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Cristina Lavareda Baixinho

Lisbon Nursing School, Portugal

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The Effect of Reflective Teaching on Critical Thinking Skills of Midwifery Students

Ying Zhou, Xiwei Zhang*, Lijun Song, Hua Zhang, Xiaohe Tian

Department of Obstetrics and Gynaecology, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

*Corresponding author: Xiwei Zhang, anna13601216142@163.com

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Abstract: *Objective:* To study and investigate the impact of the role of reflective teaching to midwifery students on the development of their critical thinking skills. *Methods:* 60 midwifery students were selected as research subjects, with 30 midwifery students in midwifery class 1 receiving traditional teaching methods and were classified as the control group. The other 30 midwifery students in midwifery class 2 received reflective teaching and were classified as the training group. The study compared the critical thinking ability scores, incremental critical thinking ability scores, post-training assessment scores, and satisfaction with the teaching between the two groups before and after the training. *Results:* Before training, the comparison of the critical thinking ability scores of midwifery students in the two groups was not statistically significant ($P > 0.05$); after training, the critical thinking ability scores of midwifery students in the two groups were effectively improved ($P < 0.05$). The total score of critical thinking ability in the training group was higher than that of the control group ($P < 0.05$); the degree of improvement of critical thinking ability in the training group was greater than that of the control group ($P < 0.05$); the assessment scores of the training group were higher than those of the control group ($P < 0.05$); and the satisfaction rate of the effect of teaching midwifery students in the training group was higher than that of the control group ($P < 0.05$). *Conclusion:* Reflective teaching training for midwifery students can help to improve teaching quality and training effect, promote midwifery students' critical thinking ability and professionalism, and gain recognition from midwifery students.

Keywords: Reflective teaching; Midwifery students; Critical thinking ability

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1. Introduction

Critical thinking can help individuals use their existing knowledge and experience reserves flexibly in various complex situations, deepen analysis and inference based on scientific logical thinking, and finally make reasonable and effective behavioral decisions. The use of critical thinking can produce relatively clear, constructive thinking results, can further explore the truth, promote justice, and promote social progress^[1-2]. From the perspective of modern medicine, the current complex medical environment and ever-changing medical needs require midwives to have the ability to make independent judgments, decisions, and implementation in clinical practice, which determines that midwives must have a certain degree of critical thinking skills^[3-4].

Midwifery students are highly malleable in the theoretical learning stage, and if they can master certain critical thinking skills, they will be able to carry out purposeful and meaningful judgment, reflection, reasoning, and decision-making independently in the future when they face complex clinical nursing problems, and then carry out their work better ^[5-6]. For this reason, this study tries to apply reflective teaching to the teaching of midwifery students and achieves good experimental results. The study detail is reported as follows.

2. Information and methodology

2.1. General information

Sixty midwifery students were selected for the study, with 30 midwifery students in the midwifery 1 class receiving traditional teaching methods and were categorized in the conventional group. The other 30 midwifery students in the midwifery 2 class received reflective teaching and were categorized in the training group. Control group: all females, age 17.5–20 years, mean age 18.75 ± 1.11 years; education: all vocational high schools. Training group: all female, age 17–20.5 years, mean age 18.88 ± 1.22 years; education: all vocational high school. Comparison of general information such as gender, age, and education of midwifery students in the two groups was not statistically significant ($P > 0.05$). Inclusion criteria: (1) midwifery students have certain nursing knowledge and thinking ability; (2) midwifery students are aware of this study. Exclusion criteria: (1) Midwifery students who gave up the training in the middle of the course; (2) Midwifery students who were absent from the training course for reasons of holiday or sick leave.

2.2. Training methods

2.2.1. Control group

The control group adopts the traditional method of training: selecting senior clinically experienced instructors to train the midwifery students, using the textbook as the main basis for teaching the routine theoretical knowledge of midwifery within the prescribed teaching time, and conducting an assessment after the training.

2.2.2. Training groups

The training group receives reflective teaching. Key points for the implementation of reflective teaching: (1) Pre-learning reflection: reflective content is integrated into the teaching design. Before the teaching is carried out, based on relevant literature, summarize the characteristics of midwifery work and the knowledge mastery ability of midwifery students, explore the main influencing factors affecting the development of the critical thinking ability of midwifery students, make reasonable adjustments and additions to the content of traditional teaching materials, and formulate the theoretical teaching content that incorporates the connotation, significance, and method of reflective learning. (2) Reflective learning: Emphasis on the teaching of theoretical knowledge of critical thinking: before teaching midwifery professional knowledge, firstly, make an in-depth analysis of the theoretical knowledge of critical thinking to help midwifery students clarify the importance of critical thinking to midwifery, and to enhance the enthusiasm and initiative of midwifery students in the development of their critical thinking ability. Adjustment of teaching methods: critical thinking teaching throughout the training, breaking the traditional teaching teacher single lecture learning mode. The instructor releases the course content in advance, the midwifery student prepares for the content of the lecture, the midwifery student carries out the study on their own according to their knowledge reserve, literature review, network search, discusses and collates the important points, difficulties and doubts in the study chapters, and the instructor carries out the lectures according to the collated and summarized information in a targeted manner. High-simulation simulation teaching: part of the midwifery skills that exist in the theoretical lectures, selecting student representatives to

