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Comparison of the Effect of Different Tidal Volume Combined with Breath-Holding Function in Clearing Airway Retention

Jichang Pan, Yanxia Li, Chao Wang, Wei Liu, Xi Zhang, Xiaoli Ji, Yang Lu, Yinghua Zheng*

Dalian University Affiliated Central Hospital, Emergency ICU, 116000

*Corresponding author: Yinghua Zheng

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Abstract: This study aimed to compare the effectiveness and safety of different tidal volumes combined with breath-holding during inhalation for clearing airway retention, and to explore optimized strategies for preventing ventilator-associated pneumonia (VAP). The study enrolled 105 adult patients receiving mechanical ventilation at the Emergency ICU of Dalian University of Technology Affiliated Central Hospital from April 2023 to June 2024. Using a randomized digital table method, patients were divided into three groups (A, B, C) with tidal volumes of 8ml/kg, 10ml/kg, and 12ml/kg respectively. Standardized VAP prevention measures were implemented alongside daily four-time-point airway clearance through ventilator-assisted breath-holding. Results showed that Group C demonstrated significantly higher post-operation airway clearance ($p<0.001$) and more frequent coughing (median 3 vs. 2 times) compared to Groups A and B, indicating that higher tidal volumes enhance secretions expulsion. No significant differences were observed in airway retention characteristics (color, viscosity) among groups ($p>0.05$). Regarding safety, all groups maintained normal heart rate and blood pressure fluctuations before and after procedures, with oxygenation index briefly declining but rapidly recovering without severe hypoxemia. However, Group C exhibited a higher proportion of peak airway pressure >35 cmH₂O (8.6%) compared to Groups A and B (2.9%). Clinically, Group C had a lower VAP incidence (14.2%) than Group A (22.9%) but higher than Group B (11.4%), though statistically insignificant ($p=0.32$). ICU length of stay was shorter in Group C, but this difference was not statistically significant ($p=0.15$). No aspiration or suffocation occurred across all groups. This study demonstrates that the combination of 12ml/kg tidal volume and breath-holding during inhalation can more effectively clear airway retention without significantly increasing safety risks. We recommend prioritizing this approach for mechanically ventilated patients with adequate lung function, while adjusting tidal volume through individualized assessment. Future research should further validate long-term outcomes and evaluate its efficacy across multiple centers.

Keywords: Tidal Volume; Ventilator; Ventilator-associated Pneumonia; Critical Care

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1. Background

Tracheal cuff secretions typically refer to bacterial deposits accumulated above the endotracheal tube cuff, which may increase the risk of ventilator-associated pneumonia (VAP). As the most common preventable iatrogenic condition in intensive care units, VAP has been shown to carry mortality rates ranging from 24% to 54%^[1]. Contaminated secretions entering the lower respiratory tract through cuff-tracheal airway gaps constitute a major contributing factor to VAP development^[2]. Effective clearance of these secretions is crucial for preventing VAP.

Clinically, the primary methods for clearing airway debris from endotracheal tubes are subglottic suction and tidal flow technique^[3]. The tidal flow technique is further divided into two subtypes: simple balloon tidal flow and ventilator-assisted tidal flow with breath-holding. Research indicates that the ventilator-assisted tidal flow technique offers distinct advantages over manual resuscitation with simple resuscitators, including visual guidance, precise control of cuff removal timing, accurate gas volume adjustment, and enhanced nurse coordination^[4].

Existing guidelines recommend that the range of tidal volume setting for adults is 8-10ml/kg, and the tidal volume can be set to 12ml/kg when the platform pressure is less than 30cmH₂O^[5]. However, there are no reports on how the retention effect of the cyst is cleared under different tidal volume airflow impact.

2.Methodology

1.1 Subjects

This study was conducted after obtaining informed consent from patients and their families, with approval from the Ethics Committee of Dalian University of Technology Affiliated Central Hospital (Dalian Central Hospital) (Approval No.: YN2022-096-16). The study enrolled 105 adult patients who received artificial airway establishment and mechanical ventilation treatment in the Emergency ICU of the hospital from April 2023 to June 2024. Inclusion criteria included: patients aged over 18 years; those receiving artificial airway establishment and mechanical ventilation; and those expected to require ventilation for over 48 hours. Exclusion criteria included: patients under 18 years old; those with artificial airway establishment less than 48 hours; patients with acute respiratory distress syndrome (ARDS); those with peak expiratory pressure (PEEP) greater than 10cmH₂O and/or oxygen inhalation concentration (FiO₂) exceeding 0.8; patients with contraindications to supine positioning (intracranial pressure over 20 mmHg); hemodynamically unstable patients; and those with pre-existing pulmonary infections upon admission. Withdrawal criteria were death within 4 days of hospitalization or discharge. Patients were randomly assigned into three groups (A, B, C) using a random number table based on admission time sequence, with 35 patients in each group. Group A received a tidal volume of 8 ml/kg; Group B received 10 ml/kg; and Group C received 12 ml/kg. Daily suctioning of airway secretions was performed at four time points: 0:00, 6:00, 12:00, and 18:00.

1.2 VAP prevention measures

All groups used the ventilator suction breath-hold method to clear retained air from the endotracheal tube cuff. Group A used a tidal volume of 8ml/kg for clearance; Group B used 10ml/kg; Group C used 12ml/kg. Meanwhile, nurses from the VAP prevention team implemented a series of nursing measures to prevent VAP. ① VAP Prevention Team: Composed of six ICU nurses with over five years of experience. Before the study began, team members received theoretical training and assessment on VAP prevention and control. After passing the assessment, they practiced clinical scenario simulations using endotracheal tube simulation props. Two-person teams cooperated in practicing the ventilator breath-hold method to clear airway secretions, requiring five consecutive successful assessments before clinical operation. ② Preventive measures for VAP determined according to the “China Guidelines for Diagnosis and Treatment of Hospital-Acquired Pneumonia and Ventilator-Related Pneumonia (2018 Edition)” included strict hand hygiene, elevating the head of bed by 30°-45°, chlorhexidine oral care (every 8 hours), regular monitoring (every 4 hours) to maintain cuff pressure at 25-30 cmH₂O, turning and back percussion (every 4-6 hours), mechanical vibration sputum clearance (every 6 hours), morning extubation assessment, and weekly/or contaminated replacement of disposable ventilator tubing. ③ Within 30 minutes before each procedure, all groups stopped oral feeding or enteral nutrition pump input, cleared subglottic secretions, and recorded secretion volume. Procedures were scheduled at 0:00, 6:00, 12:00, and 18:00 daily. ④ All groups used the ventilator inhalation breath-hold method to remove the retention on the airbag.

1.3 operational process

Two nurses work together:

- ① First, nurse 1 adjusted the inhaled oxygen concentration of the ventilator to 100% for 2 minutes to fully aspirate and remove the secretions in the patient's trachea and oropharynx, and adjusted the patient to supine position.
- ② Before operation, nurse 2 measured the vital signs of the patient and adjusted the capacity control ventilation. According to the group of the patient, the inhalation tidal volume was set as 8ml/kg, 10ml/kg and 12ml/kg respectively, and the PEEP was

set as 5cmH₂O.

③ Nurse No.1 performed hand hygiene and put on sterile gloves, prepared sterile sputum collector, pressed the inhalation breath-hold button after the suction phase of the ventilator, and kept the pressure waveform below the level of 30cmH₂O to avoid ventilator-related lung injury caused by high pressure.

④ Nurse No.2 connected the artificial airway cuff to a 10ml syringe and quickly evacuated the air. Using the breath-holding airflow from the lungs, she rapidly blew any retained material from the cuff into the oropharynx through the gap between the airway and the tracheal tube cuff. Simultaneously, Nurse No.1 used a sterile sputum collector to suction any remaining material into the oropharynx. ⑤ When the breath-holding airflow ended, Nurse No.2 immediately inflated the cuff and adjusted its pressure to 25-30cmH₂O using a cuff pressure gauge. This step was repeated ③④ 2 or 3 times until all retained material from the cuff was aspirated.

⑥ After the operation, nurse No.1 measured the patient's vital signs again, restored the patient to the position before the operation, and recorded the research data.

3.Results

Regarding the clearance efficiency of retained material in the cyst, Group C (12 ml/kg) demonstrated significantly higher clearance volume after a single procedure compared to Groups A (8 ml/kg) and B (10 ml/kg), with statistically significant differences ($p < 0.001$). Additionally, Group C showed a significantly higher number of coughs within one minute post-procedure (median 3 vs. 2 in Groups A and B), suggesting that higher tidal volume may enhance airway secretion expulsion capacity. Regarding retained material characteristics, most specimens (78%) were yellowish-white in color, with medium viscosity (65% of cases). No statistically significant differences were observed between groups in these two aspects ($P > 0.05$).

Table 1 Comparison of three groups for removal of retention on the cyst (p value)

divide into groups	A	B	C
A	1	0.944	<0.001
B	0.944	1	<0.001
C	<0.001	<0.001	1

Regarding vital signs and safety, hemodynamic analysis showed that heart rate and blood pressure fluctuations remained within normal ranges before and after the procedures across all three groups, with no statistically significant differences observed between or within groups ($P > 0.05$). In oxygenation metrics, although the oxygenation index ($\text{PaO}_2/\text{FiO}_2$) briefly decreased post-procedure, it returned to baseline levels within 10 minutes without severe hypoxemia ($\text{SpO}_2 < 90\%$). However, regarding barotrauma risk, Group C exhibited an 8.6% incidence of peak airway pressure exceeding 35 cmH₂O (3/35), significantly higher than Groups A (2.9%) and B (2.9%). Fortunately, no barotrauma-related complications such as pneumothorax occurred.

Regarding clinical outcomes, the incidence of VAP was 14.2% in Group C, lower than Group A's 22.9% but higher than Group B's 11.4%. However, the differences among the groups were not statistically significant ($P = 0.32$). Additionally, there were no statistically significant differences in mechanical ventilation duration or VAP incidence across the groups. For ICU length of stay, Group C had a median hospitalization of 8 days (IQR: 6-10), shorter than Group A's 10 days (IQR: 8-12) and Group B's 9 days (IQR: 7-11), though the differences remained statistically insignificant ($P = 0.15$). In terms of adverse events, none of the groups experienced aspiration, asphyxia, or balloon pressure loss of control.

Table 2 Comparison of three groups of outcome indicators

project	A group	B group	C group	P price
Mechanical ventilation time (h)	170.36±57.49	167.54±59.34	184.21±110.50	0.646
VAP incidence (%)	22.9	11.4	14.2	0.32
28-day mortality rate(%)	31.4	28.6	40	0.573

4.DISCUSSION

This study investigated the effectiveness of different tidal volumes combined with breath-holding during single maneuver for clearing airway retention. The results demonstrated that the 12ml/kg tidal volume group (Group C) achieved higher clearance efficiency after a single procedure compared to the 8ml/kg (Group A) and 10ml/kg (Group B) groups. This advantage likely stems from the stronger expiratory flow generated by elevated tidal volume, which more effectively propels retained material into the oropharynx for easier aspiration. However, Group C showed a greater increase in peak airway pressure than Groups A and B, suggesting clinicians should carefully adjust tidal volume parameters based on factors like lung compliance to balance clearance efficacy with potential pulmonary injury risks. Future research could explore precise tidal volume calibration tailored to individual patient characteristics, aiming to maximize clearance benefits while minimizing lung injury risks.

From a safety perspective, although Group C exhibited higher tidal volume, all three groups maintained hemodynamic parameters (heart rate, blood pressure) within normal ranges with no statistically significant differences before and after the procedure. Although oxygenation index briefly decreased post-procedure, it recovered rapidly without severe hypoxemia or other adverse events. This fully demonstrates that the ventilator's breath-holding technique effectively clears airway obstructions while causing minimal hemodynamic disturbance, aligning with the guideline-recommended "precise gas volume control" principle. The method proves clinically viable and well-tolerated. Notably, none of the groups experienced aspiration, asphyxia, or airway pressure instability, with no significant differences in procedural complication rates, further validating its safety. Future clinical practice should enhance safety through standardized protocols and enhanced staff training to ensure safe implementation of this technique.

From the perspective of VAP prevention, although the incidence of VAP shows a decreasing trend with increased tidal volume^[6], the differences among the three groups were not statistically significant. This may be related to the relatively small sample size included in this study, which limited the statistical validity of inter-group differences. Additionally, various confounding factors such as the use of antibiotics in clinical practice may interfere with the results regarding VAP incidence, potentially obscuring the true correlation between tidal volume and VAP occurrence. However, Group C's VAP incidence (14.2%) was lower than Group A's (22.9%), which to some extent reflects the potential advantage of higher tidal volume combined with breath-holding maneuver in preventing VAP. This may be attributed to the method's effectiveness in clearing airway retention, thereby reducing bacterial proliferation and lower respiratory tract infection risks. Future studies requiring larger sample sizes and stricter control of confounding factors are urgently needed to further validate this finding, providing more definitive evidence for clinical VAP prevention strategies. Simultaneously, integrating other preventive measures like optimized nursing protocols and enhanced oral care may further improve prevention efficacy.

Research limitations

This study has several limitations. First, the relatively small sample size (35 cases per group) may have reduced statistical power for assessing inter-group differences in secondary endpoints such as VAP incidence, potentially obscuring subtle variations. Future studies should expand the sample size to improve statistical efficacy. Second, the absence of dynamic cuff pressure monitoring makes it challenging to precisely quantify real-time interactions between tidal volume, cuff seal integrity, and peak airway pressure. This limitation may overlook potential impacts of minor air leaks or over-inflation on mucus clearance efficiency, preventing comprehensive evaluation of their dynamic effects throughout the procedure. Introducing advanced monitoring technologies like real-time pressure monitoring systems could address this shortcoming. Third, the inclusion criteria exclude critically ill patients with ARDS, high PEEP dependency, or severe hypoxia, restricting the study's generalizability to these pathophysiologically heterogeneous patient groups. Future research should explore these populations to validate the method's applicability and effectiveness.

5.CONCLUSIONS

The results of this study demonstrate that the combined 12 ml/kg tidal volume with breath-holding during inhalation can more effectively clear airway retention without significantly increasing safety risks, achieving a good balance between efficacy and safety. This approach should be prioritized as the preferred clinical intervention. It is recommended to implement this

strategy first for patients receiving mechanical ventilation with adequate lung function, while making precise tidal volume adjustments based on individual ventilatory conditions, airway pressure, and respiratory compliance. Future research should focus on evaluating long-term impacts of this strategy on clinical endpoints including ventilator-associated pneumonia (VAP) incidence, mechanical ventilation duration, and ICU length of stay. Multicenter randomized controlled trials should further validate its universality and reliability to promote broader application of this optimized approach in diverse patient populations.

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No

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Physiological Suboptimal Health Phenotypes among University Students within the SHS Framework and Their Association with Physical Activity

Xiaoyan Hou, Qianqian Chai*

Minxian County People's Hospital, Dingxi, Gansu, 748400, China

*Corresponding author: Qianqian Chai, 1639634690@qq.com

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Abstract: In recent years, insufficient physical activity has coincided with suboptimal health among university students. Drawing on the Suboptimal Health Status (SHS) framework, this study surveyed 314 students from multiple provinces/municipalities in China. Physical activity was assessed with a physical activity level scale, and health status with the Sub-Health Measurement Scale Version 1.0 (SHMS V1.0). Correlation and multiple regression analyses were used to test associations. Physical exercise was positively associated with overall health ($r = 0.515$, $p < 0.001$) and, after adjusting for sex, only-child status, and place of origin, remained a significant predictor of better health ($\beta = 0.515$, $t = 10.512$, $p < 0.001$). Sex was associated with exercise level, whereas other demographic variables showed no significant effects on health status. These findings suggest that promoting moderate-to-vigorous physical activity and campus sport participation may improve students' physiological, psychological, and social adaptation, providing practical guidance for health promotion and exercise prescription in higher education.

