establish an effective connection between theory and practice by simulating real clinical scenarios, which can significantly improve students' clinical thinking and clinical processing ability, help students develop the habit of lifelong learning, promote the development of students' critical thinking and problem-solving ability, and strengthen students' teamwork and communication skills.

###### **4.1.2. Application of the CBL teaching model**

Case-Based Learning (CBL) teaching method is based on typical cases, centering on specific teaching objectives, providing students with specific case situations, simulating real clinical scenarios, and guiding students to use the theoretical knowledge they have mastered to analyze and solve problems through independent thinking and group discussion. In the practice of CBL teaching in vascular interventional surgery, students are allowed to collect the patient's medical history first, then simulate real diagnostic scenarios through group discussion under the guidance of the teacher to diagnose and identify the disease, and finally formulate treatment plans. In the CBL teaching practice of vascular interventional surgery, by allowing students to collect the patient's medical history first, then simulate the real diagnosis and identification of the disease through group discussion under the guidance of the teacher, and finally formulate the treatment plan<sup>[4]</sup>. This active learning process can fully stimulate the student's interest in learning, enhance their independent thinking and problem-solving ability, make the learning process more exploratory and active, and gain a deeper understanding of the diagnosis of the disease, the process of treatment, and the surgical decision-making, to better cope with the various challenges in clinical practice.

###### **4.1.3. PBL combined with CBL teaching model application**

PBL combined with CBL teaching method is a student-centered, case-led, innovative teaching mode that closely integrates theoretical knowledge with clinical practice. In the teaching of vascular interventional surgery, the scientific application of this comprehensive teaching mode makes the teaching process more practical and



attractive, more likely to resonate with the students, effectively promotes the students' independent learning and practical ability training, helps the students to accept their future professional roles, and thus significantly improves the student's learning motivation. In the process of the discussion, the students not only pay attention to the symptoms of interventional vascular techniques, but also should analyze the relationship between special factors and multiple etiologies in detail, to obtain logical and clinical thinking in the process. This can promote the consolidation of theoretical knowledge based on the cultivation of logical thinking, helping them to master the relevant clinical skills in a more comprehensive way while improving their adaptability and innovation ability in clinical practice, thus laying a solid foundation for their future medical practice <sup>[5]</sup>.

#### **4.1.4. Other teaching methods**

In addition to PBL and CBL, the use of virtual reality (VR) and simulator technology is also an effective means of enhancing the quality of teaching and learning. VR and simulators provide a low-risk environment in which students do not need to be directly involved in patient interventional vascular surgical procedures, but rather only practice surgical procedures in simulated scenarios to gain increased technical proficiency and reduce the risk of patient surgical procedures.

#### **4.2. Strengthening teacher training**

Teachers are the key to the quality of teaching and are essential to improving the quality of teaching. Teachers not only need to have solid professional knowledge and rich clinical experience, but should also be familiar with the latest educational technology and teaching methods. Through regular professional training and seminars, teachers can constantly update their knowledge base, understand the latest medical technology development, and master the application of the latest technology, so that they can implement education and teaching with the most cutting-edge educational concepts to improve the effectiveness of teaching and learning in the practice of clinical education.

#### **4.3. Increase opportunities for clinical practice**

To effectively improve the quality of clinical teaching in vascular interventional surgery, the learning process should establish a close cooperative relationship with hospitals to provide more opportunities for clinical medical students to observe and participate in real surgeries. For example, allowing students to observe real surgeries and participate in surgeries under the supervision of specialized physicians helps students understand complex surgical procedures and improve their surgical skills. In addition, through hands-on experience, students can gain a more in-depth understanding of the various aspects of interventional surgery, including preoperative preparation, surgical operation, postoperative management, etc. This enables them to gain valuable clinical experience under the supervision of specialized physicians, thus effectively enhancing their practical skills and laying a solid foundation for them to become skilled interventional vascular surgeons in the future <sup>[6]</sup>.

#### **4.4. Promoting the sharing of educational resources**

In order to alleviate the limitations of equipment and resources in some teaching hospitals, hospitals need to establish educational alliances or cooperative networks to effectively promote the sharing of educational resources, and improve the efficiency of the utilization of teaching resources through the sharing of teaching materials, research results, teaching methods, and best practices, making it possible for even hospitals that are relatively resource-poor to have access to high-quality information on advanced medical technologies, clinical case studies, and innovative teaching methods. In addition, resource sharing facilitates the exchange of knowledge and experience among different institutions, enabling students to gain a wider range of learning

perspectives and practice opportunities, thus enhancing their clinical skills and professional knowledge comprehensively, and thus rapidly growing into new-age integrated medical talents.

## 5. Conclusion

The complexity of vascular interventional surgery teaching, equipment and resource constraints, and the difficulty of acquiring hands-on experience are key issues that need to be addressed in the current education system. To actively address this challenge, innovative teaching modes such as PBL, CBL, and the combination of VR and simulators have been implemented to achieve the goal of effectively increasing students' interest in learning, facilitating the integration of theory and practice, and enhancing students' clinical thinking and operational skills. At the same time, there is a need to further increase faculty training, establish close partnerships with hospitals to increase students' clinical practice opportunities, and promote the sharing of educational resources to train more interventional vascular surgeons with high-quality and comprehensive skills, thus providing patients with better healthcare services and promoting the development and advancement of the entire medical field.

## Disclosure statement

The authors declare no conflict of interest.

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# Clinical Effect of Combination Therapy of Milrinone and Nifedipine in Treating Chronic Pulmonary Heart Disease

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**Abstract:** *Objective:* To analyze the therapeutic effect achieved and the occurrence of adverse reactions in patients with chronic pulmonary heart disease treated with milrinone combined with nifedipine. *Methods:* 120 cases of chronic pulmonary heart disease patients treated in the hospital from May 2023 to February 2024 were selected as research subjects, and based on the randomized numerical table method, the 120 patients were divided into the study group and the comparison group, and the treatment of milrinone combined with nifedipine was carried out for 60 patients in the study group, and the conventional treatment was carried out for 60 patients in the comparison group, so as to make a comparison on the therapeutic effect and the occurrence of adverse reactions of patients in the two groups. The therapeutic effects and adverse reactions of the two groups were compared. *Results:* After receiving medication of milrinone combined with nifedipine, the patients in the study group had an exertional lung capacity of  $68.12 \pm 5.63\%$  and a maximal expiratory volume of  $82.41 \pm 7.84$  L/min, which were significantly higher than those in the comparison group, and the total rate of adverse reactions of the patients in the study group was 1.67%, which was significantly lower than that of the comparison group, with a *P* value of  $< 0.05$ , which is statistically significant. *Conclusion:* In the implementation of treatment for patients with chronic pulmonary heart disease, the treatment of milrinone combined with nifedipine can significantly improve the patient's exertional lung capacity and maximum expiratory volume, and the chance of adverse reactions in patients will also be significantly reduced.

**Keywords:** Milrinone; Nifedipine; Combination therapy; Chronic pulmonary heart disease

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## 1. Introduction

Chronic pulmonary heart disease is primarily caused by lesions in the lung tissue, thorax or pulmonary artery blood vessels, which then result in abnormal lung function and changes in the structure of the lung tissue while increasing pulmonary vascular resistance and pulmonary artery pressure, thus inducing heart disease.

This disease is harmful to the human body as milrinone combined with nifedipine has an inhibitory effect on phosphodiesterase. Cyclic adenosine monophosphate levels can be increased with the use of this drug and, at the same time, increase cardiac output, thus improving heart disease. In this study, 120 cases were selected from the patients with chronic pulmonary heart disease treated in Shaanxi Provincial People’s Hospital from May 2023 to February 2024 as the study subjects reported as follows.

2. Information and methods

2.1. General information

120 cases were selected from patients with chronic pulmonary heart disease treated in our hospital from May 2023 to February 2024, and their general information is shown in the following **Table 1**.

**Table 1** Basic data of patients with chronic pulmonary heart disease

Group	Male patients	Female patients	Age	Average age
Study group (60 cases)	29	31	47–82	58.7 ± 9.1
Comparison group (60 cases)	22	18	45–85	60.2 ± 8.9

Consent was obtained from the patients and their families for this study. There was no statistically significant difference between the general information of the above two groups (all *P* > 0.05).

2.2. Methods

2.2.1. Comparison group

For patients in the comparison group, conventional treatment is implemented, with oxygen therapy, anti-infection therapy and vasodilator therapy. During the treatment period, closely monitor the patient’s vital signs, ensure the smoothness of the airway, and adhere to the treatment for 4 weeks <sup>[1–2]</sup>.

2.2.2. Study group

On the basis of the implementation of conventional treatment for the patients in the study group, the implementation of milrinone combined with nifedipine treatment is done by mixing 250 mL of 9% sodium chloride injection with 13 mg of milrinone injection. It is done through the use of an intravenous drip way, according to the patient’s tolerance, to adjust the speed of drug delivery while letting the patient take nifedipine 3 times a day, each time taking 5mg, adhere to the treatment for 4 weeks.

2.2.3. Observation index

Compare the exertion lung volume and maximum expiratory volume of patients in the study group and the comparison group before and after treatment, and count the occurrence of adverse reactions in patients with chronic pulmonary heart disease, including rashes, allergy, dizziness and drowsiness, and low blood pressure. The formula for calculating the total occurrence rate was:

Total occurrence rate = number of adverse reactions/total number × 100%.

2.2.4. Statistical analysis

SPSS 22.0 statistical software was applied, *t*-test was used for the measurement data with the formula, mean ± standard deviation (SD), and  $\chi^2$  test was used for the count data (*n*/%), and *P* < 0.05 indicated statistical

significance.