carry out patients and midwives' high-simulation simulation roles, through the students' independent practical operation to demonstrate midwifery skills, carrying out discussions to find out the problems, analyze the root causes of the problems, and finally to summarize the problems and show the correct operation by the instructor. (3) Post-study reflection: midwifery students are required to submit one reflection note per week, which contains things observed during training, analyses of their own or teaching deficiencies and gains, and puts forward optimization suggestions for their development of critical thinking skills or teaching methods, and the teacher will check the reflection diary to improve and promote the subsequent teaching, and share and exchange the contents of the diary that have promotional value.

The teaching level of the two groups of teachers was the same, and both groups were trained for three months.

2.3. Observation indicators

2.3.1. Comparison of critical thinking ability scores and score increments before and after training of midwifery students in two groups

The Chinese version of the Critical Thinking Disability Inventory (CTDI-CV), revised by scholars such as Peng Mei-Chi and Wang Guo-Cheng was used to assess the two groups of midwifery students^[7]. The Critical Thinking Disability Inventory contains seven categories, including intellectual curiosity, analytical ability, open-mindedness, truth-seeking, cognitive maturity, systematic ability, and self-confidence in judging, with 10 entries under each category, and a total of 70 entries in the inventory. The evaluation criteria for each item of the scale: <30 is negative critical thinking ability, 30–40 is poor critical thinking ability, 40–50 is positive critical thinking ability, and >50 is strong critical thinking ability. The overall evaluation standard of the scale: <210 is negative critical thinking ability, 210–280 is poor critical thinking ability, 280–350 is positive critical thinking ability, and >350 is strong critical thinking ability. The validity coefficients of the scale for each category were 0.55–0.77, and the combined validity coefficient for the content was 0.900, suggesting that the scale had good reliability and validity.

2.3.2. Comparison of the two groups of midwifery students' post-training assessment scores

After completing the training, the two groups of midwifery students participated in the same written assessment with a full score of 100 points. The content of the assessment includes knowledge of basic obstetric nursing routines, knowledge of midwifery skills, knowledge of the use of obstetric drugs, knowledge of ethics, legal and professional norms, and so on.

2.3.3. Comparison of satisfaction with the teaching effect of midwifery students in the two groups

Satisfaction with the teaching effect was surveyed by questionnaire, which was submitted anonymously by midwifery students of the two groups. A total of 30 questionnaires were distributed and 30 questionnaires were collected.

2.4. Statistical methods

The data in this study were analyzed by SPSS 23.0 to test the differences, and the measured data and count data were tested by *t*-value and χ^2 -value, respectively, and expressed as a percentage, (mean \pm standard deviation), and the comparison of the two groups was statistically analyzed with statistical significance at $P < 0.05$.

3. Results

3.1. Comparison of the scores of critical thinking skills of midwifery students in the two groups before and after training

Before the training, the difference between the two groups of midwifery students' critical thinking ability scores was not statistically significant ($P > 0.05$). After the training, the two groups of midwifery students' critical thinking ability scores were effectively improved ($P < 0.05$), and the training group's total critical thinking ability score was higher than that of the control group ($P < 0.05$), as shown in **Table 1**.

Table 1. Critical thinking ability scores of midwifery students in both groups before and after training (mean \pm standard deviation, points)