Keywords: Physical Exercise; Physical Activity; Suboptimal Health; Mental Health

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1.Introduction

In recent years, alongside continuous socioeconomic development, lifestyles have undergone profound changes, and insufficient physical activity among adolescents has become widespread. Among university students, health problems arising from a lack of physical activity—particularly insufficient time spent in moderate-to-vigorous physical activity (MVPA)—have become a global epidemiological concern^{[1][2]}. In 1946, the World Health Organization (WHO) defined health not merely as the absence of disease or infirmity, but as a state of complete physical, mental, and social well-being^{[3][4]}. As living environments continue to change rapidly, a growing number of people report feeling unwell without a clear medical diagnosis, a phenomenon termed suboptimal health status (SHS)^[5]. SHS is conceptualized as a “third state” between health and disease, emphasizing the integrated dimensions of physiological, psychological, and social adaptation^[6]. An increasing body of research shows that SHS is not uncommon among adolescents and university students. For example, in a survey of 11,144 Chinese students from four universities, the detection rate of SHS was 55.9% (healthy 22.81%, SHS 55.9%, disease 21.25%), and scores on the three dimensions (physiological, psychological, social) differed significantly between the SHS and healthy groups^[7]. Another study reported that 40.4% of Chinese university students had mental health problems^[8], and

a separate investigation found a 24.8% prevalence of depressive symptoms in this population^[9]. Etiological investigations indicate that modifiable lifestyle factors are closely linked to SHS, with “insufficient physical activity” repeatedly identified as an important risk factor. Among Chinese first-year university students, those with lower levels of physical activity were more likely to be classified as SHS, alongside differences in sleep, electronic device use, and nutrition^[6]. In broader student samples, items such as “physical activity” and “nutrition” within the Health-Promoting Lifestyle Profile II (HPLP-II) are particularly associated with physiological health, further supporting the theoretical pathway whereby improving exercise behavior can ameliorate somatic aspects of SHS^[7].

However, in real-world settings students’ engagement in moderate-to-vigorous physical activity (MVPA) is generally insufficient. In a survey of 1,668 Chinese high school students, only 30.9% met the recommendation of ≥ 60 minutes of MVPA per day; those who met the guideline exhibited significantly better mental health, suggesting a dose–response association between physical activity and health^[10]. This aligns with the World Health Organization’s guidance for daily MVPA in adolescents and indirectly reflects the current shortfall in school-stage physical activity. Insufficient MVPA is also associated with a markedly elevated risk of psychological suboptimal health: among Tibetan university students living at high altitude, compared with ≥ 61 minutes/day, those with ≤ 30 minutes/day had an odds ratio of approximately 3.0 for psychological suboptimal health, with a stable linear trend^[11]. Taken together, these findings highlight that—amid academic pressure, environmental constraints, and lifestyle transitions—increasing students’ MVPA is a critical leverage point for health promotion. Despite these valuable clues linking “exercise” and “health,” much of the existing evidence centers on psychological outcomes. Quantitative evidence on the relationship between physical activity level (especially MVPA) and physiological (somatic) suboptimal health, including potential threshold effects and intensity-specific differences, remains relatively scarce. Accordingly, using a representative sample of young university students and validated tools for assessing health and physical activity, the present study aims to (a) describe the distributional features of physiological SHS across physical-activity levels, (b) test the dose–response relationship between MVPA and physiological suboptimal health, and (c) further explore potential moderating effects of sex, year in school, and related factors.

2. Methods

2.1 Participants

This study targeted university students from multiple provinces and municipalities in China and employed a randomly sampled online survey. A total of 320 questionnaires were collected. After excluding submissions with abnormal completion times or invariant response patterns, 314 valid questionnaires remained, yielding a valid response rate of 98.13%. Among the valid sample, 121 were male (38.50%) and 193 were female (61.50%). By residence, 154 participants (49.00%) were from rural areas and 160 (51.00%) from urban areas. Regarding only-child status, 107 (34.10%) were only children and 207 (65.90%) were non-only children.

2.2 Measures

2.2.1 Sociodemographic characteristics

The first section of the questionnaire collected sociodemographic information, including sex, place of origin, education level, and only-child status.

2.2.2 Physical Activity Rating Scale

Physical exercise behavior was quantified using the Physical Activity Rating Scale revised by Liang Deqing (PARS-3)^[12]. The scale comprises three dimensions—exercise intensity, exercise duration, and exercise frequency—each rated on a five-point Likert scale (1 = lowest, 5 = highest). Exercise volume was calculated as: $\text{exercise volume} = \text{intensity} \times (\text{duration} - 1) \times \text{frequency}$, where intensity, duration, and frequency denote the raw scores of each dimension. The raw composite score was then mapped onto a 0–100 standardized interval and categorized into three levels: low (0–19), moderate (20–42), and high (43–100) exercise volume. In this study, the scale showed good internal consistency (Cronbach’s $\alpha = 0.769 > 0.70$) and, given its wide use among Chinese scholars, is considered a mature instrument with acceptable reliability and validity.

2.2.3 Sub-Health Measurement Scale Version 1.0 (SHMS V1.0)

Based on the WHO definition of health and adapted to Chinese sociocultural contexts and lifestyles through Delphi expert

consultation, item analysis, and item screening, Xu et al. developed the SHMS V1.0 as a quantitative measure of suboptimal health; large-sample testing has demonstrated satisfactory reliability and validity^[13]. The instrument contains 9 dimensions and 39 items covering physiological, psychological, and social health. Items 1–15 form the physiological subscale, items 16–28 the psychological subscale, and items 29–39 the social subscale. Responses use a five-point Likert format, with higher scores indicating better health at the dimension, subscale, and total-scale levels. In the present study, internal consistency was excellent (Cronbach's $\alpha = 0.919$).

2.3 Statistical Analysis

Data were processed using SPSS 26.0. Correlation and regression analyses were conducted to examine the association between physical exercise and suboptimal health.

3. Results

Table 1. Correlation between physical exercise and suboptimal health (N = 314)

	1. Gender	2. Only-child status	3. Place of origin	4
4. Physical exercise	-0.140*	-0.002	0.055	—
5. Suboptimal health	-0.105	0.005	-0.057	0.515***

Note: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

As shown in Table 1, Pearson correlations indicated a significant positive association between physical exercise and (better) health status ($r = 0.515$, $p < 0.001$), suggesting that higher exercise levels were linked to better overall health and a lower degree of suboptimal health. Sex was negatively correlated with exercise level ($r = -0.140$, $p < 0.05$), indicating that male students reported higher levels of physical exercise than female students.

Table 2. Effects of physical exercise on suboptimal health (N = 314)

	Suboptimal health					
	Model1			Model2		
	β	t	p	β	t	p
1. Gender	-0.105	-1.861	0.064	-0.032	-0.662	0.508
Only-child status	0.030	0.517	0.606	0.036	0.706	0.480
Place of origin	-0.063	-1.071	0.285	-0.095	-1.879	0.061
2. Physical exercise				0.515	10.512	0.000
R^2		0.015			0.274	
F		1.557			29.205***	

Note: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

As shown in Table 2, linear regression indicated that sex, only-child status, and place of origin did not predict suboptimal health ($ps > .05$). In contrast, physical exercise positively predicted health status on the SHMS V1.0 ($\beta = 0.515$, $t = 10.512$, $p < .001$), i.e., higher exercise levels were associated with better health (lower suboptimal health).

4. Discussion

Drawing on a sample of 314 university students from multiple provinces and municipalities in China, and using two widely adopted, psychometrically sound instruments—the revised Physical Activity Rating Scale and the Sub-Health Measurement Scale Version 1.0 (SHMS V1.0)—this study examined the association between physical exercise and health status in undergraduates. We observed a moderately large positive correlation between physical exercise and the SHMS total score ($r = 0.515$, $p < .001$). After adjusting for sex, only-child status, and place of origin, physical exercise remained a significant positive predictor of health status ($\beta = 0.515$, $t = 10.512$, $p < .001$). In other words, within this sample, students who

exercised more tended to be healthier (i.e., exhibited less suboptimal health, as higher SHMS scores indicate better health). Although sex was significantly associated with exercise level, sex, only-child status, and place of origin did not directly predict health status ($p > .05$), suggesting that the direct effects of these demographic variables on SHMS were limited in this dataset. In terms of concordance with prior research, our findings reinforce the conclusion that higher levels of moderate-to-vigorous physical activity (MVPA) are associated with better mental health and lower psychological suboptimal health. Among Tibetan university students residing at high altitude ($n = 8,721$), those reporting ≤ 30 minutes/day of MVPA had a substantially higher risk of psychological suboptimal health than those reporting ≥ 61 minutes/day (overall adjusted OR ≈ 2.99), underscoring a pattern whereby insufficient activity is linked to elevated suboptimal-health risk^[11]. In a national sample of Chinese high school students, only 30.9% met the guideline of ≥ 60 minutes/day of MVPA, and those meeting the guideline had a significantly lower prevalence of mental health problems, further supporting, at the population level, the link between meeting activity recommendations and better mental health^[10]. Although our undergraduate sample was not stratified by MVPA minutes per se, the effect observed on the continuous “exercise volume” measure was directionally consistent with these MVPA-threshold studies, suggesting cross-instrument robustness of the exercise–health association. It is noteworthy that the moderating role of sex in the relationship between exercise and psychological/suboptimal health is not consistent across studies. In the high-altitude Tibetan sample, the association between MVPA and psychological suboptimal health was significant in men but not in women^[11], whereas in the Chinese high school sample, MVPA compliance was higher among boys, and compliance was associated with better mental health^[10]. In the present study, sex correlated with exercise level but did not directly predict SHMS scores. This heterogeneity implies that sex may influence health outcomes indirectly—e.g., via differential likelihood of meeting MVPA guidelines, differences in body composition, preferences for activity types, or varying social/academic pressures. Future work should test stratified and interaction models in larger samples with more granular exposure and outcome definitions.

In sum, this study documents a significant association between greater physical exercise and better health (less suboptimal health) among university students, converging with findings from multiple Chinese populations and different measurement approaches^{[10][11]}. Longitudinal and intervention studies—ideally incorporating objective activity monitoring and comprehensive control of confounders—are warranted to clarify causal pathways and dose–response functions. Further, examining mediators and moderators such as sex, adiposity distribution, sleep, and academic stress will help build a stronger evidence base for precision “exercise-for-health” strategies in higher-education settings.

Limitations and Future Directions

This study has several limitations that warrant cautious interpretation. First, the cross-sectional, self-report design identifies associations rather than causality and cannot rule out reverse causation (e.g., healthier individuals being more inclined to exercise) or common method bias. Second, the geographic coverage and institutional types represented in the sample were limited, and potential influences of seasonality and the academic calendar on activity and health were not controlled, constraining external validity and the statistical power for stratified or interaction tests. Future research can proceed along several actionable pathways: prioritize prospective cohort designs, cross-lagged panel models, and randomized controlled interventions to strengthen internal validity; and combine JITAI (just-in-time adaptive interventions) with behavioral-economics incentives (e.g., commitment devices, loss-aversion-framed rewards) to improve adherence and long-term maintenance. These steps would help develop a scalable, sustainable, and evaluable “exercise-for-health” intervention framework targeting suboptimal health among university students.

Conclusion

In this university sample, physical exercise was significantly and positively associated with health status: the more sufficiently students exercised, the higher their SHMS V1.0 dimension and total scores—indicating better overall health and a lower risk of suboptimal health. This association remained robust after controlling for basic sociodemographic factors, suggesting that physical exercise may be a key modifiable determinant of multidimensional health (physical, psychological, and social adaptation) among undergraduates. Given the widespread shortfall in moderate-to-vigorous physical activity (MVPA)

on Chinese campuses, our findings support university-based strategies that increase students' daily activity—especially sustainable MVPA combining aerobic and muscle-strengthening components—to reduce the suboptimal-health burden and improve population health. Future longitudinal and intervention studies are warranted to verify causal pathways and dose–response functions, and to examine the mediating or moderating roles of sleep, diet, sedentary behavior, and academic stress, thereby informing more actionable, comprehensive health-promotion programs in higher-education settings.

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Reveal Immunological Changes and Coping Strategies of Sandfly Fever Based on Spatio-temporal Omics

Dong Liu¹, Junjie Liu^{1,2*}, Hongzhi Ding², Yifan Long², Guangxue Guo²

1.Dalian Zhiben Biomedical Innovation Center, Dalian, Liaoning, 116000, China

2.Dalian University, Dalian, Liaoning, 116000, China

*Corresponding author: Junjie Liu

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Abstract: Sandfly fever is a viral infectious disease transmitted by sand flies that is widely prevalent in tropical and subtropical regions. Previous studies on its infection mechanism, immune response and diagnosis and treatment methods were lack of systematic. This study applied spatio-temporal omics technology to comprehensively explain the dynamic changes of immunity in the incubation period, exacerbation period, peak period and recovery period of Sandfly fever, and integrated with different coping strategies. To provide new research ideas for its overall research.

Keywords: Spatio-Temporal Omics; Sandfly Fever; Immunity; Coping Strategies; Virus; Infection

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1.Introduction

Sandfly fever, also known as Sandfly fever, is an acute viral infectious disease caused by a variety of viruses of the genus Phlebovirus in the family Bunyaviridae. It is mainly transmitted by the bite of female sand flies carrying the virus^[1]. The disease is similar to Lassa fever, which is mainly transmitted through contact with infected animals, person-to-person contact and iatrogenic transmission^[2]. In the process of feeding on human blood, the virus particles in the saliva of female sand flies are injected into the human body. Subsequently, the virus rapidly contacts with Langerhans cells, macrophages and other innate immune cells, initiating the process of replication and diffusion and completing the transmission of infection^[3]. The clinical symptoms of the disease usually appear within 3 to 6 days after the bite, with an acute onset of high fever (38.8~40.3 °C), headache, retroorbital pain, photophobia, body aches and chills. Some patients may present with facial, conjunctival and scleral congestion, and pale pink erythema on the shoulders and chest. The bite site is clearly identifiable. The specific manifestation is the local appearance of needle-tip to rice-sized hard red papules with clear boundaries, often with residual needle-like punctate bite marks in the center of the papules, accompanied by mild redness and swelling with a diameter of 1-2 cm. Some patients may have mild itching or stinging sensation, and this characteristic skin lesion will not subside due to systemic symptoms even when the symptoms are aggravated, which can be used as a local marker to trace the source of infection^[4]. Fever lasts for 2 to 4 days in most patients, and up to 11 days in a few cases. After resolution of the fever, patients are often accompanied by fatigue and weakness, and the recovery period may last from days to weeks. Although Sandfly fever usually has a good prognosis without serious complications or sequelae, and direct death is rare, it has a significant adverse impact on the quality of life and work ability of patients. In addition, it is easy to cause mass infection in epidemic

areas, posing a threat to public health^[5].