### 3. Results

#### 3.1. Comparison of exertional lung volume and maximal expiratory volume of patients before and after treatment

The exertional lung volume and maximum expiratory volume of 60 patients in the study group were significantly higher than those in the comparison group after combination treatment of milrinone and nifedipine, and the *P* of both after treatment was  $< 0.05$ , indicating that the difference between the data of the study group and the comparison group after treatment was significant and statistically significant, as shown in **Table 2**.

**Table 2** Comparison of exertional lung volume and maximal expiratory volume of patients in the study group and comparison group before and after treatment (Mean  $\pm$  SD)

Group	Before treatment		After treatment	
	Exertion spirometry (%)	Maximum expiratory volume (L/min)	Exertion spirometry (%)	Maximum expiratory volume (L/min)
Study group (60 cases)	47.62 $\pm$ 6.16	54.86 $\pm$ 7.32	68.12 $\pm$ 5.63	82.41 $\pm$ 7.84
Comparison group (60 cases)	47.53 $\pm$ 6.34	54.64 $\pm$ 7.26	57.28 $\pm$ 5.26	74.34 $\pm$ 6.48
<i>t</i>	0.079	0.165	10.898	6.146
<i>P</i>	0.937	0.869	0.000	0.000

#### 3.2. Comparison of the adverse reactions of patients

The total occurrence rate of adverse reactions of patients in the study group was 1.67%, which was significantly lower than that of the comparison group, and the difference between the data of the two groups was large, with a *p*-value of 0.028, which was statistically significant, as shown in **Table 3**.

**Table 3** Comparison of adverse reactions in patients in the study group and the comparison group (*n*, %)

Groups	Rashes allergy	Dizziness and drowsiness	Low blood pressure	Overall occurrence
Study group (60 cases)	0 (0.00)	1 (1.67)	0 (0.00)	1 (1.67)
Comparison group (60 cases)	3 (5.00)	2 (3.33)	2 (3.33)	7 (11.67)
$\chi^2$				4.821
<i>P</i>				0.028 $<$ 0.05

### 4. Discussion

Patients with chronic pulmonary heart disease usually have cough, panic, shortness of breath and weakness, and patients with more severe hypoxia may also have convulsions and coma<sup>[3-6]</sup>. Once these abnormalities occur in the body, it is necessary to go to the hospital as soon as possible to achieve early detection and treatment and avoid causing greater harm to the body.

Nifedipine belongs to the dihydropyridine calcium channel blocker, which has a good dilating effect on coronary blood vessels and peripheral blood vessels. The drug also reduces myocardial oxygen consumption and myocardial metabolism. These effects are useful in controlling the blood pressure and coronary environment. Milrinone, on the other hand, belongs to cardiotonic drugs, and when patients use the drugs, the



vital signs of patients, including blood pressure, heart rate, fluid changes, etc. have to be monitored carefully [7–10]. When the patient's blood pressure drops excessively, the infusion needs to be stopped or slowed. Through the combination treatment of milrinone and nifedipine, the cardiopulmonary function of patients will be well improved.

In this study, after receiving the combination therapy, the patients in the study group had an exertional lung capacity of  $68.12 \pm 5.63\%$  and a maximal expiratory volume of  $82.41 \pm 7.84$  L/min, which were significantly higher than those in the comparison group, and there was only one case of dizziness and drowsiness in the study group, with a total rate of 1.67%, while there were seven cases of adverse reactions in the comparison group, with a total rate of 11.67%. The total occurrence rate was 11.67%, which was significantly higher than that of the study and analysis group, with  $P < 0.05$ , which was statistically significant.

Practice shows that when milrinone and nifedipine are combined and used in treating patients with chronic pulmonary heart disease, the patients' exertional lung volume and maximum expiratory volume significantly increase, and the rate of adverse reactions is lower.

In conclusion, patients with chronic pulmonary heart disease can be treated with the combination therapy of milrinone and nifedipine under the guidance of doctors to achieve better therapeutic effects and promote the recovery of health while receiving conventional treatment.

## Disclosure statement

The authors declare no conflict of interest.

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# A Study on the Correlation Between Positive Feelings and Quality of Life of Carers of Stroke Patients

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**Abstract:** *Objective:* To investigate the correlation between stroke patient carers' positive feelings and their quality of life. *Methods:* 130 carers of hospitalized stroke patients in the First Affiliated Hospital of Xi'an Medical College from January 2020 to October 2023 were investigated using the Caregivers' Positive Feelings Scale, the Quality of Life Scale, and the General Information Questionnaire. *Results:* The positive feelings and the quality of life of stroke patient carers were at a moderately low level, and the scores of positive feelings and quality of life dimensions rated by stroke patient carers were positively correlated ( $P < 0.05$ ,  $r = 0.40$ ). *Conclusion:* The positive feelings and the quality of life of stroke patient carers need to be improved, and the enhancement of positive feelings of these carers can help to improve their quality of life so that they can better serve their patients.

**Keywords:** Positive feelings; Quality of life; Stroke carers

**Online publication:** July 23, 2024

## 1. Introduction

Stroke is a common disease with high disability, recurrence, and mortality rates, in which 50–70% of survivors have sequelae such as paralysis and aphasia of varying degrees, which seriously affects their ability to perform daily activities and requires assistance from family carers in daily life and rehabilitation exercises<sup>[1,2]</sup>. Studies have shown that the positive feelings of carers play a very important role in their physical and psychological health and higher quality of life<sup>[3]</sup>. Currently, there are few studies in this area in China, therefore, this study investigates the correlation between positive feelings and quality of life of stroke patient carers, to provide a basis for improving the quality of life of stroke patient carers, so that they can better serve stroke patients.

## 2. General information and methods

### 2.1. General information

130 cases of carers of stroke patients admitted to the First Affiliated Hospital of Xi'an Medical College from January 2020 to October 2023 who met the inclusion criteria were selected for the study. Patient inclusion



criteria <sup>[4]</sup> were those who met the Fourth National Diagnostic Criteria for Cerebrovascular Disease and were diagnosed as stroke patients by cranial CT or MRI. Inclusion criteria for carers: (1) aged 18 years or older, conscious, clear speech, no psychiatric disease; (2) in the recovery period or sequelae, spouses, parents, children, and other relatives living with them, etc.; (3) no vital organ disorders, such as heart, liver, kidney, etc.; (4) still implementing care activities for the patients for at least 1 month until the closing date of the survey; (5) agreed to participate in this study and cooperated with the survey.

## 2.2. Survey instrument

### (1) General information questionnaire

The questionnaire included the age, gender, education level, economic status, and years of caregiving experience of the carers.

### (2) Caregivers' Positive Feeling Scale

This scale included two dimensions with a total of 9 entries, including the self-affirmation dimension (entries 1–5), life outlook dimension (entries 6–9), with a range of 9–45 points, and a Likert scale of 5 levels. The higher the score, the higher the carer's degree of positive feelings.

### (3) Quality of Life Scale (SF-36)

The scale consisted of eight health concepts including different questions and entries, and the overall and dimensional scores range from 0–100, the closer the score is to 0, the lower the quality of life, and the closer the score is to 100, the higher the quality of life.

## 2.3. Survey method

A general questionnaire was used. The questionnaire was administered by highly trained nurses using uniform instructions with the informed permission of the carers. The questionnaires were issued, filled out on the spot, and retrieved. 130 questionnaires were issued and 128 valid questionnaires were retrieved, with a recovery rate of 98%.

## 2.4. Statistical methods

The software SPSS17.0 was selected for statistical data processing, and the measurement information was expressed as mean  $\pm$  standard deviation (SD), and the positive feelings and quality of life were analyzed by Pearson correlation.

## 3. Results

### 3.1. General information

Of the 128 cases of patient carers, 51 cases were male and 77 cases were female, with an average age of  $48.5 \pm 13.5$  years; in terms of literacy level, 56 cases were in primary school and below, 40 cases were in junior high school, 22 cases were in high school or middle school, and 10 cases were in junior college and above; caregiving time was from 1–8 years, with an average of  $6.6 \pm 4.0$  years; monthly income was less than 2,000 yuan in 22 cases, between 2,000 and 3,000 yuan in 50 cases, and 56 cases with a monthly income of above 3000 yuan.

### 3.2. Positive feelings of stroke patient carers

The stroke patient carers' positive feelings scores are shown in **Table 1**, and the results suggest that stroke carers have moderately low levels of positive feelings.

**Table 1.** Scores of positive feeling scale for stroke patient carers (mean  $\pm$  SD, score)

Dimension	Number of items	Score
Self-affirmation	6	20.56 $\pm$ 3.43
Life outlook	3	8.03 $\pm$ 2.35
Overall score	9	28.59 $\pm$ 5.78

### 3.3. Quality of life of stroke patient carers

The quality-of-life scores of stroke patient carers are shown in **Table 2**, and the results suggest that the overall level of stroke patient carers in all dimensions was lower than that of the normative group.

**Table 2.** Scores of quality-of-life scale for stroke patient carers (mean  $\pm$  SD, score)

Dimension	Score	Constant mode	P value
Physiological functions	81.53 $\pm$ 17.36	90.80 $\pm$ 15.07	0.000**
Role physical	43.95 $\pm$ 34.97	79.51 $\pm$ 34.70	0.000**
Physical pain	76.31 $\pm$ 21.50	82.41 $\pm$ 21.25	0.029*
General health	43.15 $\pm$ 18.60	67.30 $\pm$ 21.97	0.000**
Vitality	64.35 $\pm$ 16.58	71.44 $\pm$ 15.81	0.001**
Social Functioning	67.38 $\pm$ 24.22	85.29 $\pm$ 18.06	0.000**
Emotional role	46.77 $\pm$ 31.63	76.45 $\pm$ 38.47	0.000**
Mental health	71.48 $\pm$ 15.36	73.52 $\pm$ 15.68	0.301
Total SF-36	67.19 $\pm$ 11.61	80.25 $\pm$ 10.23	0.001**

\* $P < 0.05$ , \*\* $P < 0.01$

### 3.4. Analysis of the correlation between positive feelings and quality of life of stroke patient carers

The results of stroke patient carers' quality of life and positive feelings are shown in **Table 3**, and the results suggest that the correlation between the health status of stroke patient carers and positive feelings of each dimension is high and positively correlated ( $P < 0.05$ ).