Projects	Pre-training		<i>t</i>	<i>P</i>	Post-training		<i>t</i>	<i>P</i>
	Training group (<i>n</i> = 30)	Control group (<i>n</i> = 30)			Training group (<i>n</i> = 30)	Control group (<i>n</i> = 30)		
Curiosity	33.25 \pm 1.45	33.75 \pm 1.27	-	-	43.68 \pm 3.41	38.38 \pm 5.45	-	-
Analytical skills	37.55 \pm 2.47	37.65 \pm 2.22	-	-	45.66 \pm 3.21	36.48 \pm 3.69	-	-
Open-mindedness	35.47 \pm 1.58	35.78 \pm 1.34	-	-	44.58 \pm 3.78	36.55 \pm 3.69	-	-
Truth-seeking	33.46 \pm 1.89	33.82 \pm 1.36	-	-	45.56 \pm 3.96	39.25 \pm 3.95	-	-
Cognitive maturity	36.68 \pm 1.87	36.25 \pm 1.68	-	-	46.84 \pm 3.74	38.31 \pm 3.71	-	-
Systematic ability	33.79 \pm 3.46	33.88 \pm 3.75	-	-	41.56 \pm 1.45	35.78 \pm 2.25	-	-
Judging Self-Confidence	33.85 \pm 1.41	33.36 \pm 1.34	-	-	47.12 \pm 2.75	35.98 \pm 3.85	-	-
Total Score	245.88 \pm 10.55	246.75 \pm 9.47	0.348	0.729	315.25 \pm 10.24	265.74 \pm 10.74	18.274	0.000

3.2. Comparing the increment of critical thinking skills scores before and after the training of midwifery students in the two groups

The training group's improvement in critical thinking skills was greater than that of the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of the incremental scores of critical thinking skills between the two groups of midwifery students before and after training (mean \pm standard deviation, points)

Projects	Post-training score increment for the training group	Post-training score increment for the control group	<i>t</i>	<i>P</i>
Curiosity	9.40 \pm 1.45	2.35 \pm 1.74	-	-
Analytical skills	8.13 \pm 2.71	1.74 \pm 1.36	-	-
Open-mindedness	8.56 \pm 2.34	1.50 \pm 1.42	-	-
Truth-seeking	10.86 \pm 3.45	3.96 \pm 2.74	-	-
Cognitive maturity	8.40 \pm 12.46	0.97 \pm 1.69	-	-
Systematic ability	8.74 \pm 2.58	2.95 \pm 1.31	-	-
Judging self-confidence	8.74 \pm 2.67	0.23 \pm 3.45	-	-
Total score	68.88 \pm 7.12	15.24 \pm 4.45	34.992	0.000

3.3. Comparing the average post-training assessment scores of midwifery students in the two groups

The appraisal scores of the training group were higher than those of the control group ($P < 0.05$). See **Table 3**.

Table 3. Comparing the average post-training assessment scores of midwifery students in the two groups (mean \pm standard deviation, points)

Groups	Average performance in appraisals
Training group ($n = 30$)	90.74 \pm 1.86
Control group ($n = 30$)	83.52 \pm 4.39
t	8.294
P	0.000

3.4. Comparison of the two groups of midwifery students with the effect of teaching satisfaction

The satisfaction rate of midwifery students' teaching effect in the training group was higher than that in the control group ($P < 0.05$), as shown in **Table 4**.

Table 4. Comparison of the satisfaction rate of the effect of teaching midwifery students in the two groups [n(%)]

Groups	Very satisfied (n)	Satisfied (n)	Unsatisfied (n)	Satisfaction rate (%)
Training group ($n = 30$)	22	8	0	100.00
Control group ($n = 30$)	16	10	4	86.67
χ^2	-	-	-	4.286
P	-	-	-	0.038

4. Discussion

As the general public's demand for modern medical care continues to increase, nursing staff will inevitably take on more responsibility^[8]. As a role that involves both soothing the mind of the mother and mastering professional skills, midwives should have the comprehensiveness of clinical thinking, and they should possess the logic of critical thinking^[9-10]. Critical thinking, as one of the core competencies of midwives, can help them make correct clinical decisions, which is conducive to the effective development of midwifery^[11-12]. While midwifery students are highly impressionable, the teaching stage is an important opportunity for midwifery students to improve their theoretical reserves and thinking ability is the first part of the whole career quality training^[13-14]. The conscious integration of reflective teaching in the training of midwifery students is of great significance both for the development of their abilities and for the progress of the discipline^[15].

The conclusions of this study show that: after the training, both groups of midwifery students' critical thinking ability scores were effectively improved ($P < 0.05$), and the total score of critical thinking ability of the training group was higher than that of the control group ($P < 0.05$). The degree of improvement of the critical thinking ability of the training group was greater than that of the control group ($P < 0.05$); the assessment scores of the training group were higher than that of the control group ($P < 0.05$); the traditional teaching methods are mainly based on the textbook to teach the routine theoretical knowledge of midwifery, which restricts the development of their critical thinking. The traditional teaching method is mainly based on the textbook to teach the routine theoretical knowledge of midwifery, and students passively accept the teaching, which restricts the development of their critical thinking. Reflective teaching through the whole process of pre-study, study, and