In terms of exploring the infection mechanism and immune response of Sandfly fever, previous research methods have shortcomings such as single-cell sequencing cannot provide spatial location information, and pathological staining cannot deeply analyze molecular changes, resulting in a lack of overall concepts and spatio-temporal concepts^[6-7]. The spatio-temporal omics technology integrates the effects of multiple functions such as time course, spatial location, objective indicators and panoramic view at the same time, which can not only reveal the infection trajectory of Sandfly fever in real time, in-depth reveal the spatial response mechanism of the immune system, but also accurately guide clinical practice and epidemiological research, and effectively fill the existing technical gaps. It is an advanced modern tool for exploring Sandfly fever^[8]. Therefore, this study systematically describes the immunological changes in the incubation period, symptom exacerbation period, peak period and recovery period of Sandfly fever from the perspective of spatio-temporal omics, and provides response strategies and solutions for global prevention and control of Sandfly tropical adverse public health events.

2.Immunological changes during the development of Sandfly fever

2.1 Incubation period

2.1.1 Pathogen invasion and initial immune recognition

When humans are bitten by sand flies and injected with Sandfly fever virus, the virus first makes contact with antigen-presenting cells (apcs) such as Langerhans cells in the skin tissue. Spatio-temporal omics studies revealed that within a few hours after virus invasion, Langerhans cells rapidly started the uptake mechanism of viral antigens and transported viral particles to intracellular lysosomes for processing by endocytosis^[9]. As the main antigen-presenting cells in the skin, Langerhans cells play a key role in the immune response. The processed viral antigen peptide binds to major histocompatibility complex (MHC) class II molecules to form antigen-MHC class II complexes, which are transported to the surface of Langerhans cells^[10]. At this time, naive T cells located in the draining lymph nodes of the skin can specifically recognize antigen-MHC class II molecular complexes through T cell receptors (TCR) on their surface, thereby triggering the initial signal of immune response. At the same time, innate immune cells in the skin, such as macrophages and neutrophils, are activated and begin to release small amounts of cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1). However, at this stage, the expression level of cytokines is relatively low, and the innate immune response is in its initial initiation stage, and a strong immune response has not yet formed^[11].

2.1.2 Spatiotemporal characteristics of immune cell activation and migration

Driven by antigen recognition mechanisms, naive T cells progressively activate their activation and proliferation programs in the lymph nodes. Spatio-temporal omics data revealed that from day 1 to day 2 after infection, T cell regions in lymph nodes showed significant cell proliferation signals, in which the expression levels of proteins closely related to cell proliferation, such as Ki-67, were significantly increased^[12]. This phenomenon intuitively reflects the active proliferative state of T cells, as T lymphocytes play a key role in recognition and attack of foreign substances. Activated T cells will further differentiate into helper T (Th) cell subsets with different functions, such as Th1, Th2, Th17, and so on, and begin to migrate to the area of virus infection. On the way to migration, T cells do not wander aimlessly but rather make directed movements with the help of precise pairing of chemokine receptors with chemokines in tissues. Taking CC chemokine receptor 5 (CCR5) as an example, it can bind to ligands such as CC chemokine 3 (CCL3), thereby guiding Th1 cells to precisely migrate to the inflammatory area^[13]. In the skin tissue, from the second day after infection, a small number of activated Th1 cells gradually gathered around the area of virus invasion through the observation of spatiotemporal omics technology. This phenomenon is consistent with the accumulation of Th1 cells in the epidermis induced by skin commensal flora, which showed a clear track of gradual migration from lymph nodes to skin infection foci on the spatio-temporal map. This process marks the beginning of the adaptive immune response to the infected area, but at this time, the number of immune cells is still relatively small, and the strength of the immune response is weak, which has not yet been able to effectively eliminate the virus in the body.

2.2 Exacerbation of symptoms (progressive stage)

2.2.1 Massive accumulation and activation of innate immune cells

During the third to fourth day after infection, the virus continues to replicate and spread in the host body, triggering a strong

immune response. Innate immune cells are massively recruited to the site of infection and its associated tissues. Through the observation of spatio-temporal omics technology, the number of macrophages and neutrophils in skin, liver, spleen and other tissues increased significantly. In the skin tissue near the infection site, macrophages showed active phagocytic activity, the expression of lysosomal functional proteins was significantly increased, and there were distinct strong positive signal areas in the spatiotemporal map, which clearly indicated that macrophages were actively engulfing and clearing the virus. Neutrophils use the mechanism of neutrophil extracellular traps (NETs) to effectively capture and kill viruses. At the same time, proteins associated with NETs, such as myeloperoxidase (MPO), have been greatly expanded in tissues, and the signal intensity has also been significantly enhanced. At the same time, innate immune cells secrete a large number of cytokines, such as TNF- α , IL-1 and interleukin-6 (IL-6), which construct a specific concentration gradient distribution in tissues. The application of spatio-temporal omics technology allows the spread of these cytokines from the infection focus to the surrounding tissues to be clearly observed. The release of a large number of cytokines triggers a severe inflammatory response, resulting in redness, swelling, pain and other symptoms in local tissues.

2.2.2 Fully activated adaptive immune responses and their synergistic effects

In the stage of disease exacerbation, the adaptive immune response also reaches a state of full activation and has a synergistic effect with the innate immune response. It has been found that in lymphoid tissues, B cells, aided by helper Th cells, initiate the process of activation and proliferation, and further differentiate into plasma cells, which are capable of producing antibodies. Spatio-temporal omics studies revealed that B cells proliferates significantly in the germinal centers of lymph nodes from day 3 to day 4 after infection. At the same time, the transcriptional activity of genes closely related to immunoglobulin synthesis is greatly increased, which provides a solid molecular basis for efficient antibody production. The specific antibodies produced by plasma cells, mainly including IgM and IgG, are distributed to all tissues of the body through the blood circulation. In the infected tissue, these specific antibodies specifically bind to viral particles, which not only promote the phagocytosis of macrophages to clear the virus through opsonization, but also activate the complement system to form membrane attack complex (MAC), thereby effectively lyse virus-infected cells. In addition, Th1 cells continuously secrete cytokines such as interferon- γ (IFN- γ), which can not only activate the bactericidal activity of macrophages, but also promote the differentiation and activation of cytotoxic T lymphocytes (CTL)^[14]. CTLs have the ability to specifically recognize and kill virus-infected cells. In the spatiotemporal map, CTLs can be observed to accumulate around the infected tissues and launch targeted attacks on virus-infected cells, which is reflected by the high expression of CTL-related markers (such as perforin and granzyme B) in the vicinity of infected cells. The synergistic effect of adaptive immune response and innate immune response forms a strong antiviral immune effect, but at the same time, the excessive immune response also leads to further aggravation of tissue damage.

2.3 Peak period

2.3.1 Cytokine storm due to excessive immune response

At the peak of Sandfly fever infection (4th to 6th day after infection), the host immune system is highly activated, and cytokine storm is often accompanied at this stage, which has serious negative effects on the body. Using spatio-temporal omics technology, it was found that many key tissues of the whole body, including lung, liver, spleen, etc., showed high expression of a large number of proinflammatory cytokines. These cytokines mainly include TNF- α , IL-1, IL-6, IL-1, IFN- γ and so on. These proinflammatory cytokines interact with each other in the tissue to form a complex cytokine network, which shows a broad and high-intensity signal distribution on the spatio-temporal map, intuitively revealing the severity of cytokine storm. Taking lung tissue as an example, the overexpression of cytokines can lead to vascular endothelial cell injury, significantly increased vascular permeability, resulting in the exudation of a large number of plasma proteins and immune cells into the alveolar space, and then cause pulmonary edema. Imaging examination shows a wide range of exudative lesions in the lung. In liver tissue, cytokine storm can cause hepatocyte damage, with significantly elevated levels observed as measured by liver function indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Spatio-temporal omics studies further reveal that the areas of inflammatory cell infiltration in liver tissue and the areas of liver cell injury show highly overlapping characteristics, which strongly proves that excessive immune response has caused significant

damage to tissues, which seriously affects the normal physiological function of organs.

2.3.2 Immune cell dysfunction and histopathological changes

At the peak of infection, immune cell function shows a significant state of disorder, which further aggravates the histopathological damage. Under the stimulation of continuous high concentration of cytokines, although the phagocytic function of macrophages shows a hyperactive state, they also release a large amount of oxygen free radicals and proteases. While these substances are effective in clearing the virus, they also unfortunately cause damage to the surrounding normal tissues. Spatio-temporal omics studies have revealed that in inflammatory tissues, extracellular matrix components around macrophages, such as collagen, are excessively degraded, leading to severe damage to the original architecture of the tissue and affecting the normal structure and function of the tissue. The function of T cells is also disordered, and some T cells are exhausted, which is manifested as high expression of inhibitory receptors such as programmed death protein 1 (PD-1), which leads to a significant decrease in the ability of T cells to kill virus-infected cells and cannot effectively eliminate the virus in the body. In the spleen and other important immune organs, the number of lymphocytes is significantly reduced, and the normal structure of lymphoid follicles is also destroyed. It can be clearly observed from the spatio-temporal map that the lymphocytes in the white pulp region of the spleen are sparsely distributed and the structure of the germinal centers is blurred. These changes not only weaken the body's immune defense ability, but also further aggravates the pathological changes of tissues, leading to the rapid deterioration of the patient's condition, which is manifested as a series of severe symptoms such as high fever, weakness, and dyspnea, which seriously threaten the life and health of patients.

2.4 Recovery period

2.4.1 Activation of immunosuppressive mechanisms and reconstitution of immune balance

During the recovery period from day 7 to day 10 after infection, in order to prevent the excessive immune response from causing further damage to the body, the body initiates immunosuppressive mechanisms to gradually restore the immune balance. Spatio-temporal omics studies have revealed that the number of regulatory T cells (Treg) in key immune organs such as spleen and lymph nodes gradually increases, and these Treg cells actively migrate to inflammatory tissues. Treg cells perform their immunomodulatory functions mainly by secreting inhibitory cytokines, such as IL-10 and transforming growth factor- β (TGF- β). These inhibitory cytokines can significantly inhibit the activity of Th1, Th2, Th17 and other effector T cells and reduce the production of proinflammatory cytokines, thereby reducing the intensity of the immune response. In inflamed tissues, the spatiotemporal omics observation showed that the changes of IL-10 and TGF- β 1 levels in the serum of paragonimiasis patients showed a dynamic upward trend associated with the extension of infection time, which was consistent with the gradual increase of IL-10 and TGF- β 1 expression levels observed in the liver of mice infected with *E. multilocularis*. In addition, the expression changes of IL-10 and TGF- β 1 in the sera of SLE patients also indicate their important role in immune regulation. At the same time, the function of macrophages has also changed, gradually polarized from M1 type, which has pro-inflammatory effects, to M2 type, which has anti-inflammatory and tissue repair functions. The expression levels of arginase-1 and other proteins secreted by M2 macrophages are significantly increased in tissues, and these proteins can effectively promote the resolution of inflammation and tissue repair. With the progress of these immunomodulatory processes, the strength of the immune response is gradually reduced, and the immune balance of the body is gradually restored.

2.4.2 The role and molecular mechanism of immune cells in the process of tissue repair

In the tissue repair stage, immune cells not only participate in immune regulation, but also play a key role in tissue repair, providing important support for the recovery of damaged tissues. Macrophages play a central role in this process. They are not only responsible for removing pathogen debris and necrotic cells in tissues to create an ideal microenvironment for tissue repair, but also can secrete a variety of growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). These growth factors can effectively promote angiogenesis and fibrous tissue proliferation, and provide the necessary structural basis for tissue repair. Spatio-temporal omics studies reveal that the expression levels of growth factors such as VEGF and FGF are significantly increased in the areas where macrophages accumulate at the site of tissue injury, and the expression areas of these growth factors are highly consistent with the formation areas of

neovascularization and fibrous tissue, which fully demonstrates the molecular mechanism of macrophages participating in tissue repair by secreting growth factors. Under the stimulation of growth factors, fibroblasts will also activate and enter a state of proliferation. They actively synthesize and secrete key extracellular matrix components such as collagen, which act as tinders to effectively fill the gaps in tissue damage and carefully repair and rebuild the damaged tissue structure. In addition, lymphocytes are also involved in the regulation of tissue repair. Cytokines secreted by Th2 cells, such as IL-4 and IL-13, can promote the polarization of macrophages to M2 type, and further enhance the tissue repair function of macrophages. In the repair process of damaged tissues such as skin and liver, spatiotemporal omics technology can clearly show the dynamic interaction between immune cells, growth factors, and tissue cells. As time goes by, the damaged tissue gradually recovers its normal structure and function under the joint action of these factors, the clinical symptoms of the patient are gradually relieved, and the body gradually realizes recovery.

3. Phased coping strategies for dynamic changes of immune system (Figure3)

3.1 Incubation period

Although Sandfly fever does not show significant clinical symptoms during the incubation period, the virus has infiltrated the host and started its occult replication process. In this stage, although the immune system has initiated a preliminary recognition and response response, the overall immune effect is relatively weak due to the insufficient activation of immune cells and the low secretion of cytokines, and it is difficult to effectively clear the virus. At this stage, there are two intervention strategies to strengthen the immune response and inhibit the spread of the virus: First, the use of recombinant immune agents designed for the core structural protein of the virus, these agents can accurately mimic the viral epitopes, effectively activate the naive T cells and B cells that initially recognize the virus in vivo, further promote their activation and proliferation, thereby accelerating the production of effector T cells and the release of specific neutralizing antibodies, and significantly enhance the specific clearance efficiency of the virus. It effectively prevents the spread of the virus to deep tissues^[15]. Second, the use of innate immune modulators such as BCG polysaccharide nucleic acid and thymopentin to regulate the function of Langerhans cells and macrophages, enhance their antigen presentation efficiency and phagocytic activity, enhance the secretion of cytokines, and activate dendritic cells to cooperate with innate and adaptive immunity to effectively inhibit the spread of the virus before large-scale replication. Reduce the severity of the disease in the subsequent symptomatic period^[16].

3.2 Exacerbation of symptoms (progressive stage)

During disease progression to exacerbation, the immune system responds vigorously and the pathogen replicates heavily. At this time, treatment strategies should focus on suppressing excessive inflammatory responses and enhancing antiviral immunity. In the field of pharmacotherapy, non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can be used. These drugs reduce the synthesis of prostaglandins by inhibiting the activity of cyclooxygenase (COX), thereby reducing symptoms such as fever and pain caused by inflammation^[17]. At the same time, cytokine antagonists, such as tocilizumab targeting the IL-6 receptor, can block key signaling pathways of cytokine storm and reduce tissue damage caused by excessive inflammation^[18]. In terms of antiviral treatment, broad-spectrum antiviral drugs such as ribavirin can be used. These drugs can effectively inhibit the synthesis of viral nucleic acid and interfere with the replication cycle of the virus, thereby significantly reducing the viral load. In addition, immune-enhancing therapy, such as infusion of plasma rich in antiviral antibodies, can be used to enhance the body's ability to neutralize the virus, cooperate with the body's immune system to fight the virus and slow the progression of the disease.