**Table 3.** Correlation analysis between positive feelings and quality of life of stroke patient carers ( $r$ )

Dimension	Physiological functions	Psychological functions	Physical pain	General health	Vitality	Social functions	Emotional functions	Mental health
Self-affirmation	0.074	0.058	0.062	0.521	0.152	0.235	0.148	0.244
Life outlook	0.025	0.062	0.235	0.633	0.148	0.176	0.119	0.235

## 4. Discussion

### 4.1. Positive feelings of stroke patient carers

Carers' positive feelings, also known as carer satisfaction, have been described as rewarding, beneficial, appreciative, and meaningful in life <sup>[5,6]</sup>. The results of this study show that the positive feelings of carers are at a moderately low level, and the results in this study are similar to the results of positive feelings of primary caregivers of inpatients by Zhao *et al.* <sup>[7]</sup>, and slightly lower than the results of the study by Zhang *et al.* <sup>[8]</sup>, which is mainly manifested in the affirmation of self-worth of the carer and the future life of the carer has a strong sense of uncertainty, which is the same as the results of positive feelings of the main caregiver of

the stroke research community by Liu *et al.* <sup>[9]</sup>. Positive feelings results are consistent, the reason for this is that on the one hand, stroke patients have different degrees of physical dysfunction, and carers need to take on caregiving tasks. The carer's psychological well-being gradually declines as the patient's motor function declines. On the other hand, the reasons include the support of society, the reduction of social opportunities and recreational activities, the lack of appropriate technical training, etc., which shows that China's social group health services are insufficient. Based on the results of this study, we suggest establishing associations or groups and organizing regular lectures or symposiums for carers, and teaching them relevant knowledge and skills so that they can feel social understanding and support.

#### **4.2. Quality of life of stroke patient carers**

The present investigation showed that the SF-36 scores of all dimensions of carers of stroke patients were significantly lower than those of the domestic norm, indicating that the quality of life of carers of stroke patients was generally low, with the lowest overall health score. This is similar to the findings of Chen *et al.* <sup>[10]</sup> who investigated the quality of life level of 168 spouses of stroke patients using the General Quality of Life Index questionnaire (GQOLI), the reasons for which may be related to the carers' factors (age, physical factors, physiological status, health status, lack of knowledge, and emotional status), the patient's factors (the patient's physical handicap and self-care, and level of dependence on the carer), family factors (level of dependence and relationship with the number of family members, family economic situation), and social factors (social support and identification, interpersonal identification). Therefore, while providing therapeutic measures for stroke patients, nurses should pay close attention to the health status of carers <sup>[11]</sup>, and take effective nursing interventions to improve the quality of life of carers of stroke patients by targeting the various factors affecting their quality of life, to provide better care for stroke patients.

#### **4.3. Correlation between positive feelings and quality of life of stroke patient carers**

This study used Pearson correlation analysis to analyze the relationship between the item scores of stroke patient carer positivity as well as quality of life. The results showed that stroke patient carers' positive feelings were positively correlated with quality of life ( $r = 0.40$ ,  $P < 0.01$ ), which means that the stronger the carers' positive feelings, the higher their quality of life, and this result is consistent with the study of Mei *et al.* <sup>[12]</sup>, which showed that the positive feelings of the community stroke patients' spouses were positively correlated with life satisfaction. Liew *et al.* <sup>[13]</sup> showed that a certain degree of positive feelings can alleviate the impact of negative feelings on quality of life, and He *et al.* <sup>[14]</sup> found that positive emotions have a positive expected effect on life satisfaction. The reason for this analysis may be that positive experiences enable carers to give purpose and meaning to their lives, and learning new skills, mastering processes, and overcoming caregiving difficulties, etc. can increase internal strength and sense of control. Therefore, healthcare professionals should pay more attention to positive feelings while focusing on the quality of life of carers of stroke patients <sup>[15]</sup>.

### **5. Conclusion**

In conclusion, this study concluded that enhancing the positive feelings of stroke patient carers can reduce their sense of uncertainty, thus improving the quality of life of carers of stroke patients and enabling them to better serve their patients.

## Disclosure statement

The authors declare no conflict of interest.

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# Study On the Mechanism of Action of Qili Qiangxin Capsule in the Treatment of Heart Failure: Based on Network Pharmacology and Molecular Docking Method

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**Abstract:** *Objective:* To investigate the pharmacodynamic substances and mechanism of action of Qili Qiangxin Capsule in the treatment of heart failure based on network pharmacology and molecular docking technology. *Methods:* The active ingredients and drug targets of Qili Qiangxin Capsule were obtained from databases such as TCMSP, GeneCards, OMIM, PharmGkb, TTD, and DrugBank databases were searched for heart failure disease targets. The drug targets and disease targets were corrected by the UniProt database, then the Venn diagram was drawn, and the intersecting genes were screened. Cytoscape 3.8.0 software was used to draw the active ingredient-disease target network for topological analysis. PPI network was constructed in the STRING database platform to predict the core targets. Bioconductor package was used to perform KEGG pathway analysis. autoDock Vina software was used to molecularly dock the core targets with the main active ingredients, and Pymol software visualised the results. *Results:* Screening of 209 active ingredients of Qili Qiangxin Capsule, including quercetin, luteolin, cryptotanshinone, etc. 11,432 heart failure disease targets, 249 genes intersecting with drugs, including the core targets containing *TP53*, *STAT3*, *JUN*, *MAPK1*, etc. These genes are mainly involved in the AGE-RAGE, fluid shear stress, and atherosclerosis, PI3K-Akt signaling pathways. *Conclusion:* This study initially revealed the multi-component, multi-target, multi-pathway mechanism of action of Qili Qiangxin Capsule in the treatment of heart failure, which provides a theoretical basis for further research.

**Keywords:** Qili Qiangxin Capsule; Heart failure; Network pharmacology; Molecular docking; Mechanism of action

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## 1. Introduction

Currently, about 26 million people worldwide suffer from heart failure, which is the end stage of all types of heart diseases, with high morbidity and high economic burden, and is regarded as the “cancer of the



cardiovascular field”<sup>[1]</sup>. Of the 13,687 heart failure patients enrolled in the China-HF study from January 2012 to September 2015 in 132 hospitals in China, the in-hospital mortality rate was as high as  $4.1 \pm 0.3\%$ <sup>[2]</sup>. The goals of current heart failure treatment are to improve symptoms, slow disease progression and prolong survival. Various guidelines recommend strategies for the treatment of heart failure, including improvement of ventricular remodelling, vasodilatation, cardiotonic diuresis, etc. Commonly used drugs such as  $\beta$ -blockers, aldosterone receptor antagonists, angiotensin receptor enkephalinase inhibitors, nitrate esters, calcium sensitizers, digitalis, and collaterals are used as diuretics. These drugs can significantly relieve patients’ symptoms, such as dyspnea and oedema and improve the quality of life, but some patients are accompanied by a series of adverse reactions, which bring greater physical and mental suffering<sup>[3]</sup>. In this context, the concept of combining Chinese and Western medicine has created a new situation for the treatment of heart failure in China. Qili Qiangxin Capsule has been recommended by several domestic guidelines to be applied to patients with heart failure, and has achieved good clinical effects<sup>[4,5]</sup>.

Traditional Chinese medicine classifies heart failure under the categories of “asthma”, “cardiac paralysis”, “cardiac water” and “oedema.” Modern Chinese medicine classifies heart failure into three syndromes: “qi” deficiency and blood stasis, “yang qi” deficiency and blood stasis, and “qi yin” deficiency and blood stasis<sup>[6]</sup>. Academician Wu Yiling believes that heart “qi” deficiency and blood stasis are the central link and fundamental pathogenesis of heart failure, and based on the idea of “by the collaterals to pass, the meeting of the biochemistry”, he put forward the “qi, blood, and water treated together but eliminate separately”, and then developed an innovative traditional Chinese medicine, Qili Qiangxin Capsule, to treat the heart failure<sup>[7]</sup>. This paper intends to apply the technical methods of network pharmacology and molecular docking to construct the component-target network of Qili Qiangxin Capsule for the treatment of heart failure, to explore the intrinsic mechanism of action, and to provide theoretical support for subsequent experimental validation and clinical application.

## 2. Materials and methods

### 2.1. Active ingredients and predicted targets of Qili Qiangxin Capsule

The TCM Systematic Pharmacology Database and Analysis Platform (TCMSP) was searched for the active ingredients related to 11 Chinese medicines in Qili Qiangxin Capsule, and those with oral bioavailability (OB)  $\geq 30\%$  and drug-like properties (DL)  $\geq 0.18$  were screened out. In the Uniprot database, the search condition was set to Organism: *Homo sapiens* (Human), and the active ingredients and genes were converted to standardize the names of the target genes of the active ingredients that met the criteria.

### 2.2. Prediction of heart failure-related targets

Using “Heart Failure” as the keyword, we searched related genes in GeneCards, PharmGkb, Drugbank and TTD databases, and combined the valid information retrieved from the five databases to obtain all the disease targets of heart failure.