post-study conscious integration of critical thinking content, promotes midwifery students to take the initiative to observe and think about the problem, solve the problem, in the learning and problem-solving in the extension of the original knowledge, improve independent learning and creativity, and effectively promote the depth of the use of critical thinking skills. High-simulation simulation teaching integrates theoretical knowledge into specific clinical scenarios to help midwifery students quickly and skillfully master the essentials of nursing operations and independently and actively judge and analyze problems, which is more conducive to the exercise of their professional operation ability, thinking ability, communication ability, emergency analysis, and treatment ability. The writing of a post-course reflection diary, on the one hand, encourages midwifery students to accumulate lessons and insights, and on the other hand, it is beneficial to the improvement of the ability to analyze and summarize problems. The satisfaction rate of midwifery students in the training group was higher than that of the control group ($P < 0.05$), which fully indicates that the implementation of reflective teaching training has given midwifery students more opportunities to give play to their subjective initiative, and has been recognized by the students.

In conclusion, the implementation of reflective teaching training for midwifery students can help to improve the quality of teaching and training effects, promote the critical thinking ability and professionalism of midwifery students, and gain the recognition of midwifery students.

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Application of Hierarchical and Progressive Teaching Methods in Gastroscopy Simulation Training Education of Emergency Department Physicians

Pengman Chen, Yuting Chen, Juntao Liu, Jiaman Li, Yi Luo*

Department of Trauma Surgery, Zhanjiang Central People's Hospital, Zhanjiang 524000, Guangdong Province, China

*Corresponding author: Yi Luo, 116532270@qq.com

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Abstract: The purpose of this study is to explore the application of hierarchical progressive teaching methods in emergency department physicians. Traditional medical education methods usually adopt a unified teaching plan, which cannot meet the learning needs of different students. Therefore, this study introduced the hierarchical and progressive teaching method and developed a personalized learning plan according to the gastroscopy skill level and needs of physicians. Methods through comparative research, including assessing trainees' skill level, group learning, implementing personalized education, providing real-time feedback, and regular assessment. The results showed that the students who applied the hierarchical progressive teaching method showed a significant improvement in the gastroscopy skill assessment. They were more actively involved in classroom activities, and their learning satisfaction was improved significantly. Compared with traditional teaching methods, the hierarchical progressive teaching method has higher educational efficiency, enabling students to master skills more quickly. Furthermore, standardized assessment tools make it easier to measure trainees' skill levels. Therefore, this study concluded that the hierarchical progressive approach is an effective educational strategy that can be used to improve the gastroscopy skills and medical quality of ED physicians. Future studies could further explore how to further improve and optimize this educational approach.

Keywords: Emergency department doctor; Gastroscopy simulation practice education; Hierarchical and progressive teaching method; Education effect

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1. Introduction

In the process of treating all kinds of acute and critical patients, emergency department doctors need to make rapid and accurate diagnoses and take timely and effective treatment measures. Gastroscopy is one of the important means to diagnose digestive tract diseases, which is of great significance in clarifying the cause, guiding the treatment, and judging the prognosis. However, due to the complex and changeable conditions of

patients in the emergency environment, physicians need to make accurate judgments in a very short time, which puts forward extremely high requirements on the professional skills and adaptability of emergency department physicians ^[1]. This requires learning gastroscopy through the emergency department physician gastroscoposcopy simulation training education system to improve the professional skills of the emergency department physicians.

Gastroscopic simulation practice education for emergency department doctors refers to the teaching method of gastroscopy through practical operation in a simulated environment ^[2]. Its main characteristic is practical operation, emphasizing skill training and ability improvement ^[3-4]. In the teaching process, teachers will design different practical training projects and scenarios according to the requirements of the teaching syllabus and the learning progress of the students, to improve the students' practical operation ability and diagnosis and treatment level ^[5].

At present, the simulated practice education of gastroscopy for emergency department doctors in China is mainly carried out through the simulated practice classroom. Training classrooms are usually equipped with professional gastroscoposcopy simulators and related equipment to meet the operational needs of students ^[6-7]. In the actual teaching, the teachers will make detailed practical training plans and teaching contents according to the requirements of the teaching syllabus and combined with the actual situation of the students.

At present, the education of emergency department doctors in China is not perfect and there are some problems. On the one hand, traditional teaching methods often pay too much attention to the indoctrination of theoretical knowledge and ignore the training of practical operation skills, which leads to students often facing difficulties in practical operation. On the other hand, the existing simulation training equipment and space are limited, which cannot meet the training needs of all students ^[8]. These problems have seriously affected the improvement of their practice ability, diagnosis, and treatment level.