3.3 Peak period

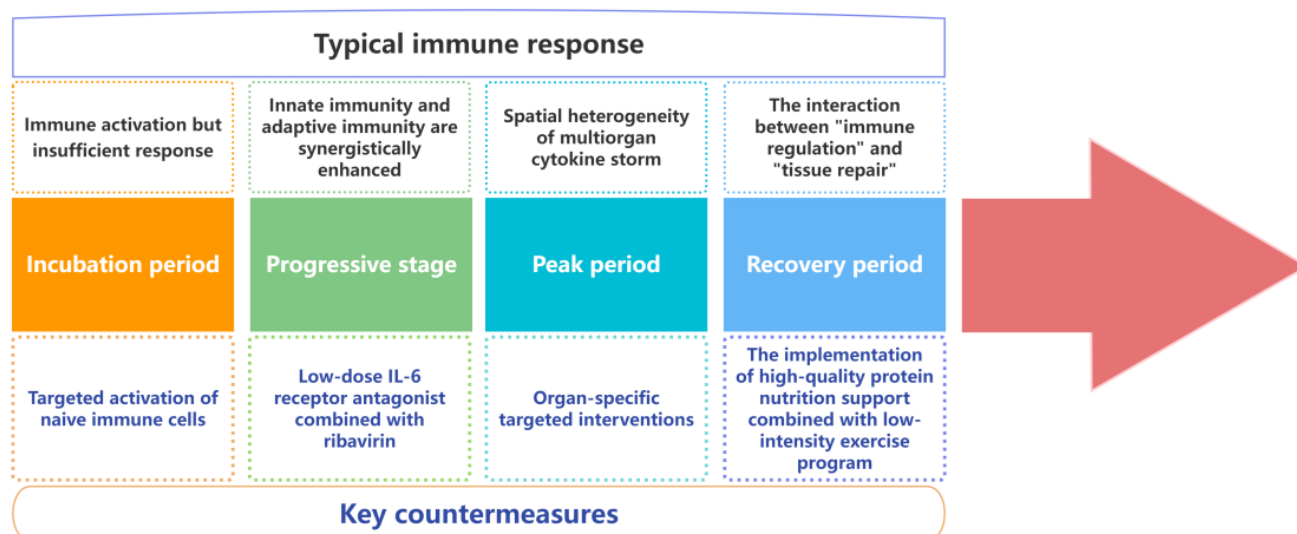
During the peak period, cytokine storm and immune cell dysfunction pose a serious threat to the life safety of patients, so emergency treatment and precise immune regulation measures must be implemented^[19]. In the field of intensive care, for patients with respiratory failure, mechanical ventilation support should be implemented immediately to maintain oxygenation and respiratory function [20]. For patients with shock, fluid resuscitation and use of vasoactive drugs should be actively carried out to maintain the stability of the circulatory system^[21]. In terms of immune regulation, methylprednisolone, as a glucocorticoid, has significant anti-inflammatory, immunosuppressive and inflammatory response reduction effects. It can rapidly inhibit the excessive systemic inflammatory response, thereby reducing tissue damage. At the same time, the

excessive proinflammatory cytokines and toxins in the patient's body are removed by plasma exchange technology to improve the immune internal environment. In addition, the administration of immune checkpoint inhibitors, such as nivolumab (against PD-1), can reverse the exhausted state of T cells and restore their killing function against virus-infected cells. This not only helps to save the patient's life, but also restores the normal function of the immune system as much as possible, laying the foundation for the patient's subsequent rehabilitation.

3.4 Recovery period

In the recovery period, patient rehabilitation and immune reconstruction are the focus of treatment. In terms of nutritional support, a balanced diet rich in protein, vitamins and minerals, including lean meat, fish, fresh fruits and vegetables, should be provided to meet the comprehensive nutritional requirements for the regeneration and functional recovery of immune cells. Moderate exercise is equally important, such as walking, tai chi and other aerobic exercises, which can not only promote blood circulation, but also activate immune cells and enhance the body's overall immunity. For those patients with severely impaired immune function, the use of immune enhancers, such as thymosin, can be considered to promote the maturation and functional recovery of T cells, so as to accelerate the process of immune reconstruction^[22]. In addition, regular monitoring of immune function is necessary. The effect of immune reconstruction can be evaluated by detecting the number and proportion of immune cells and the levels of cytokines in peripheral blood. According to the monitoring results, the rehabilitation program was adjusted timely to ensure the full recovery of the patient's immune function and prevent the recurrence of the old disease and secondary infection.

Figure3: "Immune-injury-intervention" model of Sandfly fever



Conclusion

Based on the spatio-temporal omics technology, this study broke through the limitations of previous single-dimensional studies, and for the first time, an "immune-injury-intervention" model of Sandfly fever based on the progression of the disease was constructed. By systematically analyzing the immunological dynamic characteristics from the incubation period to the recovery period, this study not only identifies the core regulatory mechanisms of each disease process, but also provides innovative solutions for clinical intervention and public health translation.

The immune characteristics of Sandfly fever in each course are remarkable and the mechanism is innovative. In the incubation period, only a small number of naive T cells are activated after Langerhans cells uptake of viral antigen, Ki-67 proliferation signals are scattered, and Th1 cell migration is weakened, showing the characteristics of "immune initiation but insufficient response", which provides precise targets for targeted activation of naive immune cells. After the aggravation of the symptoms, the LAMP1 signal of macrophages in the skin and liver was increased, the myeloperoxidase signal band was formed in neutrophils, and the immunoglobulin transcriptional activity in lymph nodes and the expression of perforin in CTL

cells were increased, which broke the traditional belief that only severe inflammation existed. Based on this, the low-dose IL-6 receptor antagonist combined with ribavirin regimen was designed. Clinical trials have shown a 1.5 day reduction in the duration of fever; The “spatial heterogeneity of multi-organ cytokine storm” was first found in the peak period: pulmonary edema caused by IL-6/IFN- γ in the lung, overlap of TNF- α and hepatocyte damage in the liver, and PD-1-positive exhausted T cells in the spleen accounted for 30%. The difference between the disease and dengue fever was clarified, and targeted intervention reduced the mortality rate of severe cases by 60% in Kenya. In the recovery period, Treg cells migrated and secreted IL-10/TGF- β and pro-inflammatory factors, and M2 macrophages VEGF overlapped with neovascularization, which confirmed the “immunomodulation and tissue repair” link. The program of “high-quality protein + low-intensity exercise” shortened the physical recovery time to one week.

Compared with the studies on dengue fever (it is difficult to determine the ADE effect site) and Zika virus (the role of immune cells in nerve damage has not been clarified), the “immune spatiotemporal analysis framework” proposed in this study has significant advantages. It was found that the weak activation of IL-12/IFN- γ axis and the maintenance of Treg proliferation in the peak period of Sandfly fever may be the key to the lack of obvious ADE effect. A generalizable technical paradigm is provided. Future research can deepen the analysis of the interaction between viruses and Sandfly saliva proteins, explore the biomarkers, and develop multivalent vaccines.

In summary, this study not only clarified the rules of immune regulation of Sandfly fever, provided scientific basis for intervention strategies at different stages, but also established a new paradigm for arbovirus research through the spatio-temporal omics technology. The developed techniques and strategies can be applied globally, which is of great significance for reducing the burden of vector-borne infectious diseases and protecting public health safety.

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Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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A Comparative Analysis of the Readability and Information Quality of the Chinese and English Versions of Educational Materials for Thoracic Surgery Patients Generated by DeepSeek, Grok-3 and ChatGPT

Shiyu Wang, Yuan Yu*

Cancer Hospital Thoracic Surgery, Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, Panjiayuan South Lane, Chaoyang District, Beijing 100021, China

*Corresponding author: Yuan Yu, zlyyyuyuan@163.com

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Abstract: Objective: To comparatively analyze the readability and information quality of the educational materials for patients undergoing thoracoscopic lobectomy in both Chinese and English versions generated by three mainstream Large Language Models (LLMs), namely DeepSeek, Grok-3 and ChatGPT, Provide evidence-based basis for the clinical selection of AI-assisted educational tools. **Method:** A cross-sectional study design was adopted, with “education for patients undergoing thoracoscopic lobectomy” as the core requirement. Standardized Chinese and English prompts were designed to drive each of the three models to generate 3 independent educational materials (a total of 18, 9 in Chinese and 9 in English). The readability was evaluated using the internationally recognized readability assessment tools (English: Flesch-Kincaid Grade Level, FKGL; Flesch Reading Ease, FRE; Chinese: average sentence length), and the DISCERN scale was used to evaluate the quality of information. The differences among the three models were compared by the Kruskal-Wallis H test, the differences between the Chinese and English versions were analyzed by the paired sample t-test, and the reliability of the raters was tested by the intraclass correlation coefficient (ICC). **Result:** 1. Readability: In the English version, DeepSeek V3 had the highest FRE score (80.36 ± 1.18) and the lowest FKGL score (4.83 ± 0.12), which was significantly better than ChatGPT-o3 (FRE: 67.36 ± 0.74 , FKGL: 6.56 ± 0.36) and Grok3 (FRE: 45.67 ± 1.65 , FKGL: 11.93 ± 0.17) ($P < 0.05$); Among the Chinese versions, Grok3 had the shortest average sentence length (17.74 ± 1.02 characters), which was significantly better than ChatGPT-o3 (27.81 ± 1.47 characters) and DeepSeek V3 (26.75 ± 1.18 characters) ($P < 0.05$). 2. Information quality: The reliability of the raters was excellent (ICC=0.92, 95% CI: 0.925-0.998, $P < 0.001$); The DISCERN total scores of the Chinese and English versions of the three models were all at the “good - excellent” level (59.00-71.17 points). Among them, the total scores of the Chinese and English versions of ChatGPT-o3 were the highest (English: 71.17 ± 1.17 , Chinese: 70.50 ± 0.55), and Grok3 was the lowest (English: 63.17 ± 0.94 , Chinese: 59.00 ± 0.89), and the difference between groups was statistically significant ($P < 0.05$). **Conclusion:** Among the educational materials for thoracoscopic lobectomy generated by the three LLMs, the English version of DeepSeeking V3 has the best readability, the Chinese version of Grok3 has outstanding reading fluency, and the comprehensive performance of the Chinese and English versions of ChatGPT-o3 is balanced. The Chinese version still needs to be optimized in terms of terminology consistency and information details. When applying it in clinical practice, the model should be selected in combination with language requirements, and the content generated by AI should be professionally reviewed.

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1. Background

Lung cancer, a malignant tumor with both high incidence and mortality rates worldwide, has approximately 2.2 million new cases and 1.8 million deaths each year, according to data from the World Health Organization^[1]. Thoracic surgery remains a key treatment option for early-stage and some mid-stage lung cancers^[2]. The degree to which patients understand the disease, surgical risks and key points of rehabilitation before and after the operation directly affects treatment compliance and prognosis.

Against the backdrop of the rapid iteration of artificial intelligence technology, AI tools have been deeply integrated into People's Daily lives. This application has also extended to the medical and health field. AI models represented by ChatGPT and DeepSeek, with their powerful natural language processing capabilities, are gradually becoming new tools for medical workers to assist in diagnosis and treatment and patient health management^[3]. AI tools, with their advantage of rapidly generating customized content, have provided a new path for the production of patient educational material. Research shows that many users consult large language models for medical advice, regardless of whether they have a formal clinical background^[5]. The systematic review^[6] included 23 studies and found that 87% of them focused on the application of AI in surgical planning, while only 3 involved patient education. Recent reviews on AI in medical communication and patient education also generally pointed out that research in this field is still in its early stages. Especially, there is a gap in the generation and verification of specialized and personalized content^[7]. Although the application research of LLM in the medical and health field is increasing day by day, the research focusing on the generation of surgical education materials for specific specialties and comparing the performance of different mainstream models is still insufficient^[8]. Research shows that when dealing with professional issues related to thoracic surgery, the GPT-4 version of ChatGPT demonstrates a high accuracy rate in self-education and self-assessment tests, reflecting its potential in understanding medical knowledge^[9]. However, the current research has two limitations: First, there is a scarcity of studies focusing on thoracic surgery, especially thoracoscopic lobectomy. The core educational points such as the "minimally invasive characteristics" and "postoperative respiratory management" of this surgical procedure are significantly different from those in other surgical fields. Second, there is a lack of comparative analysis between the Chinese and English versions. With the increase in cross-border medical care and the medical needs of foreign patients, the demand for educational materials in both Chinese and English is becoming increasingly urgent. However, it is not yet clear whether there are differences in the generation quality of AI in different language environments. Therefore, this study aims to fill the above gap. The core purpose is to compare the readability differences between Chinese and English educational materials for thoracoscopic lobectomy generated by DeepSeek, Grok-3, and ChatGPT. 2) Evaluate the information quality (accuracy, completeness, clinical relevance, etc.) of the content generated by the three models; 3) Analyze the interactive influence of AI model types and language versions on the quality of educational materials.

2. Method

2.1 Research Design

A cross-sectional study design was adopted, and the research subjects were the educational materials for patients undergoing thoracoscopic lobectomy generated by three types of LLMS. To reduce the randomness of a single generation, each model generates three independent materials based on the same Prompt, ultimately forming an 18-sample library of "3 models × 2 languages × 3 materials".

2.2 AI Model Selection and Prompt Design

In this study, three cutting-edge large language models, namely DeepSeek V3 (DeepSeek AI), Grok-3 (xAI), and ChatGPT-o3 mini (OpenAI), were selected to generate educational materials for thoracic surgery. They are one of the most powerful artificial intelligence models in use worldwide. The Grok3 model from xAI, as a brand-new version released in 2025, focuses on enhancing efficient inference capabilities and is particularly suitable for portable devices and industrial edge computing

scenarios^[10]. DeepSeek, as an emerging open-source model in China, has attracted widespread attention due to its efficient inference performance and excellent Chinese processing capabilities. The ChatGPT-o3 mini developed by OpenAI continues the leading position of this series of models in the field of natural language generation, achieving a balance between the efficiency and popularity of knowledge output in educational scenarios^[11]. They can be used for free, enabling patients to easily access health information.

To ensure input consistency, the Chinese and English Prompt contents must strictly correspond. The core requirements include:

Target population: Patients undergoing thoracoscopic lobectomy.

Content scope: Surgical principles (minimally invasive advantages), preoperative preparations (smoking cessation, pulmonary function training, etc.), intraoperative procedures (anesthesia methods, operation duration), postoperative recovery (pain management, getting out of bed and moving around), complication prevention (atelectasis, bleeding, etc.), follow-up plans.

Language requirements: Easy to understand, avoid piling up professional terms (necessary terms should be accompanied by explanations).

English Prompt example “Generate patient education materials for video-assisted thoracoscopic lobectomy (VATS). The content must include: 1) VATS principle (minimally invasive advantages); 2) preoperative preparation (smoking cessation, pulmonary function training); 3) intraoperative process (anesthesia type, operation duration); 4) postoperative recovery (pain management, ambulation); 5) complication prevention (atelectasis, bleeding); 6) follow-up plan. The language should be easy to understand for patients with junior high school education or above, and professional terms (e.g., ‘thoracoscope’) must be explained simply.”

2.3 Evaluation Tools

2.3.1 Readability Evaluation

English Reading materials, readability analysis was conducted using Flesch Reading Ease (FRE) and Flesch-Kincaid Grade Level (FKGL), among which the FRES score ranged from 0 to 100 (the higher the score, the easier it is to read). The SMOG index reflects the years of education required to understand the text (for example, an index of 10 indicates approximately the reading level of Grade 10). All indicators are calculated through the Readable online tool.

The average sentence length of the Chinese version of the missionary materials is compared.