### 2.3. Construction of active ingredient-disease target network

The active ingredient targets of Qili Qiangxin Capsule were compared with the disease target genes of heart failure, and the R software was used to find out the targets of the two, and then a Venn diagram was drawn. Cytoscape 3.8.0 software “network analyser” mode was used to construct the “active ingredient-disease target” network diagram.

## 2.4. Constructing protein-protein interaction (PPI) networks

The protein-protein interaction (PPI) network was constructed by importing the co-interacting targets into the STRING database, setting the species as “*Homo sapiens*”, setting the minimum interaction threshold  $\geq 0.95$ , and hiding the free sites. Then, import to Cytoscape 3.8.0 software and use CytoNCA plug-in to carry out protein network topology analysis, and calculate the core protein based on the six centrality topology parameters BC, CC, DC, EC, IC and LAC.

## 2.5. KEGG pathway enrichment analysis

The data were processed by Bioconductor package in R software, and the top 30 pathways were selected for KEGG analysis according to the number of enriched target genes in order of  $P < 0.05$  standard.

## 2.6. Molecular docking validation of active ingredients with key targets

Screening of drug candidates in Cytoscape 3.8.0 network, finding the 2D structure of candidate components using Pubchem database and force field conformation optimisation by ChemBio3D software. Candidate compound format was saved as pdbqt format using AutoDock Tools as an alternative. Download the pdb format file of the core protein from the PDB database. Pymol software deleted the irrelevant small molecules in the protein, then imported them into AutoDock Tools software to remove water, ligand, and hydrogenation and finally saved them as a pdbqt file. Create the centre grid point of the receptor protein and set the box size. Finally, molecular docking of the drug candidate components with the core target protein receptor was performed by Autodock vina software, and the binding mode with the lowest energy was selected for the graph.

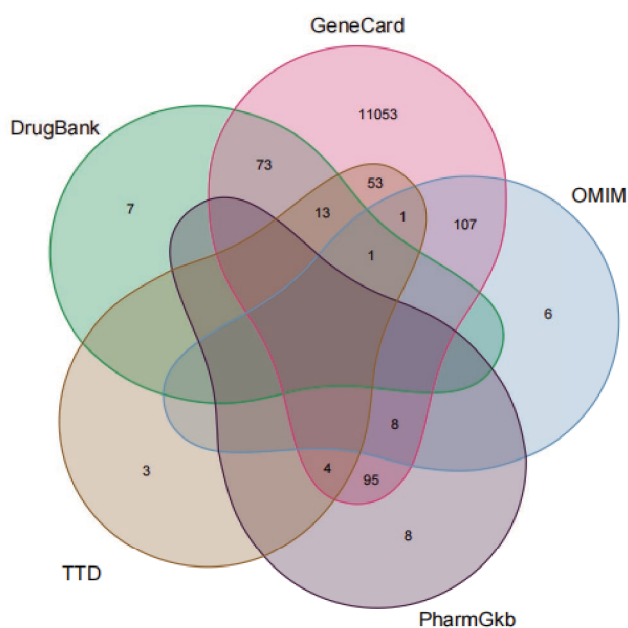
# 3. Results

## 3.1. Prediction of active ingredients and targets of Qili Qiangxin Capsule

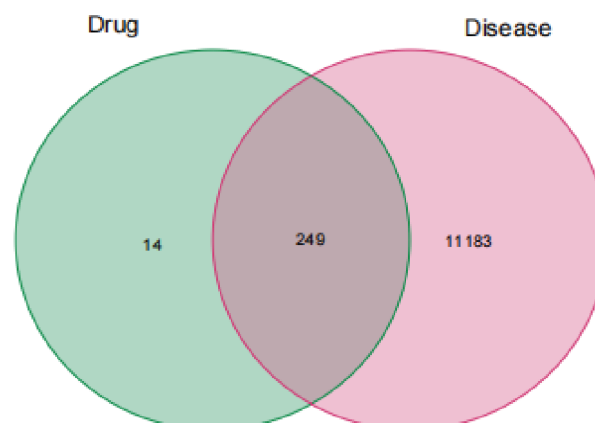
209 active ingredients of Qili Qiangxin Capsule were finally obtained from TCMSP database, including 5 Chenpi, 65 Danshen, 21 *Rhizoma Pinelliae*, 7 Gui Zhi, 22 Safflower, 20 Astragalus, 22 Panax Ginseng, 12 *Draba nemerosa*, 17 *Cortex periplocae*, 8 Yuzu, and 10 *Alisma plantago-aquatica*. Searching for the targets corresponding to the active ingredients, the Uniprot database was used to find the gene SYMBOL, and a total of 2349 genes were obtained for the predicted targets, of which 82 were Chenpi, 801 were Danshen, 26 were *Rhizoma Pinelliae*, 59 were Gui Zhi, 391 were Safflower, 395 were Astragalus, 212 were Panax Ginseng, 272 were *Draba nemerosa*, 65 were *Cortex periplocae*, 37 were Yuzu indica, and 9 were *Alisma plantago-aquatica*.

## 3.2. Potential targets of Qili Qiangxin Capsule for the treatment of heart failure

By searching GeneCards (Relevance score 1), OMIM, Drugbank, PharmGkb, and TTD databases, 11,408, 239, 138, 115, and 80 heart failure disease-related target genes were collected, respectively, and a total of 11,432 disease-targeted genes were obtained after de-emphasis (**Figure 1**). Venn analysis (automatic weight removal) was performed on the 2349 predicted target genes corresponding to the active ingredients of Qili Qiangxin Capsule and the 11432 heart failure disease target genes, and the intersection was obtained, which is the intersection of Qili Qiangxin Capsule for the treatment of heart failure with 249 potential effector target genes (**Figure 2**).



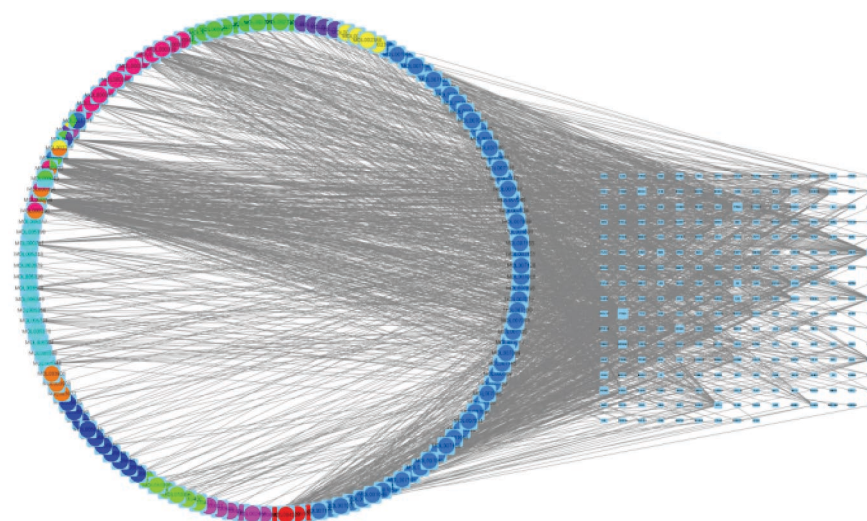
**Figure 1.** Heart failure disease targets.



**Figure 2.** Qili Qiangxin Capsule and heart failure target Venn diagrams.

### 3.3. “Active Ingredient-Disease Target” interaction networks

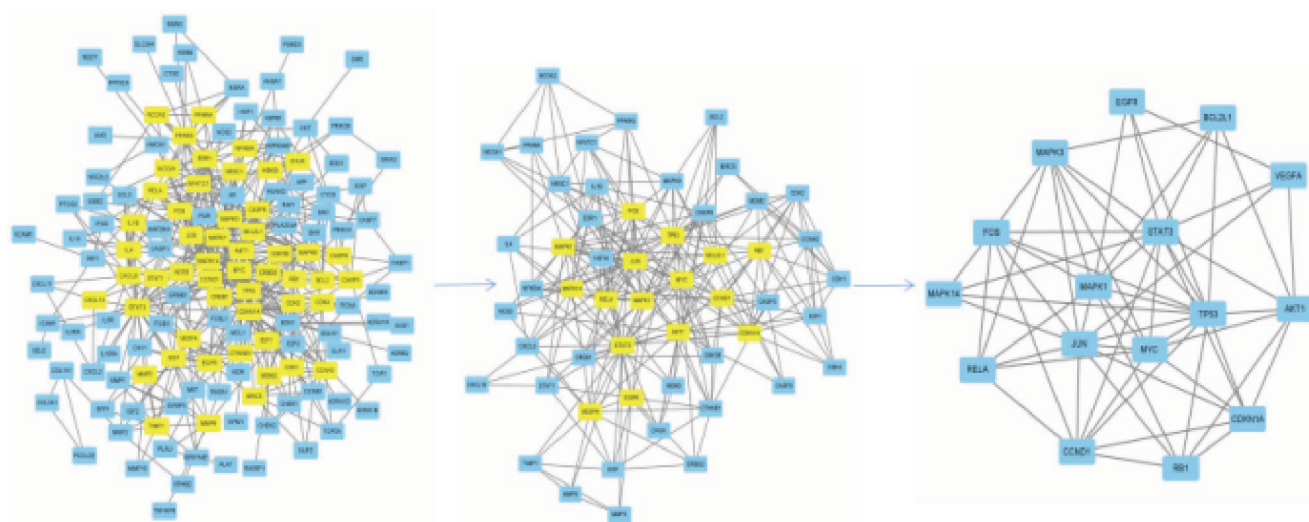
Cytoscape 3.8.0 software was used to construct the “Active Ingredient-Disease Target” network, in which the left circle represents the active ingredient of Qili Qiangxin Capsule, and the different colours represent the different ingredients of the traditional Chinese medicine, and the right grid represents the target genes of the active ingredient, which are represented by blue rectangles (**Figure 3**).