However, due to various reasons, there are still some problems in the current gastroscoposcopy simulation training education for emergency department physicians. First of all, the quality and performance of the training equipment are uneven, and the operation sense and reality of some simulation equipment are not high, which affects the learning effect of students. Secondly, the number of practical training classrooms is limited, which cannot meet the learning needs of all students. Thirdly, some teachers' understanding and application of the hierarchical and progressive teaching method are not deep enough, which leads to a poor teaching effect. Finally, there are also some problems in the time arrangement of practical training courses and the design of teaching content, which cannot meet the learning needs of students. Given the above problems, this study analyzed them from the following aspects.

Equipment problems: The current simulation equipment cannot provide a real operation experience, which has a certain impact on the students' skill training ^[9]. In addition, there are also some problems in the maintenance and management of the equipment, such as equipment aging, damage, and so on.

Teaching resources: Due to the limited number of practical training classrooms, it cannot meet the learning needs of all students ^[10]. In addition, some teachers' understanding and application of the hierarchical and progressive teaching method are not deep enough, which leads to a poor teaching effect.

Teaching methods: Traditional teaching methods pay too much attention to the indoctrination of theoretical knowledge, and ignore the training of practical operation skills. In addition, there are also some problems in the selection and design of teaching methods, such as the lack of pertinence and flexibility ^[11].

The above problems are only superficial phenomena, which reflect some deep-seated problems in the simulation training education of gastroscopy in the emergency department. First of all, the teaching mode is still in the traditional theoretical teaching stage, without making full use of modern educational technology, such as multimedia, networks, and so on, to improve the teaching effect. Secondly, the teaching evaluation system is

not perfect enough, and the teachers pay too much attention to the assessment of theoretical knowledge, while ignoring the evaluation of practical operation skills^[12]. Thirdly, the quality of the teachers still needs to be improved, and some teachers' teaching ideas and methods are still relatively backward, and cannot adapt to the new teaching mode. Finally, the management system also needs to be further improved to ensure the quality and effect of practical training and education.

Therefore, this study aims to explore the application of an effective teaching method — the hierarchical progressive teaching method in the practice education of emergency department physicians. Through the theoretical analysis, practical application, and effect evaluation of the hierarchical progressive teaching method, it is expected to provide theoretical support and practical reference for improving the current situation of gastroscopy simulation training education for emergency department doctors and improving the diagnosis and treatment skills and service level of doctors^[7, 13–15].

2. Contrastive Study

2.1. The theoretical basis of the traditional teaching method

The traditional teaching method is usually teacher-centered, using a “one-size-fits-all” approach^[16]. This teaching method ignores the individual differences of students, which often leads some students to keep up with the teaching progress, while others feel bored and unmotivated. In addition, traditional teaching methods often pay too much attention to the indoctrination of theoretical knowledge, And ignore the training of practical operational skills^[12, 17–18].

2.2. Methods of traditional teaching methods

Thirty emergency department physicians aged between 25–40 years old from December 2020 to December 2021 were selected as the study subjects. Inclusion criteria: (1) age between 25 and 40 years old; (2) emergency department resident or attending physician; (3) have not studied gastroscopy; (4) by department arrangement or independent registration. Using traditional teaching method: First, introduce the basic knowledge of gastroscopy through a theoretical explanation for about one week, then conduct a theoretical assessment (above 80 points means passing), after passing the next stage of practice; then use the model demonstration operation; then students group simulation practice; finally, evaluate students every month (above 80 points means passing) until pass.

2.3. Effect of the traditional teaching method

The effect of the traditional teaching method is shown in **Table 1** as follows.

2.4. The theoretical basis of the hierarchical and progressive teaching method

The hierarchical and progressive teaching method is a student-centered teaching mode, and its core concept is “teaching students according to their aptitude”^[19]. According to the theory, each student's learning ability, learning style, and learning speed are different. Therefore, teachers should adopt different teaching methods and strategies according to these differences among the students to improve the teaching effect^[20]. Specifically, the hierarchical progressive approach includes the following steps: First, the students are assessed to determine their learning level and needs; second, the students are divided into different levels or groups according to their ability level; and then, the teaching content and methods are designed for each level or group^[21]; Finally, adjust and improve the teaching methods and strategies through repeated practice and feedback.