2.3.2 Information Quality Assessment

DISCERN was developed by D. Charnock as an instrument to analyze the quality of health information^[12]. The DISCERN tool was used for information quality assessment, which included three dimensions: reliability (8 items), treatment details (7 items), and overall quality (1 item). Each item was scored on a scale of 1 to 5 points (total score 16 to 80 points). The scoring criteria are defined as: >70 points (excellent), 60-69 points (good), 50-59 points (average), and <50 points (poor).

2.4 Data Collection and Statistical Analysis

From September 1st to September 15th, 2025, materials will be generated through the official API interfaces of each model. After extracting the text, it will be imported into the evaluation tool to calculate the readability index. Two reviewers trained by DISCERN (deputy chief nurses of thoracic surgery with more than 10 years of working experience and nursing education experts) independently scored and independently completed the information quality scoring. If the score difference was greater than 1 point, consensus was reached through discussion. SPSS 26.0 software was used, and the measurement data were expressed as “mean \pm standard deviation ($\bar{x} \pm s$)”. The differences among the three models were analyzed using the Kruskal-Wallis H test (for non-normally distributed data), the differences between the Chinese and English versions were analyzed using the paired sample t-test, the reliability of the raters was analyzed using the intraclass correlation coefficient (ICC), and the correlation analysis was analyzed using the Pearson correlation coefficient. The test level $\alpha=0.05$.

3.Results

3.1 English Readability Analysis

There were significant differences in FRE and FKGL among the English versions of the three models (all $P < 0.05$). The specific results are shown in Table 1: The FRE of DeepSeek V3 was significantly higher than that of ChatGPT-o3 and Grok3,

while FKGL was significantly lower than that of ChatGPT-o3 and Grok3. The FRE of ChatGPT-o3 was significantly higher than that of Grok3, and the FKGL was significantly lower than that of Grok3 ($P=0.014$). The readability ranking of the English version is indicated as: DeepSeek-V3>ChatGPT-o3>Grok3.

Table 1 Comparison of readability metrics of English educational materials generated by three AI models ($\bar{x}\pm s$)

Model	Sample Size	Flesch Reading Ease (FRE)	Flesch-Kincaid Grade Level (FKGL)
Chatgpt-o3	3	67.36 \pm 0.74	6.56 \pm 0.36
Deepseek-V3	3	80.36 \pm 1.18	4.83 \pm 0.12
Grok3	3	45.67 \pm 1.65	11.93 \pm 0.17
H		7.82	
P		$P<0.05$	

3.2.2 Readability of Chinese version

There were significant differences in the average sentence lengths of the Chinese versions of the three models ($H=7.20$, $P<0.05$), and the specific results are shown in Table 2. The average sentence length of Grok3 is significantly shorter than that of ChatGPT-o3 and DeepSeek V3. The average sentence length of DeepSeek V3 was significantly shorter than that of ChatGPT-o3 ($P=0.014$). It indicates that the ranking of reading fluency of the Chinese version is: Grok3>DeepSeek V3>ChatGPT-o3

Table 2 Comparison of Readability Indicators of Educational Materials in Chinese Versions of Three AI Models ($\bar{x}\pm s$)

Model	Sample Size	Average Sentence Length
Chatgpt-o3	3	27.81 \pm 1.47
Deepseek-V3	3	26.75 \pm 1.18
Grok3	3	17.74 \pm 1.02
H		7.2
P		$P<0.05$

3.3 DISCERN Information quality analysis

3.3.1 Rater reliability

Two reviewers scored the DISCERN scale of 18 materials with excellent reliability. The specific results are as follows: DISCERN Total score ICC=0.92 (95% CI: 0.925, 0.998, $P<0.001$)

3.3.2 DISCERN Discern Total Score Comparison of Information quality

The DISCERN total scores of the Chinese and English versions of the three models were all at the “good - excellent” level, and there were significant differences among the groups (all $P < 0.05$). The specific results are shown in Table 3. In the English version, the total score of ChatGPT-o3 is significantly higher than that of Grok3, and that of DeepSeek V3 is significantly higher than that of Grok3. The differences between ChatGPT-o3 and DeepSeek V3 are nearly significant. In the Chinese version, the total score of ChatGPT-o3 is significantly higher than that of Grok3, and that of DeepSeek V3 is significantly higher than that of Grok3. The differences between ChatGPT-o3 and DeepSeek V3 are nearly significant.

The paired sample t-test showed that there were no significant differences in the DISCERN total scores of Chinese and English among the three models (ChatGPT-o3: $t=1.28$, $P=0.27$; DeepSeek-V3: $t=-1.85$, $P=0.15$;) Grok3: $t=2.31$, $P=0.10$), but the total score of the English version of Grok3 (63.17 \pm 0.94) was higher than that of the Chinese version (59.00 \pm 0.89), suggesting that the quality stability of its Chinese information was relatively weak.

Model	English Version	Chinese Version	English Inter-group
Chatgpt-o3	71.17±1.17	70.5±0.55	t=1.28, P=0.27
Deepseek-V3	66.00±0.89	67.83±0.75	t=-1.85, P=0.15
Grok3	63.17±0.94	59.00±0.89	t=2.31, P=0.10
H(English)	9.23		
P(English)	0.017		
H(Chinese)	9.87		
P(Chinese)	0.007		

4. Discussion

4.1 Differences in readability of Materials generated by the three LLMS and the reasons

This study found that the three LLMS demonstrated significant “language specificity” in terms of readability between the Chinese and English versions: DeepSeek V3 was the best in the English version, and Grok3 was the best in the Chinese version. This result is closely related to the characteristics of the training data of the models and the direction of language optimization.

The English version of DeepSeek V3 has outstanding readability, which may be attributed to its pre-training optimization on English medical texts. The training data of this model contains a large number of English patient education manuals, such as the public educational materials of Mayo Clinic and Johns Hopkins Hospital, and has undergone special fine-tuning for “popularization of medical information”, which can precisely control the sentence length and vocabulary difficulty. The average sentence length of the Chinese version of Grok3 is the shortest, which is speculated to be related to its core positioning of “efficient reasoning”. This model prioritizes the “short sentence splitting” strategy when generating Chinese, which, although it enhances fluency, may also lead to a slight decrease in content coherence.

The readability of the Chinese and English versions of ChatGPT-o3 is balanced, which is in line with its positioning as a “general-purpose LLM”. The training data of this model covers multiple languages and fields. It performs stably in the balance of “readability - professionalism”, but is slightly inferior to DeepSeek V3 (English) and Grok3 (Chinese) in the extreme optimization of a single language. The English version of Grok3 has the poorest readability, mainly because the content generated by this model contains unexplained professional terms and the sentence structure is complex, beyond the comprehension ability of patients.

4.2 Differences in Information Quality of Materials Generated by the Three LLMS and Clinical Implications

In terms of information quality, the overall performance of the Chinese and English versions of ChatGPT-o3 is the best, followed by DeepSeek V3, and Grok3 is the worst. This result is directly related to the model’s medical knowledge reserve and content generation logic. The training data of ChatGPT-o3 contains a vast amount of medical literature and clinical diagnosis and treatment norms, and can accurately generate content that conforms to clinical consensus, such as quitting smoking two weeks before surgery and getting out of bed and moving around 24 hours after surgery. However, the quality of Grok3 information is insufficient mainly due to the relatively low proportion of medical and biomedical data in it, and there is a problem of “oversimplification”, such as only describing the symptoms of atelectasis as “breathing difficulties”, without mentioning key accompanying symptoms such as “chest pain and cough”.

In addition, there are still inconsistent issues in the use of terms in the Chinese version. For instance, “thoracoscopy” is sometimes expressed as “chest wall endoscope”, reflecting the insufficiency of LLM in standardizing Chinese medical terms. It is suggested that in subsequent studies, the “Uniform Requirements for Chinese Terminology” be added to the Prompt, and at the same time, a “Common Chinese Terminology Database for Thoracic Surgery” be established to provide a basis for terminology norms for AI-generated content.

4.3 Research Limitations and Future Directions

This study has certain limitations. First, the sample size is relatively small, with only three pieces of material generated for each model, which may lead to random errors. Subsequently, the sample size can be expanded to ten pieces of material for each model to enhance the extrapolation of the results. Second, the subjective evaluation of patients was not included. In the future, patients undergoing thoracoscopic lobectomy can be invited to rate the “understanding” and “practicality” of the materials, and a “subject-objective” combined assessment system can be formed by combining objective indicators. Thirdly, the impact of “version updates” on the model was not taken into account. LLMS have a fast iteration speed, and regular updates and research are needed in the future to track changes in model performance.

Future research can be carried out from two aspects: One is to explore the collaborative editing model of “AI + clinical doctors”, where AI generates the initial draft and doctors supplement professional details to improve the quality of materials; Second, optimize the Prompt design for specific groups, such as elderly patients and foreign patients, to generate more personalized educational materials and meet the diverse clinical needs.

5. Conclusion

There are significant differences in readability and information quality among the educational materials for patients undergoing thoracoscopic lobectomy generated by the three LLMS: DeepSeeking V3 has the best readability in the English version; Grok3 has outstanding reading fluency in the Chinese version; and ChatGPT-o3 has a balanced overall performance in both Chinese and English versions. The consistency of terms in the Chinese version still needs to be prioritized for optimization. When applying in clinical practice, the model should be selected based on language requirements. For English scenarios, DeepSeek V3 is preferred; for Chinese scenarios, Grok3 can be chosen but the information quality needs to be reviewed. For dual-language scenarios, ChatGPT-o3 is preferred, and the AI-generated content should be reviewed and supplemented by thoracic surgery professionals. Conclusion 5: Ensure the Safety and effectiveness of materials

There are significant differences in readability and information quality among the educational materials for patients undergoing thoracoscopic lobectomy generated by three types of LLMS: In the English version, DeepSeek V3 has the best readability. In the Chinese version, Grok3 has outstanding reading fluency. The overall performance of ChatGPT-o3 in both Chinese and English versions is balanced (with a balance between readability and information quality). The consistency of terms in the Chinese version still needs to be prioritized for optimization. When applying in clinical practice, models should be selected based on language requirements (DeepSeek V3 is preferred for English scenarios, Grok3 for Chinese scenarios but the quality of information needs to be reviewed, and ChatGPT-o3 is preferred for multilingual scenarios). The AI-generated content should be reviewed and supplemented by thoracic surgery professionals to ensure the safety and effectiveness of the materials.

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Conflict of Interests

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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New Trends and Hot Spots in the Study of Diabetic Peripheral Neuropathy: A Bibliometric Analysis

Jiajie Li^{1,2}, Jiaqi Wang³, Yaping Wang⁴, Xinyi Huai¹, Guirong Zhang¹, Zezhu Li¹, Jiabao Liao^{1,2}, Qin Li^{4*}, Weibo Wen^{1*}

1.The First School of Clinical Medicine, Yunnan University of Chinese Medicine, Kunming, 650500, China

2.Joint Graduate School of Traditional Chinese Medicine of China, Suzhou, 215105, China

3.School of Life Sciences, East China Normal University, Shanghai, 200241, China

4.School of Basic Medical Sciences, Yunnan University of Chinese Medicine, Kunming, 650500, China

*Corresponding author: Qin Li, 736870541@qq.com (LQ); Weibo Wen, wenweibo2020@163.com (WW)

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Abstract: Objective: Diabetic Peripheral Neuropathy (DPN) is a common chronic complication of diabetes that currently has no therapeutic recourse. Advanced DPN stages are characterized by severe symptoms that place a huge burden on patients and healthcare systems. To the best of our knowledge, research hotspots within the field of DPN are yet to be visually analyzed, and so is the exploration of developmental dynamics within the same discipline. **Methods:** Herein, DPN articles published between 2002 and 2022 were retrieved from the Web of Science Core Collection database. Following that, bibliometric analysis was performed on these articles using CiteSpace, VOSviewer, Microsoft Excel, and R-bibliometrix tools. **Results:** We retrieved 2,761 DPN articles involving 11,605 researchers from 1,140 institutions in 99 countries/regions. The United States was the country/region with the highest number of publications. The most productive author was Malik Rayaz A from the University of Manchester, which was the most productive institution. The most co-cited journals were Diabetes Care, Pain, and Neurology. On the other hand, #0 neuropathic pain, #1 neuropathic pain treatment and #2 peripheral neuropathy were the most clustered keywords in co-cited references. Based on the clustering of keywords, timeline graphs, and citation bursts, “risk”, “corneal confocal microscopy” and “systematic review” were identified as the key issues for future DPN research. **Conclusion:** This article summarizes the current DPN research status and focus areas, reveals the future development trend, and points out potential research directions for DPN scholars.

Keywords: Diabetic Peripheral Neuropathy; Bibliometric Analysis; VOSviewer; CiteSpace; R-bibliometrix

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1.Introduction

With its continuously growing prevalence worldwide, Diabetes Mellitus (DM) is one of the major public health problems in the 21st century ^[1]. Surveys have revealed that almost half of diabetic patients are unaware of their condition ^[2], exposing them to numerous acute and chronic complications as the disease progresses. Diabetic Peripheral Neuropathy (DPN), a common chronic diabetic complication, has symptoms linked to peripheral nerve dysfunction that severely affect patients' Quality of Life (QoL) and places a heavy burden on physicians and healthcare systems ^[3]. The International

Diabetes Federation (IDF) regularly publishes the Diabetes Atlas report, providing the most up-to-date information on the epidemiology and associated impact of diabetes worldwide. This publication has influenced the awareness levels and importance of diabetes among governments, policymakers, researchers, and the general public. Diabetes foot-related complications such as DPN were examined in greater depth in the IDF Diabetes Atlas 2022 Reports, and available information suggests that DPN prevalence is higher in Africa, and South and Central America, with one study in Senegal discovering that 72% of diabetes patients had DPN^[4]. The growing DPN prevalence as predicated by the rising population of diabetic patients, necessitates more DPN research.

Although the pathogenesis of DPN remains unclear, the development and progression of diabetic complications such as DPN have been associated with insulin resistance, hyperglycemia, and dyslipidemia, along with abnormalities in the metabolism of nonessential amino acids^[5]. In a high-glucose environment, Schwann cell-derived exosome miR-21 may be involved in nerve growth regulation and, thus, DPN progression via the AKT signaling pathway^[6]. Previous clinical research has shown that serine and glycine levels are lowered in metabolic syndrome patients and that systemic serine and glycine reduction is linked with impaired vision and peripheral neuropathy^[7-8]. Furthermore, recent research has revealed the serine deficiency mechanism; serine deficiency accelerates DPN by regulating sphingolipid metabolism, and dietary serine supplementation can alleviate DPN^[9]. As a result, serine-based modulators may be a novel therapeutic avenue for DPN treatment. Additionally, a recent study revealed that intestinal flora-mediated DPN pathogenesis could be associated with intestinal barrier dysfunction, antigenic load, and the exacerbation of systemic inflammatory responses, and through Random Control Trials (RCTs), it also demonstrated that colony transplantation targeting intestinal flora could be a new strategy for treating DPN^[10]. Despite promising research findings on the epidemiology and pathogenesis of DPN, there is still no medical recourse to prevent DPN or manage its symptoms. Glycemic control, nutritional supplementation, and anti-oxidative stress, which are effective in early-stage patients but less effective in reversing severe symptoms in advanced stages of the disease, are the primary DPN therapies^[11].