**Figure 3.** Network diagram of “Active Ingredient-Disease Target.”

### 3.4. PPI network topology analysis and core target screening

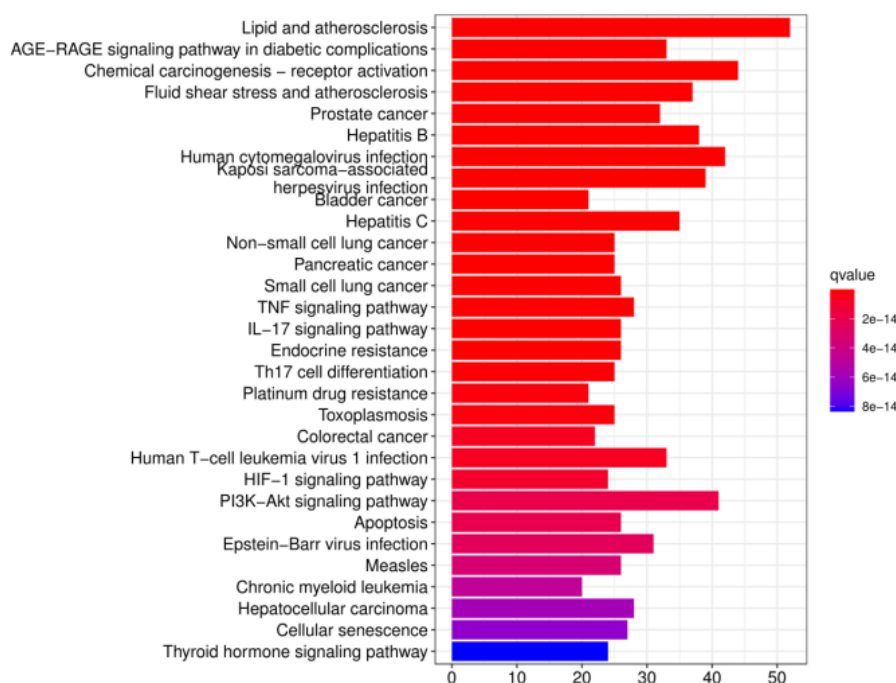
The 181 protein interactions obtained from STRING 11.0 platform were imported into Cytoscape 3.8.0 software, and 16 core targets were screened out by using CytoNCA plug-in, which were: *AKT1*, transcription factor JUN, transcription factor *FOS*, *MYC*, *EGFR*, *VEGFA*, *BCL2L1*, *CCND1*, *MAPK14*, *TP53*, *RB1*, *MAPK3*, *CDKN1A*, *MAPK1*, *STAT3*, *RELA* (**Figure 4**).



**Figure 4.** Screening diagram of PPI network.

### 3.5. Enrichment analysis of core target genes

In order to understand the role of intersecting genes in the treatment of heart failure, KEGG enrichment analysis was performed on 16 core target genes of Qili Qiangxin Capsule, which were mainly enriched in 183 pathways, and the top 30 signalling pathways were extracted to draw a barplot histogram. The vertical coordinate represents the pathway name, the horizontal coordinate represents the number of genes, and the colour represents the significance of the enrichment. The top 30 KEGG-enriched pathways, according to the ascending order of *P*-value, are shown in **Figure 5**. It can be seen that Qili Qiangxin Capsule can act on the effects of lipid and atherosclerosis, AGE-RAGE signalling pathway in diabetic complications, chemical carcinogenesis-receptor activation, fluid shear stress and atherosclerosis, PI3K-Akt signalling pathway, etc. This suggests that the treatment of heart failure with Qili Qiangxin Capsule involves the modulation of different signalling pathways which are interrelated and synergistic.



**Figure 5.** KEGG pathway enrichment results.

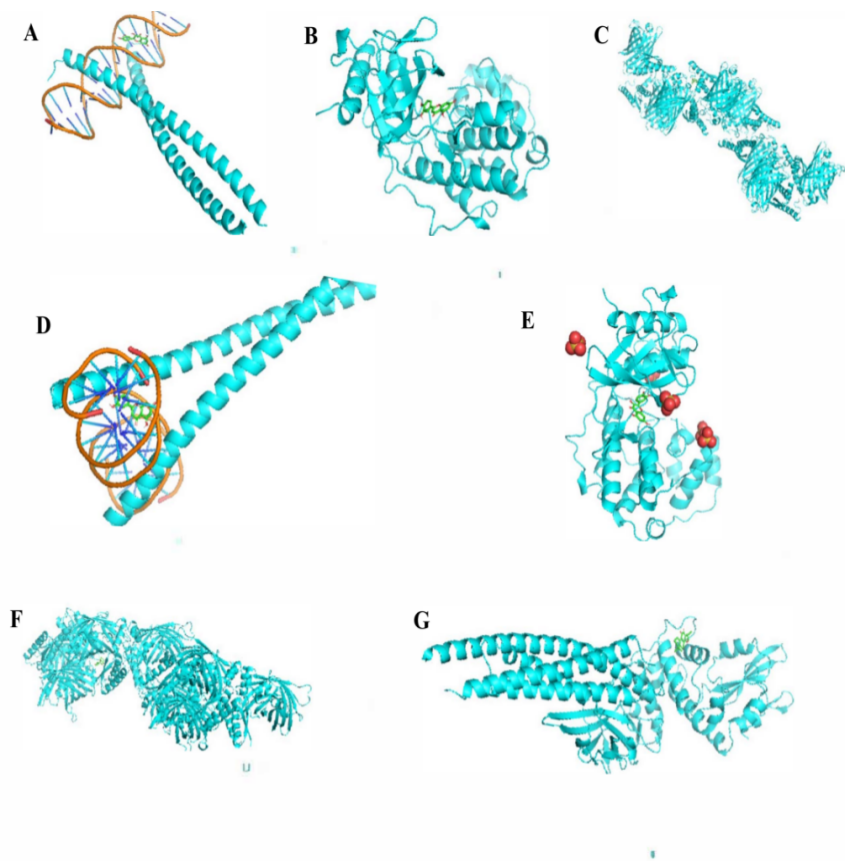


3.6. Analysis of molecular docking results

The three relevant active ingredients of Qili Qiangxin Capsule (quercetin, luteolin, cryptotanshinone) and the four core proteins (MAPK-3, STAT3, JUN, TP53) with the largest degree values in the PPI network were subjected to molecular docking by AutoDock Vina software. The minimum binding energy represents the energy required for the compound to bind to the target protein. The less energy, the more stable the binding is, the result is less than -5 kal/mol, which indicates that the binding is important, see **Table 1**. **Figure 6** represents the best combination of the four core proteins docked with the corresponding active ingredients, which includes MAPK1, JUN and TP53 with quercetin and luteolin, respectively, and STAT3 with cryptotanshinone. The docking results illustrated the good binding ability between the active ingredients and target proteins in Qili Qiangxin Capsule.

**Table 1** Docking results of the top 4 core proteins with the main active ingredients

Target gene	PDB ID	Compound	Minimum binding energy (kal/mol)
MAPK1	4FUY	quercetin	-8.9
MAPK1	4FUY	luteolin	-9.0
JUN	5T01	quercetin	-8.6
JUN	5T01	luteolin	-8.8
TP53	7BWN	quercetin	-8.9
TP53	7BWN	luteolin	-8.6
STAT3	6NUQ	cryptotanshinone	-7.7



**Figure 6.** Molecular docking of JUN with luteolin (A), MAPK1 with luteolin (B), TP53 with luteolin (C), JUN with quercetin (D), MAPK1 with quercetin (E), PT53 with quercetin (F), and STAT3 with cryptotanshinone (G).



## 4. Discussion

Ancient medical practitioners proposed that the key to treating heart failure lies in diarrhoea and tonifying heart “yang”, which is the method of warming yang and water-liquefying, which is the method that later medical practitioners focus on <sup>[8]</sup>. Modern Chinese medicine practitioners believe that the pathogenesis of heart failure is caused by different reasons that lead to the deficiency of heart “qi” and blood, “yin and yang”, and the generation of pathological products such as stasis of blood, water stagnation, and cold congealment, with the mixture of emptiness and solidity, and the underlying deficiency and solidity of this deficiency <sup>[9]</sup>. Li *et al.* (2013) found that Qili Qiangxin Capsule could significantly reduce plasma NT-proBNP levels and increase left ventricular ejection fraction (LVEF) of patients with heart failure, improve 6-minute walking distance (6MWD), and improve the quality of life of patients with heart failure <sup>[10]</sup>. Modern pharmacological studies have confirmed that Qili Qiangxin Capsule can play a role in the treatment of heart failure by inhibiting the activation of the RAAS system, protecting the cardiac microvessels, inhibiting lipid metabolism disorders, and diuretic effect, but its active ingredients, targets, and molecular mechanisms are not yet completely clear.

In this study, we found that the active ingredients of Qili Qiangxin Capsule for the treatment of heart failure mainly include: quercetin, luteolin, and cryptotanshinone. Quercetin induces muscle sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase activity, maintains cellular calcium homeostasis <sup>[11]</sup>, inhibits angiotensin II-induced cardiac fibrosis <sup>[12]</sup>, and delays the development of heart failure <sup>[13]</sup>. The mechanisms by which luteolin improves cardiac function focus on regulating myocardial contractility, promoting cardiomyocyte autophagy and inhibiting ventricular remodelling <sup>[14]</sup>. Cryptotanshinone can regulate NO, Ca<sup>2+</sup>, ROS levels and ATP content in cardiomyocytes under hypoxic conditions, preventing hypoxia-induced cardiomyocyte damage and mitochondrial dysfunction <sup>[15]</sup>.