Table 1. The effect of the traditional teaching method

Number	Age	Theoretical assessment results	Gastroscopy skill assessment results in the first month	Results of gastroscopy skill assessment in the second month	The results of the third month	Time (month)	Post-class evaluation (1. Interested; 2. Not interested)
1	32	80	61	80		2	1
2	30	82	60	81		2	2
3	35	80	54	79	81	3	2
4	29	86	70	90		2	1
5	27	88	58	85		2	1
6	30	90	64	81		2	1
7	31	86	88			1	1
8	34	88	67	80		2	1
9	25	80	68	82		2	1
10	32	86	66	86		2	1
11	40	90	80			1	1
12	38	86	69	82		2	1
13	25	80	66	84		2	1
14	39	80	69			2	1
15	37	86	80			1	1
16	27	82	60	76	88	3	2
17	30	84	76	88		2	1
18	32	84	76	90		2	1
19	36	88	80			1	1
20	40	86	65	84		2	1
21	32	90	64	88		2	1
22	33	94	67	87		2	1
23	34	84	69	89		2	2
24	35	82	70	90		2	1
25	38	80	66	84		2	1
26	39	80	61	82		2	1
27	40	80	62	81		2	2
28	28	80	64	87		2	1
29	29	82	68	88		2	1
30	26	84	72	89		2	1

2.5. The steps and methods of gastroscopy simulation training education for emergency department physicians by applying the hierarchical and progressive teaching method

Thirty emergency department physicians aged 25–40 years old between May 2, 2023 and October 2023 were selected as study subjects. Inclusion criteria: (1) age between 25 and 40 years old; (2) emergency department resident or attending physician; (3) have not studied gastroscopy; (4) by department arrangement or independent registration. The hierarchical and progressive teaching method is adopted to teach gastroscopy skills through

gastroscopy simulation practical training, which mainly includes the following steps.

First of all, teachers need to understand the student's learning ability and technical level through observation and testing, then conduct theoretical tests and assessments, and then stratify according to the test results ^[22]. Generally speaking, students can be divided into three levels: primary, intermediate, and advanced. Primary-level students first supplement theoretical knowledge, then perform basic operation training, such as gastric tube insertion and extraction; intermediate-level students can perform some complex operations, such as gastroscopy and treatment; advanced-level students can perform more advanced operations, such as surgery, for about three days. After the early basic teaching, the theoretical knowledge assessment (more than 80 points means passing), until the students pass the assessment before the next teaching.

Secondly, the teachers need to design different practical training contents and methods for the students at each level. For example, for primary-level students, teachers can adopt intuitive and vivid teaching methods, such as physical demonstration, animation demonstration, and so on ^[23]; For intermediate-level students, teachers can adopt more complex teaching methods, such as problem-solving and discussion; for advanced students, teachers can adopt more advanced and more complex teaching methods, such as research learning, project learning, and so on ^[24]. The process took about four days.

Finally, teachers need to adjust and improve the teaching methods and strategies through repeated practice and feedback. For example, teachers can observe the actual operation of the students, understand their mastery degree and existing problems, and then provide targeted guidance and help ^[25]. The process is about a week to three weeks. At the same time, teachers can also understand the learning progress and effect of students through regular testing and evaluation, and then adjust and improve in time. Pass the assessment by the students (80 points or above means passing). The assessment is shown in **Table 2** below.

Table 2. The assessment results for the hierarchical and progressive teaching method

Number	Age	Initial interest in gastroscopy (1. Want to learn independently; 2. Department arrangement)	Theoretical achievement before the study	Theoretical results after the study	Practice results	Post-class evaluation (1. Interested; 2. Not interested)	Time (month)
1	25	1	60	90	90	1	0.5
2	32	1	70	100	96	1	0.5
3	35	2	60	80	86	1	0.5
4	40	2	50	80	84	1	1
5	39	1	60	90	92	1	1
6	37	1	60	100	94	1	0.5
7	25	2	60	80	88	1	0.5
8	40	1	60	90	87	1	0.5
9	39	1	70	100	90	1	0.5
10	35	1	60	80	80	1	0.5
11	36	2	70	90	92	1	0.5
12	37	1	60	80	88	1	0.5
13	28	2	60	80	86	1	0.5
14	29	2	60	80	87	1	1
15	30	1	60	90	89	1	0.5
16	31	2	60	90	90	1	0.5

Table 2 (Continued)

Number	Age	Initial interest in gastroscopy (1. Want to learn independently; 2. Department arrangement)	Theoretical achievement before the study	Theoretical results after the study	Practice results	Post-class evaluation (1. Interested; 2. Not interested)	Time (month)
17	34	2	70	90	83	1	0.5
18	36	1	80	100	85	1	0.5
19	37	1	70	100	88	1	0.5
20	25	1	60	80	86	1	1
21	27	2	70	100	94	1	0.5
22	28	1	60	90	86	1	0.5
23	26	2	70	100	87	1	0.5
24	32	1	70	90	89	1	1
25	33	1	70	90	86	1	0.5
26	34	2	70	90	90	1	0.5
27	30	1	50	80	80	1	0.5
28	26	2	60	80	87	1	0.5
29	27	2	70	90	86	1	0.5
30	29	2	80	100	92	1	0.5