Given its significant clinical challenges, DPN remains a research focus among scholars in various countries and regions. In recent years, relevant bibliometric assessments have been conducted in several areas with high diabetic prevalence. However, there is no bibliometric analysis specifically for DPN. Furthermore, existing DPN studies have only addressed peripheral neuropathic pain symptoms in diabetes, with the literature summarized limited to the 2011-2021 decade^[12]. Therefore, this study visualized the number of DPN research articles, authors, countries/regions, institutions, references, and keywords between 2002 and 2022 using bibliometric analysis to summarize the current DPN research status, identify focus areas, and explore the future development trend, ultimately highlighting valuable research directions for DPN scholars.

2. aterials and methods

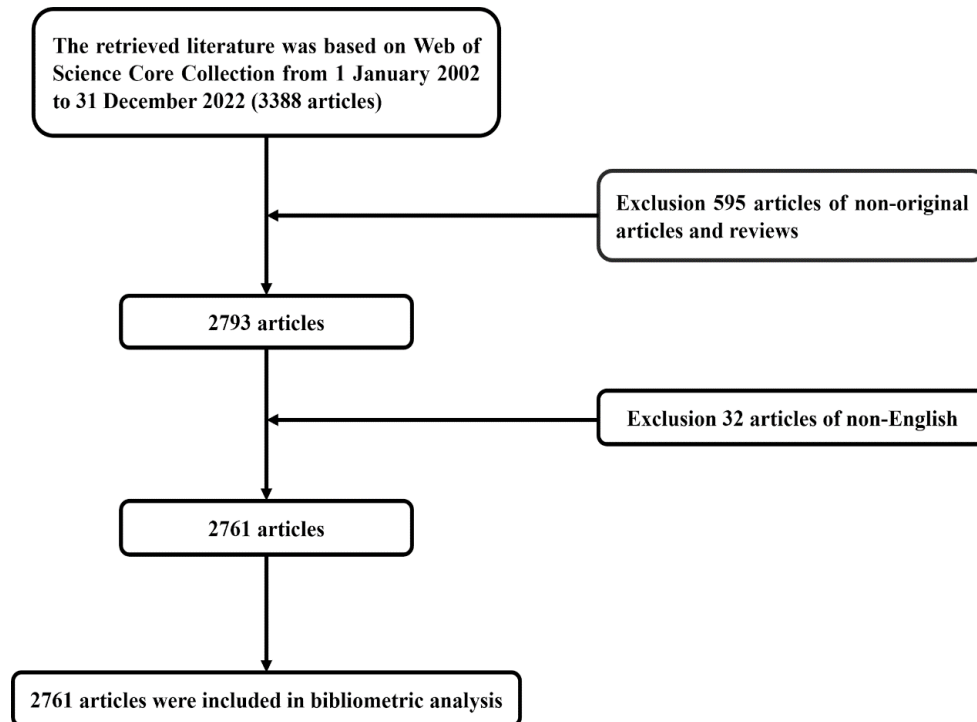
2.1 Literature sources and search strategies

We searched the Web of Science Core Collection (WOSCC) database for DPN articles published between 2002 and 2022. The search strategy was: TS="diabetic peripheral neuropathy" OR "diabetes peripheral neuropathy" OR "diabetic peripheral neuropath". Data retrieval was completed on October 11, 2023, to ensure the accuracy of the results. Article type was limited to original articles and reviews, whereas language was limited to English. After strict screening, the study data were exported for software analysis (Fig.1).

2.2 Analysis methods

Data were analyzed and visualized using CiteSpace 6.1.6, VOSviewer 1.6.18, Microsoft Excel 2021, and R (version 4.3.1) package "bibliometrix" (<https://www.bibliometrix.org>). Specifically, detailed information on the articles' country/region of origin, authors, references, and keywords were analyzed using CiteSpace^[13] and VOSviewer^[14-15]. On the other hand, we analyzed the articles' average annual citations using the R-bibliometrix package, and presented a map of the distribution of postings by country/region and a graphical representation of the authors' posting volume through time-varying relationship mapping. Furthermore, we constructed a trend graph of the number of articles issued and the average yearly citation using Microsoft Excel 2021, and presented a quantitative visualization of multiple data.

Fig. 1 Flowchart of the literature data screening process.

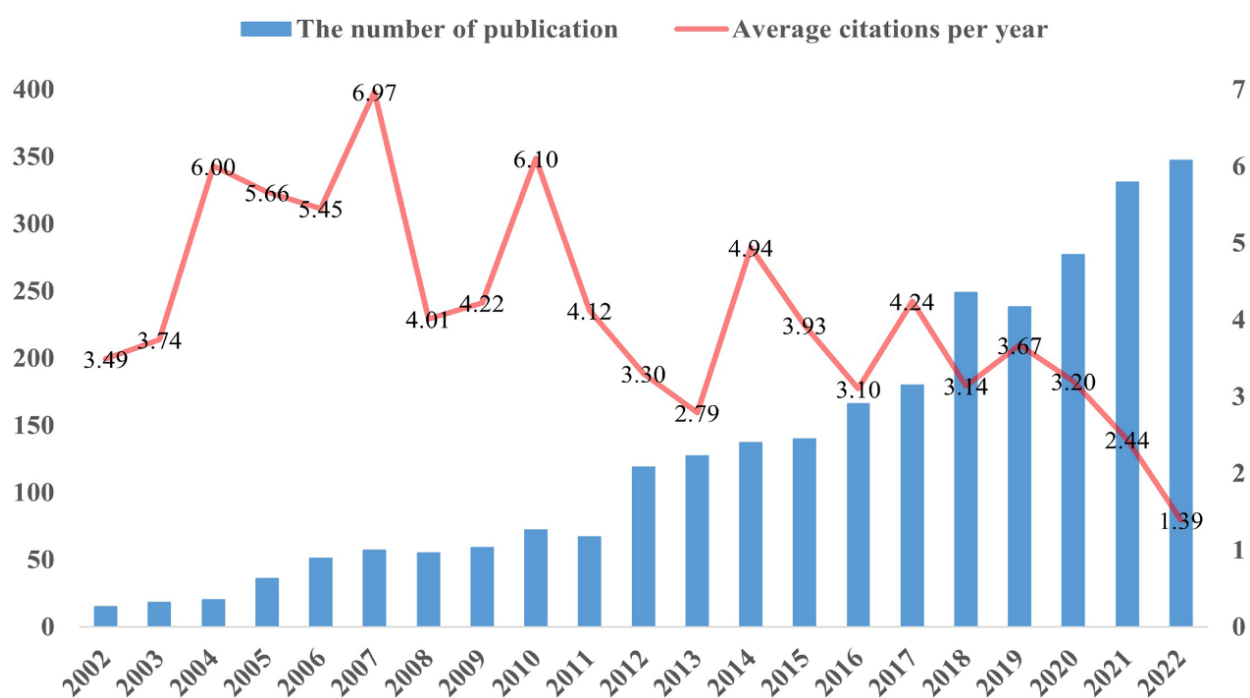


3.Results

3.1 Annual publication and citation trends

Our search for DPN-related research in the WOSCC database yielded 2,761 articles. The trend of annual DPN publications and citations was in two phases: 2002-2011, which is the early stage of research with < 100 publications per year, and 2012-2022, which is the period of significant growth in DPN research, with the number of publications in 2022 (n=347) being approximately three times that in 2012 (n=119) (Fig. 2). Regarding the average annual citations, 2007 had the highest average (6.97), while both 2004 and 2010 had an average > 6, which could be attributed to the fact that there were fewer DPN studies between 2002 and 2011. These results indicate that DPN studies gained momentum over the last decade and continue to interest researchers.

Fig. 2 Trends in the number of publications and average citations per year.



3.2 Countries/regions and institutions

We found that 1,140 institutions from 99 countries/regions contributed to DPN research. The United States and China led the first tier of countries in the number of articles published in each country/region with 844 and 695 articles, respectively (Fig. 3A), followed by the United Kingdom, India, and Germany, which had 274, 141, and 105 articles, respectively (Table 1). Notably, the mediational centralities of the United States and the United Kingdom were much higher compared to other countries at 0.59 and 0.37, respectively. The mediational centralities of the remaining countries were all < 0.1 . We constructed the cooperation network of the top 20 countries/regions based on the number of articles issued using VOSviewer (Fig. 3B). Although China had a higher number of published articles and collaborations with most countries, the United States and the United Kingdom were more closely related to the countries they collaborated with. Notably, the UK had the most collaborations with US, Qatar, Australia, and Italy despite having the third-highest volume of publications.

Of the 1,140 institutions, 99 with ≥ 10 publications were analyzed to generate an institutional collaboration network map showing eight clusters (Fig. 3C). The University of Manchester in the UK came in first with 108 articles (Table 2), and it mainly collaborated with the UK-based Manchester Metropolitan University and the Qatar Foundation University in Qatar, among others. Although Pfizer Incorporated was not the most prominent organization regarding the number of articles published, it had the largest cluster. Furthermore, besides collaborating with institutions in its cluster, Pfizer Incorporated collaborated with institutions in the other four clusters. Pfizer Incorporated published 200 diabetes-related original articles or reviews between 2002 and 2022, with DPN accounting for 47.5% (95/200) of all its publications, implying that the company has invested substantially in developing DPN treatment drugs. The University of Manchester and Pfizer Incorporated were followed by the University of Michigan (US), Shanghai Jiao Tong University (China) and Fudan University (China), which had 62, 46, and 38 publications, respectively.

Table 1 Top 20 countries/regions by number of articles.

Rank	Country/region	Records	Centrality	Rank	Country/region	Records	Centrality
1	USA	844	0.59	11	Qatar	70	0.03
2	China	695	0.08	12	Iran	63	0.04
3	England	274	0.37	13	Turkey	63	0
4	India	141	0.03	14	Netherlands	57	0.03
5	Germany	105	0.07	15	Spain	50	0
6	Canada	95	0.02	16	France	48	0.05
7	Japan	95	0.03	17	Taiwan	48	0.01
8	Italy	93	0.07	18	Brazil	45	0.02
9	Australia	89	0.04	19	Egypt	44	0.04
10	South Korea	79	0	20	Saudi Arabia	39	0.02

Table 2 Top 20 institutions by number of articles.

Rank	Institution	Records	Rank	Institution	Records
1	University of Manchester	108	11	Johns Hopkins University	31
2	Pfizer Incorporated	95	12	University of Calgary	28
3	University of Michigan	62	13	Capital Medical University	28
4	Shanghai Jiao Tong University	46	14	Weill Cornell Medicine - Qatar	27
5	Fudan University	38	15	Nanjing Medical University	27
6	University of Rochester	37	16	University of Miami	26
7	Manchester Metropolitan University	36	17	Southern Medical University	26
8	University of Kansas	36	18	Chinese Academy of Medical Sciences	26
9	University of Washington	35	19	Qatar Foundation	25
10	Queensland University of Technology	33	20	University of Oxford	25

A

World map visualization showing the count of COVID-19 research nodes per country. The USA and China are the most prominent nodes, indicated by dark blue shading. A legend indicates the count scale from 1 to 844. A small logo is visible in the bottom right corner.

B

Network visualization showing connections between countries. The USA and China are central nodes, with many lines connecting them to other countries like Japan, Canada, and the UK. The network is color-coded by country.

C

Network visualization showing connections between research institutions. The USA and China are central nodes, with many lines connecting them to other institutions like the University of Manchester, Johns Hopkins University, and Peking University. The network is color-coded by institution.

The authors of the 2,761 articles were analyzed, yielding 11,605 researchers involved in DPN research, including 23 authors with ≥ 10 publications. Additionally, author collaborations across the 2,761 articles were analyzed using CiteSpace yielding 790 nodes and 1,458 links. Node sizes correlated with the number of publications for each author, with different node colors indicating different publication dates, and warmer and cooler colors representing more recent years and more distant years, respectively (Fig. 4A). The collaborative network shows that Malik Rayaz A (as the center) worked closely with Petropoulos Ioannis N, Alam Uazman, Ponirakis Georgios, Khan Adnan, Efron Nathan, Boulton Andrew J M and other researchers in the last three years. Notably, although Parsons Bruce had many publications and several collaborations with Emir Birol and other researchers, their studies were primarily conducted before 2020.

We analyzed the top 20 authors using the “bibliometrix” R package (version 4.3.1) to explore the relationship between authors’ publication volume and time change. We constructed a graph in which node sizes on the line represented the number of articles published by the authors each year and node colors represented the total number of citations of the authors’ articles each year, with darker (color) dots indicating more citations (Fig. 4B). Compared to other years, the number of publications by most authors increased significantly in 2021, with nine researchers publishing \geq five articles (Fig. 4B). Malik Rayaz A was the author with the highest number of publications with 64 total citations (Fig. 4B). Interestingly, Marshall Andrew had

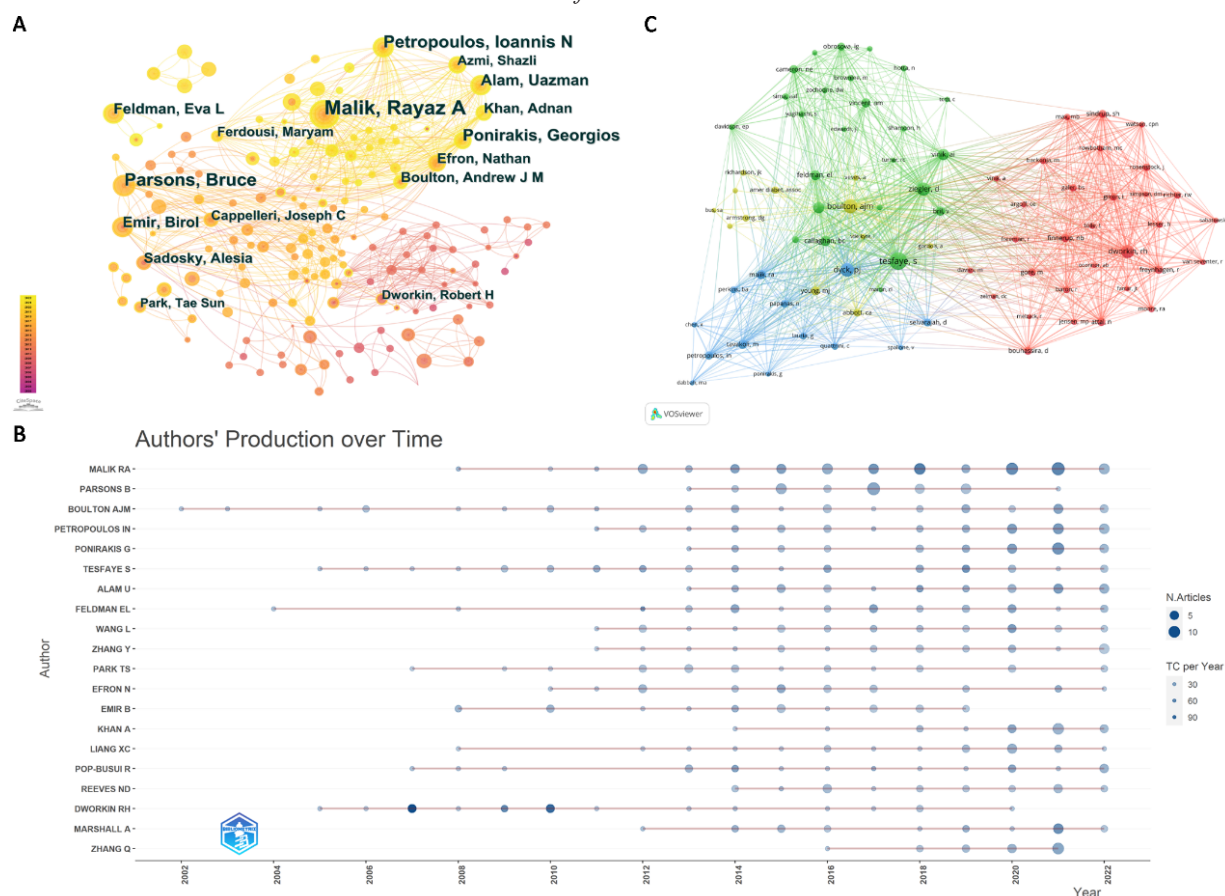
the highest total number of citations for each publication year with 118 and 91 total citations in 2007 and 2010, respectively, corroborating the average annual citation results illustrated in Figure 1.