The PPI network includes 16 core targets, mainly tumour suppressor p53 (TP53), transcriptional activator protein-3 (STAT3), transcription factor JUN, mitogen-activated protein kinase 1 (MAPK1), and so on. In recent years, it has been found that TP53 is maintained at very low levels in the normal heart, and severe or persistent hypoxia induces TP53 expression, resulting in disturbances in energy metabolism of cardiomyocytes, apoptosis, and ultimately heart failure <sup>[16]</sup>. STAT3 enhances the expression of a variety of encoded genes, such as anti-apoptotic genes (*Bcl-xl*, *MCL-1*), antioxidant genes (*MnSOD*, metallothionein), and vascular endothelial growth factor (VEGF). Studies have shown that STAT3 expression in mitochondria can affect ATP synthesis, the opening of mPTP, and reactive oxygen species production. Thus, STAT3 plays an important role in promoting myocardial differentiation, participating in neovascularisation, regulating  $\beta$ -adrenergic function, and maintaining extracellular matrix homeostasis <sup>[17]</sup>. Mitogen-activated protein kinases (MAPKs) have been shown to be key signalling factors involved in cardiac remodelling, with family members mainly including p38 kinase, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase 1/2 (ERK1/2), as well as BMK1, which, once activated by phosphorylation, are involved in the regulation of a number of biological processes such as growth, differentiation, proliferation, inflammation, stress, and others. MAPK1 is also known as the *ERK2* gene, and Jochmann S *et al.* (2019) found that the ERK1/2 signalling pair inhibited cardiac fibrosis and cardiomyocyte apoptosis in a stress-loaded mouse model <sup>[18]</sup>. In addition, targets such as MYC, FOS, and MAPK3 are also present. A total of 183 signalling pathways related to heart failure therapy were obtained by signal pathway enrichment analysis. Among them, the significantly enriched and star pathways in recent years included AGE-RAGE signalling pathway, fluid shear stress and atherosclerosis, PI3K-Akt signalling pathway, etc. AGEs (advanced glycosylation end products) are produced and accumulated in plasma and vascular tissues for a long period of time, which induces monocyte chemotaxis, oxidative stress response in vascular smooth muscle cells, and release of cytokines (IL6, TNF- $\alpha$ ), growth factors (TGF- $\beta$ 1), etc. thereby causing an

inflammatory response, leading to vasodilatory and constrictive dysfunction; although the specific molecular mechanism of the AGE-RAGE axis involved in heart failure is still unclear, AGE and esRAGE have become an important predictor of the occurrence and development of heart failure <sup>[19]</sup>. Fluid shear stress can affect the morphology and function of endothelial cells and plays an important role in cardiovascular system diseases. PI3K/Akt signalling pathway is widely present in human cardiomyocytes as an important pathway for the transduction of membrane receptor signals to the intracellular level. AKt is a key downstream target of PI3K, whose Akt1 isoforms have a close relationship with the progression of heart failure, and PI3K/Akt signalling pathway can be mediated through the downstream target BAD by mediating the effects of a variety of apoptotic factors (*Bcl-2*, *Bcl-x1*, etc.) <sup>[20]</sup>, and it can also attenuate cellular inflammatory response and improve myocardial energy metabolism.

Through molecular docking, it is known that effective compounds such as quercetin, luteolin and cryptotanshinone can bind well with receptor proteins and play a role in intervening in the development of heart failure by regulating cell autophagy, improving oxidative stress, inhibiting cell fibrosis, and other biological processes, and on the other hand, the activation of receptor proteins modulates the relevant signalling pathways to regulate cardiovascular tissues. The target sites are enriched with various signals.

In conclusion, the treatment of heart failure with Qili Qiangxin Capsule is a multi-component, multi-target, multi-pathway process, and it can be used through multiple core targets, such as TP53, STAT3, JUN, MAPK1, and multiple pathways such as AGE-RAGE, fluid shear stress, and signalling pathways such as atherosclerosis and PI3K/Akt. This study was conducted on an existing public database, and the completeness of the data has an important impact on the predicted results. Since this study focuses on theory, more basic experiments are needed to validate the predicted targets and related pathways, which will provide a strong theoretical basis for the clinical use of Qili Qiangxin Capsule in the treatment of heart failure.

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## Disclosure statement

The author declares no conflict of interest.

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# Two Cases of Acute Myocarditis with Suspected Acute Myocardial Infarction

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**Abstract:** Case 1: The patient is a 19-year-old male who was admitted to the hospital with a cough for three days and chest pain for a day, aggravated for two hours. Electrocardiogram showed 1. Sinus tachycardia 2. First-degree atrioventricular block 3. ST-T changes, not excluding acute extensive anterior wall myocardial infarction. Case 2: The patient was a 47-year-old woman admitted to the hospital with a fever for three days. Electrocardiogram showed: 1. Sinus tachycardia, 2. Complete block of the right bundle branch, 3. ST-T changes, not excluding acute extensive anterior myocardial infarction. The study of these two cases strengthened the departmental staff's knowledge of ECG in acute myocarditis and provided a rapid and accurate ECG diagnosis in the clinic.

**Keywords:** Acute myocardial infarction; Myocarditis; ECG diagnosis

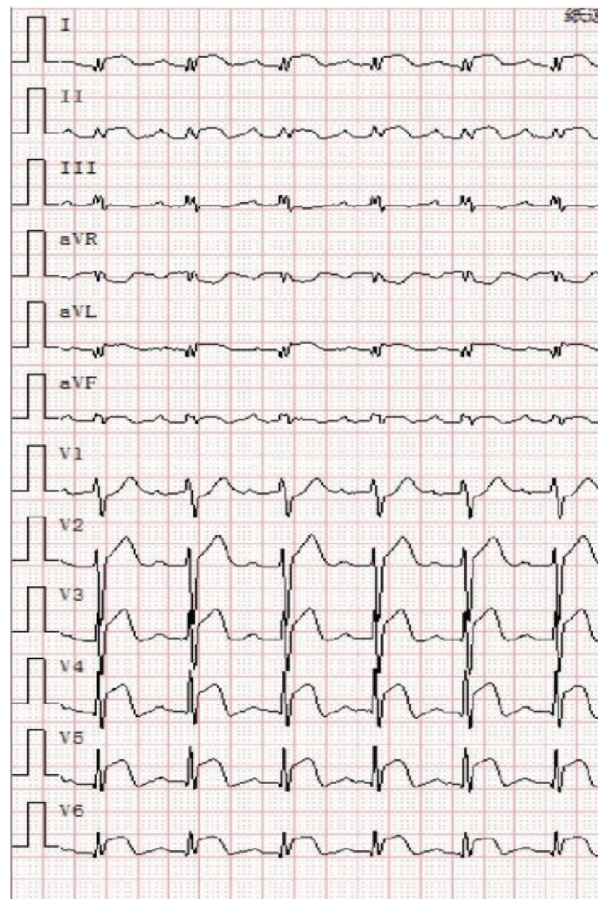
**Online publication:** July 23, 2024

## 1. Case 1

The patient is a 19-year-old male, who was admitted to the hospital with cough for three days, chest pain for one day and aggravation for two hours. The patient experienced a cold three days ago and had a runny nose after catching a cold without a fever. He took medication orally on his own and felt that his cold symptoms had improved. The next day, when drinking alcohol after getting up in the morning, coughing symptoms develop and are accompanied by chest pain; chest pain is located in the sternum, accompanied by upper limbs losing strength. However, because the pain can be tolerated by the patient, so he did not pay attention. Yesterday afternoon at about 17:00, the patient felt that the pain worsened, during which there was nausea and vomiting once, so he came to the hospital. He was physically fit and denied any history of hypertension or diabetes mellitus. Examination: T 36.7 °C, P 85 beats/min, R 20 beats/min, BP 100/60 mmHg, heart rate 85 beats/min, regular rhythm, no pathologic murmur, the abdomen is flat and soft, no pressure and rebound pain, liver and spleen were not touched under the ribs, and there was no swelling of both lower limbs. Auxiliary examination: electrocardiogram (**Figure 1**): (1) Sinus tachycardia, heart rate 101 beats/min; (2) First-degree atrioventricular block, PR interval 0.20 seconds; (3) ST-T changes, not excluding acute extensive anterior wall myocardial infarction, with obvious bow-back elevation of the ST segments of the I, avL and V2–V6 leads, the