2.6. Comparative analysis of the results

2.6.1. Comparison of the theoretical results of the two groups of methods

After the *t*-test through Graphpad Prism 8 analysis, the theoretical scores of the stratified progressive teaching method are significantly higher than that of the traditional teaching method, and the difference has statistical significance ($P < 0.05$). In **Table 1**, the students in the stratified progressive teaching method have full marks, while most of the students in the traditional teaching method are on the pass line.

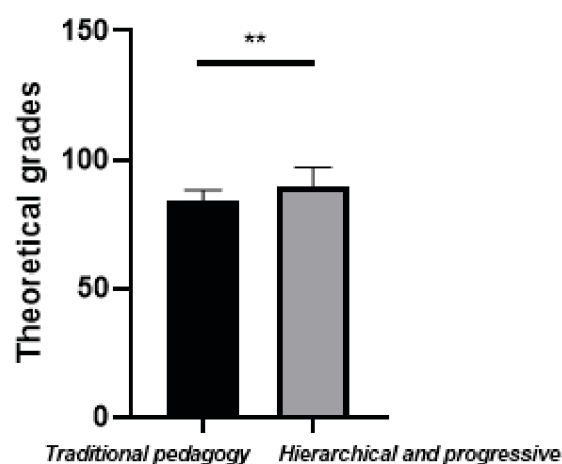


Figure 1. Comparison of the theoretical results of the two groups of methods

2.6.2. Comparison of the practical results of the two groups of methods

After the *t*-test through Graphpad Prism 8 analysis, the practical results of the hierarchical progressive teaching method are higher than that of the traditional teaching method, and the difference has statistical significance (P

< 0.05). In **Figure 2**, the students of the stratified progressive teaching method are more skilled than those of the traditional teaching method.

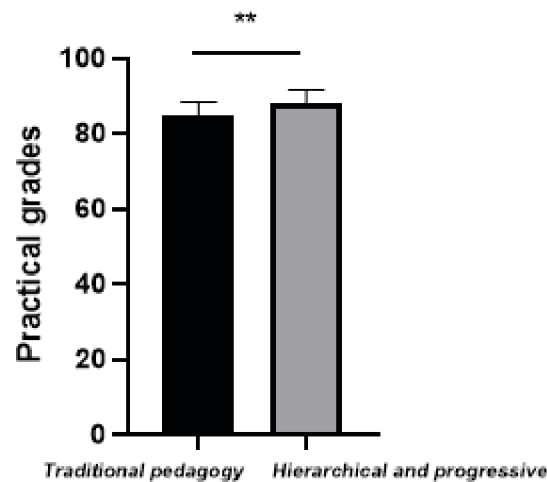


Figure 2. Comparison of the practical results of the two groups of methods

2.6.3. Comparison of teaching assessment passing time of the two groups of methods

After the *t*-test through Graphpad Prism 8 analysis, the teaching assessment passing time of the stratified progressive teaching method is shorter than that of the traditional teaching method, and the difference has statistical significance ($P < 0.05$). In **Figure 3**, the time is shortened from 2 months to half a month, so that students of the stratified progressive teaching method can learn gastroscopy skills in a short time.

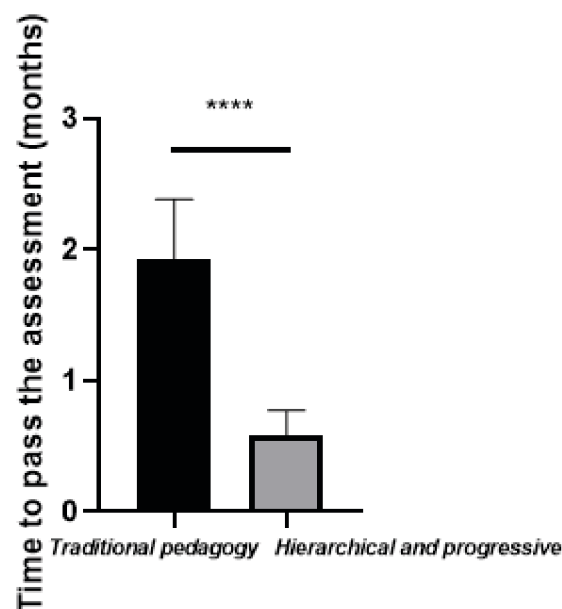


Figure 3. Comparison of teaching assessment passing time of the two groups of methods

2.6.4. Comparison of post-class satisfaction of the two groups of methods

After the *t*-test through Graphpad Prism 8 analysis, the satisfaction of the stratified progressive teaching method is higher than that of the traditional teaching method, and the difference has statistical significance ($P < 0.05$). In **Figure 4**, students of the stratified progressive teaching method get rid of the boredom of the traditional

teaching method, can join the classroom atmosphere more easily, and are more interested in the classroom.