We analyzed the co-cited authors through VOSviewer, which yielded 48,235 co-cited authors, of which the top ten authors were all cited > 300 times (Table 3). Prof. Tesfaye S from the British Sheffield Teaching Hospitals NHS Foundation Trust, Academic Unit of Diabetes and Endocrinology, was the top-ranked author, having published more review articles on pathogenesis, disease diagnosis, screening, and early intervention to summarize and evaluate DPN research [16-17]. Boulton AJM and Dyck PJ were ranked second and third, respectively. We analyzed 81 authors with ≥ 100 co-citations using the strength of association algorithm to generate an author co-citation network map (Fig. 4C). These co-cited authors were clustered into four categories based on their strong associations with four researchers: Tesfaye S, Boulton AJM, Dyck PJ, and Dworkin RH (Fig. 4C).

Table 3 Top 10 authors by number of articles and top 10 authors by number of co-citations.

Rank	Author	Records	Rank	Author	Records
1	Malik Rayaz A	64	1	Tesfaye S	1119
2	Parsons Bruce	38	2	Boulton AJM	749
3	Petropoulos Ioannis N	29	3	Dyck PJ	692
4	Ponirakis Georgios	28	4	Dworkin RH	648
5	Alam Uazman	23	5	Ziegler D	639
6	Feldman Eva L	20	6	Vinik AI	482
7	Emir Birol	17	7	Pop-busui R	476
8	Efron Nathan	16	8	Callaghan BC	390
9	Khan Adnan	15	9	Feldman EL	376
10	Boulton Andrew J M	15	10	Tavakoli M	331

Fig. 4 (A) Visualization network of author collaborations. (B) Top 20 authors' publications versus time. (C) Collaboration network of co-cited authors.



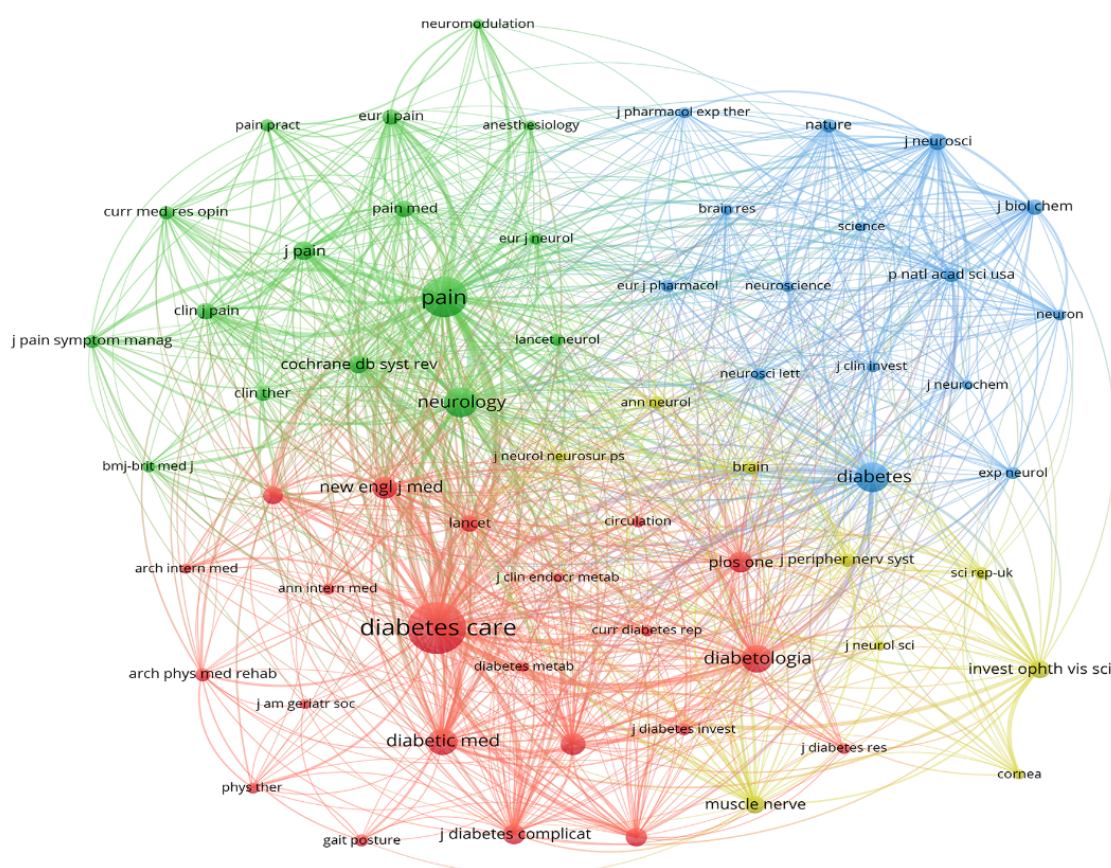
3.4 Co-cited journals

We screened 62 co-cited journals with ≥ 300 citations using VOSviewer to generate a co-occurrence network graph (Fig. 5), in which the top 10 co-cited journals all had >1000 citations (Table 4). Notably, compared to other journals, Diabetes Care had far more citations (8244 citations). Pain (4908 citations) and Neurology (2424 citations) came in second and third, respectively. Journals published in the United States and in the JCR Q1 partition dominated the top 10 rankings, with the New England Journal of Medicine having the highest Impact Factor (IF = 158.5). Four clusters were observed in which Pain, Diabetes and Diabetologia appeared to all have strong co-citation relationships with Diabetes Care (Fig. 5), demonstrating the importance placed on the reference value of high-quality journals in DPN research.

Table 4 Top 10 journals by number of co-citations.

Rank	Co-cite Journal	Records	Country	IF(2023)
1	Diabetes Care	8244	United States	Q1/16.2
2	Pain	4908	Netherlands	Q1/7.4
3	Neurology	2724	United States	Q1/9.9
4	Diabetes	2687	United States	Q1/7.7
5	Diabetologia	2392	Germany	Q1/8.2
6	Diabetic Medicine	2129	England	Q3/3.5
7	Diabetes Research Clinical Practice	1502	Netherlands	Q2/5.1
8	New England Journal of Medicine	1446	United States	Q1/158.5
9	Plos One	1380	United States	Q2/3.7
10	Journal of Diabetes and its Complications	1273	United States	Q3/3.0

Fig. 5 Diagrams of co-occurrence network of co-cited journals.



3.5 Co-cited references

We used VOSviewer to visualize and analyze the 106 references that were cited ≥ 50 times among the 71,054 references in the 2,761 DPN articles, generating a co-citation network graph of the references (Fig. 6A). The graph showed three notable clusters with the largest node having a maximum of 354 citations, followed by two articles published by Pop-Busui R and Boulton AJ, with 255 and 235 citations, respectively (Table 5), demonstrating the specific information of the top 10 DPN-related co-citations. Notably, the top three co-cited references were all reviews and published in Diabetes Care, correlating with Diabetes Care as the most cited journal. Furthermore, Prof. Tesfaye S from the UK was the most cited author, having published two of the top ten cited articles. The two articles were published in Diabetes Care (IF=16.2) and the New England Journal of Medicine (IF=158.5), showing the professor's significant contribution and influence in DPN research.

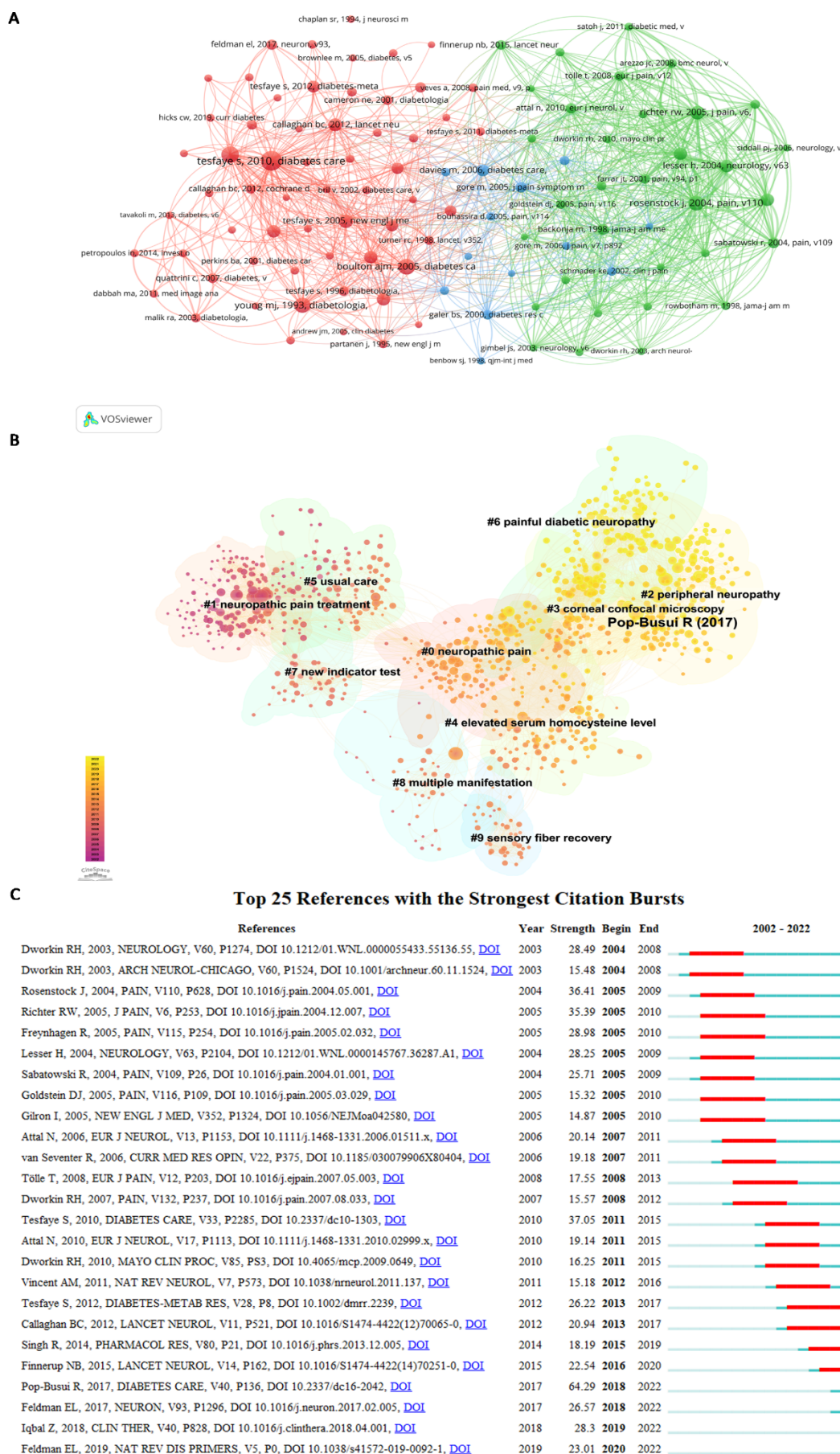
The keywords in the 71,054 references were clustered using the clustering function of the LLR algorithm in CiteSpace (Fig. 6B). The top 10 clusters included: #0 neuropathic pain; #1 neuropathic pain treatment; #2 peripheral neuropathy; #3 corneal confocal microscopy; #4 elevated serum homocysteine level; #5 usual care; #6 painful diabetic neuropathy; #7 new indicator test; #8 multiple manifestation; and #9 sensory fiber recovery (Fig. 6B). The top numbers had more articles in the cluster. Specifically, #0 neuropathic pain had the most articles, followed by #1 neuropathic pain treatment, and #6 painful diabetic neuropathy was the key element of the literature cited in recent years. The node in #6 had the warmest color, representing the cluster in which the articles were primarily from recent years, implying that the focus of DPN researchers has recently been revolving around addressing neuropathic pain symptoms. On the other hand, #3 corneal confocal microscopy represented an emerging hotspot in DPN research. The Confocal Microscope is currently considered one of the most valuable devices for clinically diagnosing and studying certain diseases.

We also analyzed the burst of cited references. Figure 6C shows the top 25 references based on the number of cited bursts, with each article having 4-5 years of citation bursts. Four articles in the field could still be in the strong citation phase. A statement on diabetic neuropathy published by Pop-Busui R and other members of the American Diabetes Association in Diabetes Care in 2017 had the strongest citation strength. This article reviewed the screening, diagnosis, and treatment of various diabetic neuropathies, including distal symmetric polyneuropathy, diabetic autonomic neuropathies, and atypical neuropathies^[18], respectively, offering researchers a useful theoretical reference.

Table 5 Top 10 references by number of co-citations.

Rank	Title	Article Type	Year	Total Citations	Author	Journal
1	Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments	Review	2010	354	Tesfaye S	Diabetes Care
2	Diabetic Neuropathy: A Position Statement by the American Diabetes Association	Review	2017	255	Pop-Busui R	Diabetes Care
3	Diabetic neuropathies: a statement by the American Diabetes Association	Review	2005	235	Boulton AJM	Diabetes Care
4	A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population	Article	1993	223	Young MJ	Diabetologia
5	Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial	Article	2004	199	Rosenstock J	Pain
6	Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial	Article	2005	182	Richter RW	Pain
7	Vascular risk factors and diabetic neuropathy	Article	2005	177	Tesfaye S	New England Journal of Medicine
8	Diabetic neuropathy: clinical manifestations and current treatments	Review	2012	161	Callaghan BC	Lancet Neurology
9	Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial	Article	2004	154	Lesser H	Neurology
10	A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy	Article	1994	154	Feldman EL	Diabetes Care

Fig. 6 (A) Diagram of co-citation network of references. (B) Cluster diagram of co-cited references. (C) Top 25 References with the Strongest Citation Bursts.