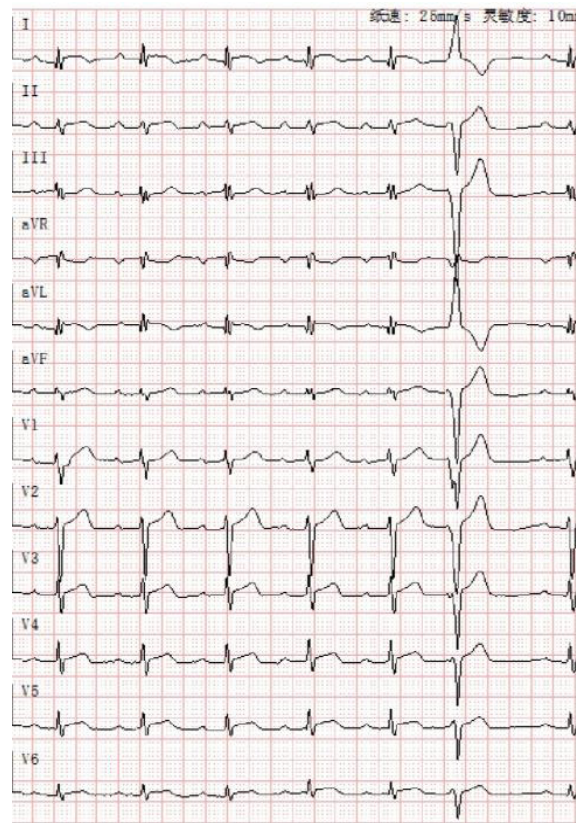


amplitude of which was around 0.2–0.5 mv, and fusion of the T wave and the ST segment in a T-wave and ST-segment fusion is a single curve. Chest X-ray: Enlarged heart shadow; Cardiac ultrasound: Small mitral valve regurgitation, small tricuspid valve regurgitation, left ventricular systolic function measurement is normal; Emergency series: K 3.52 mmol/L, blood glucose 7.28 mmol/L, AST 199 IU/L, ALT 69 IU/L, creatine kinase 1641 IU/L, creatine kinase isoforms 116.65 U/L; Coagulation function: Normal; Blood routine: WBC  $9.36 \times 10^9$ /L, basophil percentage 0.2%; Blood gas analysis was normal; Infarction three: CK-MB 62.85 ng/ml, cTnl 29.14 ng/ml, MYo 324.8 ng/ml; Preliminary clinical diagnosis: Acute extensive anterior wall myocardial infarction, cardiac function grade I. After admission, emergency surgery was performed: Percutaneous selective arterial cannulation, intracoronary local drug release therapy and percutaneous super-selective arteriography. Coronary angiography confirmed: The coronary artery was right dominant, the left main trunk did not show significant stenosis, the anterior descending branch did not show significant stenosis, distal flow TIMI (Grade 3); The diagonal branch did not show significant stenosis, distal flow TIMI (Grade 3); The gyratory branch did not show significant stenosis, distal flow TIMI (Grade 3); The obtuse marginal branch did not show significant stenosis, distal flow TIMI (Grade 3). Angiographic diagnosis: Normal coronary artery. Postoperative review of electrocardiogram compared with the previous electrocardiogram showed no significant changes. The clinical diagnosis was clarified: Acute myocarditis and pulmonary infection. The ECG was reviewed 1 day after admission (**Figure 2**): (1) Sinus rhythm, heart rate 76 beats/min; (2) First-degree atrioventricular block, PR interval 0.23 seconds; (3) Premature ventricular contractions, seen early appearance of wide and aberrant QRS-T wave clusters; (4) ST-T changes, I, avL, V2–V6 ST segments upward elevation has been gradually retracted, I, avL inverted. After anti-inflammatory and myocardial nutritional treatments, the patient was discharged from the hospital with improved condition.



**Figure 1.** Admission emergency electrocardiogram of case 1.



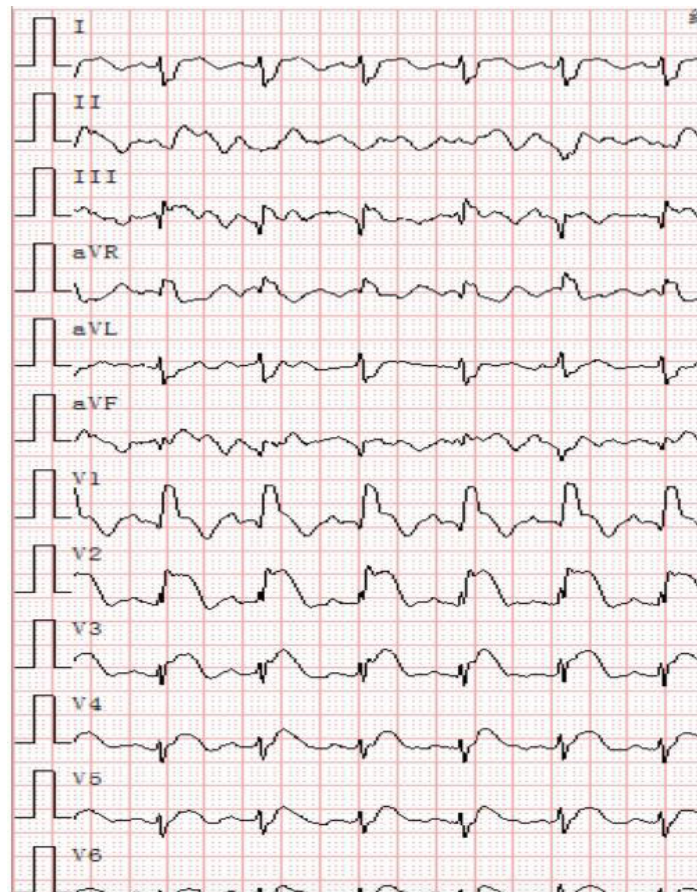


**Figure 2.** Electrocardiogram of case 1 one day after admission.

## 2. Case 2

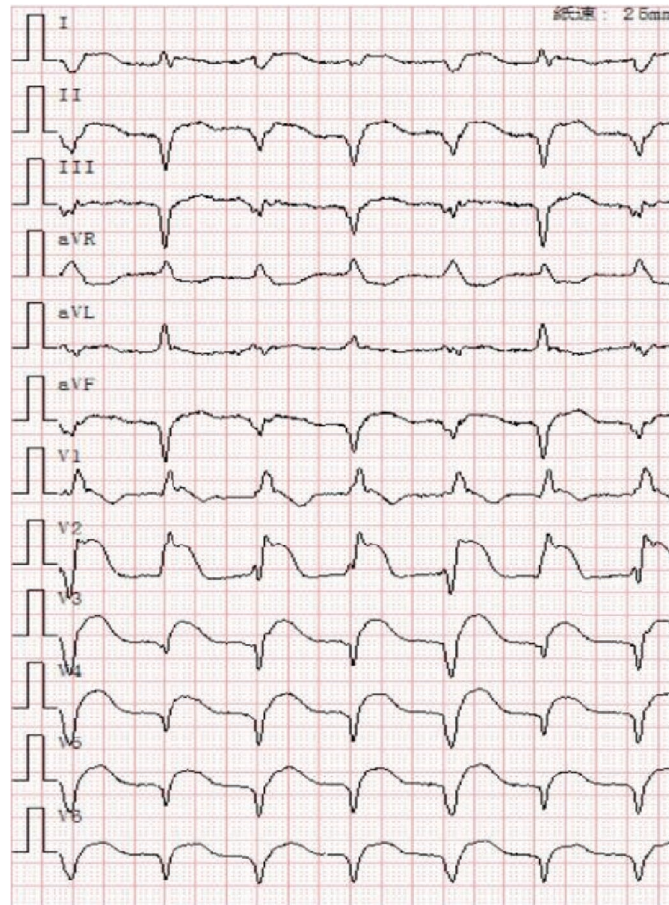
The patient is a 47-year-old female admitted to the hospital with a fever for three days. The patient started to have a fever three days ago without obvious triggers, with a maximum temperature of 39.5 °C, accompanied by a sore throat and chest tightness. Examination: T 37 °C, P104 beats/min, R24 beats/min, BP 76/59 mmHg. heart rate 104 beats/min, rhythmic. Auxiliary examination: Electrocardiogram showed (**Figure 3**): (1) Sinus tachycardia, heart rate 114 beats/min; (2) Complete right bundle branch block with qR pattern in lead V1, widening of S-wave in leads I, avL, V5, V6, S-wave > 0.04 s, QRS wave > 0.12 s; (3) ST-T changes, not excepting acute extensive anterior wall myocardial infarction, with obvious bow-back elevation of ST-segment in leads V1–V5, amplitude of elevation at around 0.10–0.70 mv, and fusion of T-wave and ST-segment in a single T-wave and ST-segment fusion in a single curve. Emergency series: K 3.47 mmol/L, Na 129 mmol/L, Ca 2.08 mmol/L, creatine kinase 1061 IU/L, creatine kinase isoenzyme 69.08 U/L; coagulation function: prothrombin time 14.20 s; Blood routine: WBC  $10.47 \times 10^9/L$ , neutrophil 76.40%; lymphocyte 13.40%; neutrophil 8.40%. Neutrophil count  $8.00 \times 10^9/L$ ; monocyte count  $0.79 \times 10^9/L$ . Cardiac ultrasound showed: Atrial orthotropy, normal size of each atrium. The left ventricular myocardium was thickened, the left ventricular myocardial motion was diffusely weakened at rest, the left ventricular ejection fraction and short-axis shortening rate were reduced, and the EF was 48%. The morphology of each valve was still active, and a small amount of regurgitant signals could be detected in the mitral valve and the tricuspid valve. The internal diameters of the main artery and the pulmonary artery were normal. The electrocardiogram was reviewed four hours after admission (**Figure 4**): (1) Ventricular tachycardia, P wave disappeared, QRS wave was wide and distorted; (2) ST-T changes, ST segment bow-back elevation in leads V1–V6 was greater than 0.1 mv. The

preliminary clinical diagnosis was fulminant cardiomyopathies (the diagnosis was confirmed after emergency PCI), acute decompensated heart failure, cardiogenic shock and cardiac function class IV. After admission, emergency surgery was performed: Percutaneous selective arterial cannulation, intracoronary local drug release therapy and percutaneous super-selective arteriography. Coronary angiography confirmed: The coronary artery was right dominant, the left main trunk did not show significant stenosis, the anterior descending branch did not show significant stenosis, the diagonal branch did not show significant stenosis, and the distal flow TIMI (Grade 3); The echogenic branch did not show significant stenosis, and the distal flow TIMI (Grade 3); The obtuse marginal branch did not show significant stenosis, and the distal flow TIMI (Grade 3). Diagnostic imaging: Normal coronary artery. Three days after admission, the ECG was reviewed (**Figure 5**): (1) Sinus rhythm, heart rate 65 beats/min; (2) Complete right bundle branch block, with a qR pattern in the V1 lead, widening of the S wave in the I, avL, V5 and V6 leads, with an S wave of  $> 0.04$  seconds and a QRS wave of  $> 0.12$  seconds; (3) ST-T changes, with significant ST-segment regression in the II, III, avF, and V1–V5 leads, only the V1–V4 leads showing a ST-segment regression, and the V1–V5 leads showing a ST segment regression. V1–V4 leads showed horizontal elevation of 0.05–0.1 mv, and T-wave inversion in I, avL and V1–V6 leads. The patient was discharged with stable condition 12 days after PCI.

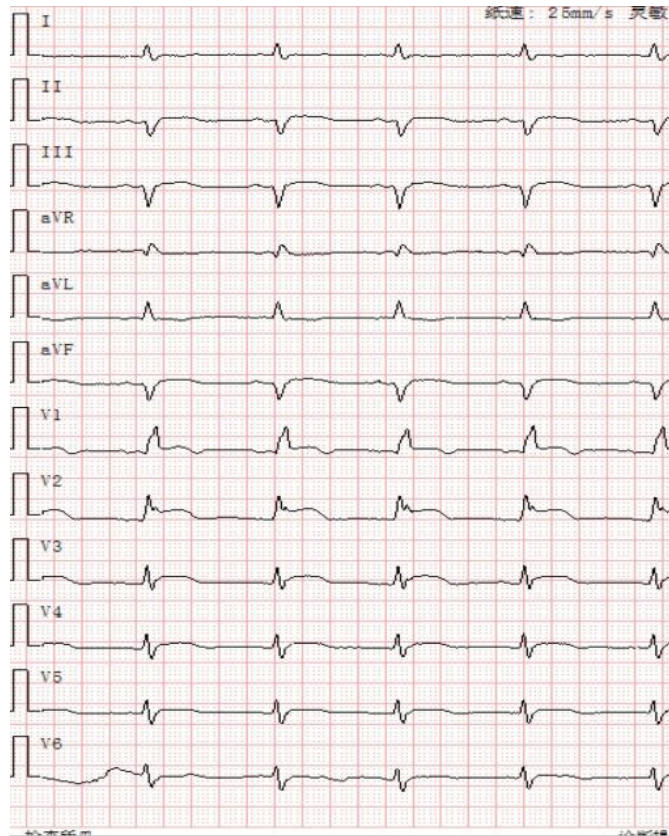


**Figure 3.** Admission electrocardiogram of case 2.





**Figure 4.** Review of electrocardiogram 4 hours after admission of case 2.



**Figure 5.** Repeat ECG of case 2 after being admitted to hospital 3 days later.

### 3. Discussion

Myocarditis refers to limited and diffuse inflammation of the myocardium and its interstitium caused by various reasons, including viral myocarditis, toxic myocarditis (bacterial infection or drug poisoning) and rheumatic myocarditis. Electrocardiographic changes vary due to the nature of the lesion and the type and degree of pathological changes <sup>[1]</sup>. An electrocardiogram (ECG) is a commonly used clinical examination in patients with acute myocarditis, and about 85% of patients may present with different ECG manifestations <sup>[2]</sup>. The myocardium is metabolically active and sensitive to hypoxia and toxins <sup>[3]</sup>, both of which can cause limited and/or diffuse myocardial lesions that replicate within myocardial cells, leading to myocardial lysis and a series of myocardial autoimmune responses <sup>[4]</sup>, such as myocardial parenchymal and interstitial inflammation, resulting in myocardial cell lysis, necrosis, denaturation, swelling and infiltration of inflammatory cells into the perivascular connective tissue between the myofibers, followed by a series of myocardial autoimmune reactions <sup>[5]</sup>. Inflammatory cell infiltration is followed by the formation of scar tissue, myocardial injury, myocardial ischemia, etc., which are the basis for the formation of abnormal myocardial electrophysiological activity.

The diagnosis of myocarditis is usually exclusive and the clinical symptoms of myocarditis are almost indistinguishable from those of acute coronary syndromes, cardiomyopathy, valvular disease, and pericarditis, which may be accompanied by chest pain, elevated levels of markers of myocardial injury and abnormalities on the electrocardiogram (including depression or elevation of the ST-segment, inversion of the T-wave and disease-induced Q-wave formation). In a recent observational study of myocarditis confirmed by endomyocardial biopsy, approximately 92.6% of patients had ECG abnormalities, the most common being ST-T changes in 59.0%. This was followed by bundle branch conduction block in 10.6% <sup>[5]</sup>. Emergency coronary angiography is feasible to clarify the diagnosis at an early stage and develop a rescue treatment plan early to buy time and emergency angiography does not increase the mortality rate of patients <sup>[6]</sup>, but attention should be paid to reducing the amount of contrast agent to reduce its negative inotropic effect. Acute myocarditis is similar to myocardial infarction, where clinical manifestations of severe myocarditis with ST-segment elevation and elevated troponin levels are mainly seen in young patients with acute viral myocarditis, especially in men <sup>[7]</sup>. Case 1 was a young man, which may be related to the fact that the onset of myocarditis is predominantly in young adults and that the autoimmune response in men is stronger. Case 2 is a middle-aged woman and the patient has symptoms such as chest tightness, fatigue, poor appetite, significantly elevated myocardial enzyme profile, electrocardiogram shows myocardial ischemic changes as well as new-onset right bundle branch block, recurrent ventricular arrhythmia, which is similar to the sympathetic electrical storm after myocardial infarction. Therefore, it is easy to be misdiagnosed as acute myocardial infarction, which leads to emergency PCI.

Myocarditis has an acute onset and rapid progression and is extremely dangerous, i.e., heart failure, cardiogenic shock, sudden death and other adverse events can occur within a short period of time after the onset of the disease and even combined with malignant arrhythmia, which is hazardous to the patient's life. Therefore, treating myocarditis as early as possible is necessary to prolong the survival period. However, after the occurrence of myocarditis, there are often precursor symptoms of viral infection, such as fever, myalgia, respiratory symptoms or gastrointestinal symptoms <sup>[8]</sup>, and clinically, it is mostly seen in young adults. Therefore, clinical attention should be paid to the early diagnosis and treatment of myocarditis and the pathological features of myocarditis should be analyzed in depth. In addition, myocarditis can also cause an increase in cardiac enzyme profiles and ST-segment damage type elevation in the electrocardiogram, which needs to be differentiated from acute myocardial infarction. On cardiac ultrasound, patients with myocardial infarction show abnormalities of ventricular myocardial wall motion and hypodiastolic and systolic hypoplasia, all of which are higher than in the myocarditis group. Previous studies have found that

ventricular wall motion abnormalities in patients with viral myocarditis are mainly due to a decrease in the amplitude of myocardial contractile motion, which results from myocardial fibrosis caused by inflammatory factors invading the heart <sup>[9]</sup>. In patients with acute myocardial infarction, segmental ventricular wall motion abnormalities, abnormal ventricular wall thickness, ventricular wall tumors, septal perforation, papillary muscle insufficiency, intraventricular appendage thrombus and decreased cardiac systolic and diastolic function were the main findings <sup>[10]</sup>. Although both groups of patients showed different ventricular wall motion abnormalities, hypodiastolic and systolic dysfunction, myocardial injury and necrosis in acute myocardial infarction are related to the region of myocardial blood supply innervated by occluded coronary arteries, which is distinctly regional in nature. As a result, acute myocardial infarction is more prone to ventricular wall motion abnormalities, diastolic hypokinesis, and systolic hypokinesis. Other studies have shown that myocarditis patients with clinical manifestations similar to those of acute myocardial infarction are best diagnosed by cardiac magnetic resonance <sup>[11]</sup>. Cardiac magnetic resonance can not only correctly diagnose both diseases but can also assess the prognosis of both diseases. Cardiac magnetic resonance can detect the surviving myocardium, evaluate myocardial reperfusion and myocardial fibrosis, etc. It can be used to risk stratify patients with myocarditis and acute myocardial infarction, predict adverse cardiovascular events, and thus guide the improvement of clinical treatment programs.

Both patients in Case 1 and Case 2 had a history of upper respiratory tract infection, elevated body temperature and ST-segment elevation on the electrocardiogram, which was similar to that of acute myocardial infarction without the presence of necrotic Q waves. After symptomatic treatment, the ST segment in the electrocardiogram quickly fell back to the baseline level without any obvious electrocardiographic evolution. The myocardial enzyme profile fell back to normal after hospitalization without the enzyme peak evolution pattern of myocardial infarction. All of the above manifestations were helpful in differentiating from acute myocardial infarction. By studying these cases, the staff of the department will have a better understanding of the electrocardiogram in acute myocarditis and will be able to provide rapid and accurate electrocardiogram diagnosis for the clinic.

## Disclosure statement

The authors declares no conflict of interest.

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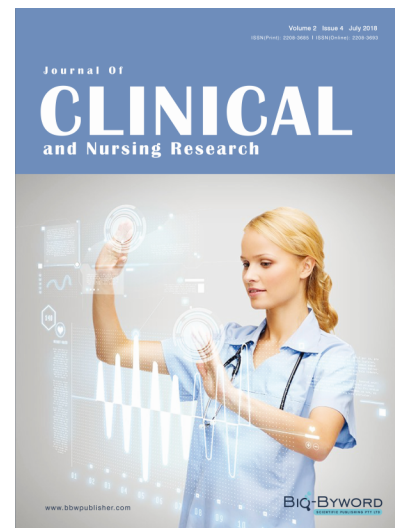
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