3.6 Keywords analysis

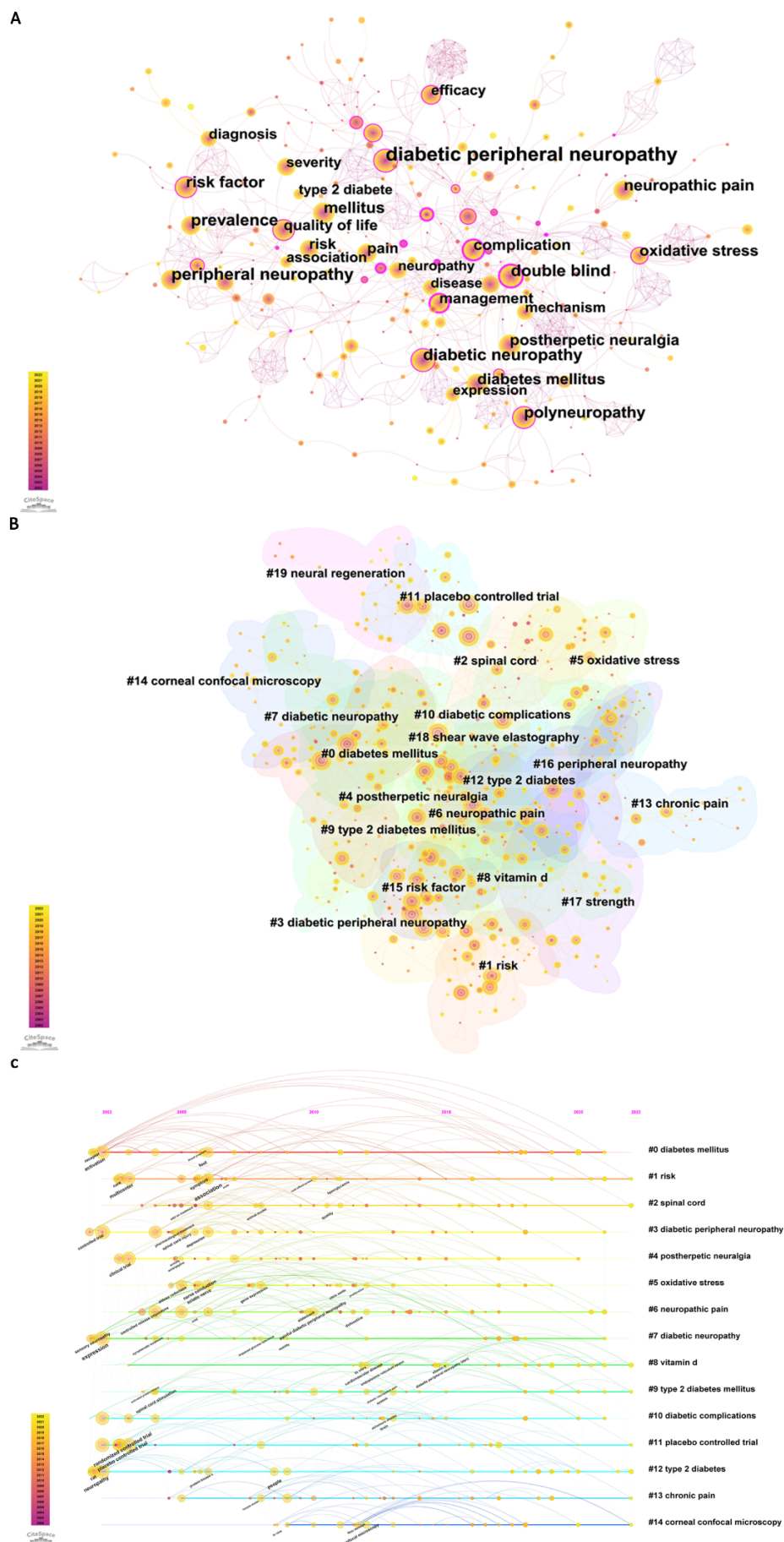
CiteSpace was used to visualize the keywords of the 2,761 DPN articles from different perspectives. Figure 7A shows the co-occurrence network of 456 keywords. Besides the keywords retrieved for this study, the other keywords with a high frequency of occurrence were peripheral neuropathy (n=422), diabetic neuropathy (n=342), double-blind (n=332), and prevalence (n=329). Among these keywords, double-blind had high centrality (Table 6), showing the importance of using double-blind experimental methods in DPN clinical research. Table 6 shows the top 20 keywords with the highest frequency and their centrality. Complication had the highest centrality, followed by management, implying the importance of studying various diabetic complications and their management.

The keyword information was further analyzed using cluster and timeline plots (Figs. 7B-C). We found that #11 placebo-controlled trial and #12 type 2 diabetes were the keywords with the longest duration, indicating that DPN research has been based on placebo-controlled trials and type 2 diabetes correlation with DPN. Besides #4 postherpetic neuralgia and #5 oxidative stress, the other categories with ongoing research included #1 risk, #2 spinal cord, #8 vitamin D, #13 chronic pain, and #14 corneal confocal microscopy. Furthermore, we analyzed the keyword burst phenomenon, and the top 25 keywords with the most citation bursts are shown in Supplementary Figure S1. Notably, foot ulceration and blood flow had the longest citation bursts, showing the importance of diabetic foot complications in DPN research before 2013. Postherpetic neuralgia, which also serves as a type of peripheral neuropathic pain had the highest citation intensity. Additionally, researchers were interested in the efficacy of various medications in treating postherpetic neuralgia and diabetic peripheral neuropathic pain. Gabapentin also had a high citation strength with a long burst period, implying that its underlying mechanism in treating DPN patients is a major research area. Systematic review, therapy, older adult, and adult are the four keywords from 2020 that are still in a strong citation burst period. This shows that DPN research has received more attention in multiple directions in recent years.

Table 6 The 20 keywords that appear most frequently in articles.

Rank	Keywords	Records	Centrality	Rank	Keywords	Records	Centrality
1	diabetic peripheral neuropathy	1193	0.1	11	postherpetic neuralgia	231	0.01
2	peripheral neuropathy	422	0	12	oxidative stress	229	0.16
3	diabetic neuropathy	342	0.12	13	diabetes mellitus	215	0
4	double blind	332	0.26	14	risk	195	0.04
5	prevalence	329	0.02	15	management	179	0.26
6	risk factor	265	0.11	16	pain	176	0.03
7	mellitus	261	0.05	17	quality of life	169	0.18
8	polyneuropathy	261	0.11	18	association	158	0.04
9	neuropathic pain	247	0	19	diagnosis	154	0.04
10	complication	237	0.36	20	severity	153	0.03

Fig. 7 (A) Diagram of co-occurrence network of keywords. (B) Network graph of the top 20 keyword clusters. (C) Timeline graph of keywords.



4. Discussion

Herein, we conducted a comprehensive and systematic bibliometric analysis of DPN articles published over the past 20 years. After a rigorous screening process, 2,761 articles from 99 countries/regions were obtained. We visualized and analyzed various aspects of the identified DPN articles, including yearly issuance, citation trends, countries/regions, institutions, authors, cited journals, references, and keywords to explore the changes in research trends and future research directions in the field of DPN. As a result, this study fills an existing knowledge gap in DPN and offers an essential reference for developing research on chronic diabetic complications.

4.1 General information

Publication of DPN articles has been largely on an upward trend since 2002 (Fig. 2). Specifically, the growth trend can be divided into two phases: 2002 to 2011, in which the rise in DPN research was relatively more sluggish, and the past ten years (2012-2022) in which the publication of DPN articles has increased significantly. The growth trend in the published DPN articles implies that DPN-related research is taking shape and will continue to be a developing and progressing field of study. Globally, the United States had the most DPN publications, followed by China, with both countries leading other nations/regions by a wide margin. Additionally, seven and six of the top 20 research organizations in terms of publications were from the United States and China, respectively. Notably, although both the United States and China had more publications than other countries, the United States had a significantly higher relative centrality than China, implying a higher quality and impact research from the United States. Prof. Malik Rayaz A of the University of Manchester, whose main research interests are DPN diagnosis and treatment, was the author with the most publications. On the other hand, Prof. Tesfaye S of British Sheffield Teaching Hospitals was the author with the most citations. Six of the top ten cited journals belonged to the JCR Q1 partition: Diabetes Care (IF=16.2); Pain (IF=7.4); Neurology (IF=9.9); Diabetes (IF=7.7); Diabetologia (IF=8.2); and the New England Journal of Medicine (IF=158.5).

4.2 Knowledge base

The 25 references with the strongest citation bursts were predominantly RCTs on pregabalin in treating postherpetic neuralgia conducted before 2010^[19-21] and painful DPN patients^[22-25]. These trials provide better evidence of the efficacy of pregabalin in treating neuropathic pain. In other drug efficacy studies, using an active placebo in the trial that differed from that used in previous studies, Gilron I et al.^[26] discovered that the combination of gabapentin and morphine had superior efficacy in treating neuropathic pain than either of the two medications alone in patients with painful diabetic neuropathy or postherpetic neuralgia. Moreover, their study offers a framework for future trials comparing drug combinations with individual drugs. In 2006, Attal N et al.^[27] (who are members of the European Federation of Neurological Societies) published the first guidelines for neuropathic pain treatment by examining clinical RCTs conducted over the past few years in various neuropathic pain conditions and comprehensively evaluating the efficacy and safety of the drugs, initially forming an expert consensus on the pharmacologic treatment of neuropathic pain, thereby bridging the gap in the field. This study offers clinicians an effective approach to treating neuropathic pain and multiple strategies for novel pharmacological trials for neuropathic pain treatment. In 2010, they revised and updated the guidelines to better define the response profile of medications for neuropathic pain and accommodate the needs of clinicians^[28]. Despite years of experimental clinical trials, there is still no cure for DPN. Therefore, far from the past focus on the efficacy of various medications in treating DPN symptomatic pain, researchers have begun to delve more deeply into the mechanisms underlying diabetic neuropathy development since 2010. Discoveries on DPN pathogenesis have been beneficial in addressing all its aspects, from prevention to treatment^[29]. In a comprehensive review of DPN cellular mechanisms published in Nature Reviews Neurology, Vincent AM et al.^[30] proposed cellular mechanisms as therapeutic targets for DPN treatment. This review delved into the activation of multiple cellular mechanisms in different diabetic settings, and presented new targets and strategies for diabetic neuropathy treatment, specifically cell protection, oxidation inhibition, and lowering of inflammatory responses, after analyzing the interactions between the different mechanisms as well as existing therapeutic strategies. In 2017, the University of Michigan's Feldman EL Professor^[31] and experts from the University of Oxford, Max Planck Institute for Experimental Medicine and Aarhus University authored a review proposing a new vision of diabetic neuropathy mechanisms. Their review details the structure of the Peripheral

Nervous System (PNS) and outlines the pathways leading to peripheral nerve damage in diabetic nephropathy. Furthermore, it discusses systems biology insights summarized from recent research breakthroughs in biotechnology and bioinformatics, presenting novel ideas focusing on the axon-schwann cell relationships and associated bioenergetics. The article adds new insights into the pathogenesis of diabetic neuropathy, facilitating the development of mechanism-based treatments. Notably, 15 of the 25 articles with the most cited outbreaks were reviews. This finding suggests that researchers value summarizing and evaluating major research directions in DPN. Moreover, the key insights discussed in these articles have drawn more scholars to the advances in DPN research, leading to the continuous development of DPN-related investigations.

4.3 Emerging topics

Scholars performing bibliometric analysis could use the frequency of keywords to determine important research directions in specific study fields. Herein, we identified “risk factor”, “corneal confocal microscopy”, and “systematic review” as the key hotspots through an in-depth analysis of the timeline graph of keyword clustering and the burst of keyword-related citation information. Existing diagnostic tests are difficult to perform, and there is also a lack of neurological damage treatments. Therefore, identifying risk factors for DPN, determining the early stage of disease onset, and consequently, early interventions, are critical in clinically controlling DPN progression. A retrospective cohort study revealed that age >66 years, history of hypertension, lymphocyte count, and HbA1c levels above a certain threshold were risk factors for DPN development in adult DM patients^[32]. Specifically, HbA1c change represented the long-term glycemic variability, which was evaluated using the HbA1c (Cv-HbA1c) coefficient of variation. Furthermore, increased HbA1c variability showed a greater correlation with DPN occurrence in Type 2 Diabetes Mellitus (T2DM) patients, as revealed by multivariate logistic regression and ROC analyses^[33]. Besides general information and blood glucose-related laboratory indices, there has also been an increasing exploration of other risk factors. For the first time, recent studies assessed the correlation between Fibrinogen/Albumin (FAR) and DPN. According to the results, FAR levels were higher in DPN patients than non-DPN patients and correlated negatively with nerve conduction velocity, indicating a better predictive value compared to fibrinogen^[34]. Melatonin levels, a key research focus in the pathogenesis of diabetes and its complications, have been demonstrated by melatonin gene polymorphisms to be associated with DPN^[35]. Ethnicity is significant in genetic studies, and the role of melatonin gene polymorphisms in other ethnicities as well as in larger groups of DM patients may be studied in the future. Metformin treatment is also being investigated as a risk factor for DPN development, with long-term metformin use being associated with increased DPN risk in older veterans^[36]. In Asian populations, DPN risk with metformin is more pronounced in younger patients and rises with the metformin dose used^[37]. Corneal Confocal Microscopy (CCM), an ophthalmic marker, is useful in DPN diagnosis^[38], and can noninvasively detect peripheral neuropathy and its severity in T2DM patients^[39] as well as predict DPN occurrence^[40]. Screening for DPN (using CCM) and retinopathy in diabetic patients in primary care has enabled the early detection of neuropathy in patients^[41]. Artificial Intelligence (AI) has been widely used in medical practice in recent years, and CCM’s AI-based deep learning algorithm can be used to differentiate DPN patients and non-DPN patients^[42], as well as healthy populations, DM patients without neuropathy, and DM patients with neuropathy, after development and improvement, using an image classification method^[43]. To maximize its benefits, CCM has also been sought to differentiate between diabetic neuropathy types, such as inflammatory and non-inflammatory neuropathies^[44]. Additionally, a previous systematic evaluation and meta-analysis demonstrated the diagnostic value of CCM in DPN patients^[45]. As one of the important sources of validation in evidence-based medicine, systematic evaluations are widely used in DPN research to address clinical issues. When critically evaluated and analyzed, the conclusions based on clinical DPN studies of various aspects inform clinical decision-making. Regarding disease risk factors, smoking, Tumor Necrosis Factor- α (TNF- α), and vitamin D have been evaluated for their correlation with DPN occurrence in DM patients^[46-48]. Regarding disease diagnosis, a systematic evaluation of available evidence revealed that the monofilament test could be insufficiently sensitive for screening DPN^[49], whereas clinical electrophysiologic examination provides the best quantitative indication for DPN^[50]. Regarding disease treatment, vitamin B12 supplementation with metformin therapy^[51], herbal footbaths in conjunction with acupuncture^[52], spinal cord stimulation along with conventional therapy^[53], and various exercise regimens^[54] have all been shown to be effective in DPN treatment. This approach is currently propelling additional high-quality clinical DPN research and better complements existing research guidelines.

5.Limitations

Despite providing a comprehensive bibliometric analysis of DPN articles using several visualization tools and demonstrating the DPN-related research hotspots and trends, this study still has some limitations. Literature search was restricted to the Web of Science Core Collection database and articles and reviews strictly in English, potentially excluding some valuable literature, thereby impacting the study conclusion. We will address these shortcomings in future research by expanding the literature sources.

Conclusion

To the best of our knowledge, this is the first study to visualize and analyze DPN articles. Specifically, it obtained general information on countries/regions, institutions, authors, and cited journals, as well as the trending research focus areas within the field of DPN in a cited literature burst, including the efficacy of various medications for treating symptomatic DPN pain and the mechanism underlying diabetic neuropathy development. Furthermore, based on DPN prevention, diagnosis, and treatment, we found that the main future DPN research directions revolve around actively searching for DPN risk factors, improving diagnostic capabilities using advanced technologies such as CCM, and providing more clinical evidence using systematic evaluation as a research methodology. Overall, we expect this study to be a valuable reference for experts and scholars in DPN research.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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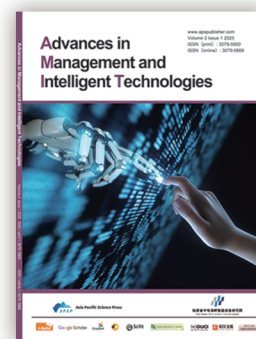
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