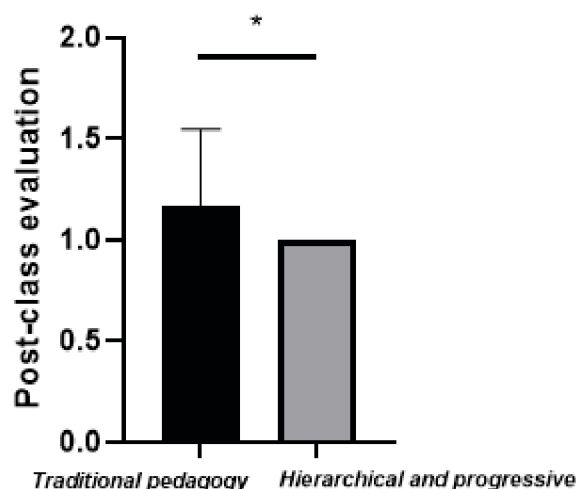


Figure 4. Comparison of post-class satisfaction of the two groups of methods

3. Conclusion

Through the analysis of the results, it is shown that the hierarchical progressive teaching method has obvious advantages in the practical practice of gastroscopy in emergency department doctors. First of all, it can meet the learning needs of different students, so that the students' theoretical results and practical results can be improved to different degrees, and the whole learning time is shortened from the original 2 months to half a month. Because each student has a different learning ability and technical level, different teaching methods and strategies need to be adopted. Secondly, it can stimulate students' interest and enthusiasm in learning. Because each student can find their training content and methods, so they will more actively participate in the training ^[26]. Finally, it can help teachers to better understand and evaluate the students' learning situation, and improve the quality of teaching. Because teachers can observe the actual operation of students, understand their mastery degree and existing problems, and then provide targeted guidance and help.

In contrast, the hierarchical and progressive teaching method is more flexible and personalized. It divides students according to their ability and technical level and then designs different training contents and methods for students at different levels ^[27]. This teaching method can not only meet the learning needs of different students and improve the teaching effect but also stimulate the student's interest and enthusiasm in learning. The learning effect of the students has also been significantly improved, and the learning time is shorter. Teachers' workload has also eased. Because teachers no longer need to spend a lot of time and effort to evaluate and group trainees, their work burden is reduced.

However, it should be noted that the hierarchical and progressive teaching method is not a panacea. In practical application, some other factors also need to be considered, such as teacher training and support, and the acceptance and participation of trainees. Therefore, studies need to continuously explore and improve the hierarchical progressive teaching method in practice, to better apply it to the gastroscopy simulation training education of emergency department physicians.

The advantages of the hierarchical progressive teaching method are mainly reflected in the following aspects. First, it can effectively meet the learning needs of different students and improve the teaching effect. Second, it can stimulate students' interest and enthusiasm in learning and improve their learning

motivation^[28]. Third, it can help teachers to better understand and evaluate the learning situation of students and improve the quality of teaching. However, the hierarchical progressive approach has some limitations. First, it takes a lot of time and energy to evaluate and group students, which may increase the burden on teachers. Second, it may cause some students to feel ignored or excluded, affecting their learning enthusiasm. Third, it may restrict the free development of students and hinder the development of their personality and innovation ability. In addition to the education field, the stratified and progressive teaching method is also widely used in other fields. For example, in enterprise management, an enterprise can divide employees into different levels or groups according to their abilities and strengths, and then design suitable work tasks and development paths for employees at each level or group. In physical training, coaches can divide the athletes into primary, intermediate, and advanced levels according to their technical level and physical condition, and then design suitable training plans and methods for the athletes at each level^[29].

Although the hierarchical progressive teaching method has many advantages in the simulated training education of gastroscopy in emergency department doctors, it will also encounter some problems in practical application. First, the stratified division may increase the work burden of the teachers. Because teachers need to spend a large amount of time and effort to evaluate and group students. Secondly, it may cause a proportion of the trainees to feel neglected or excluded. Because not all students can adapt to different levels of training content and methods. Finally, it may restrict the free development of the trainees. Because students may feel that they can only do things at their level, rather than try a higher level of training content and methods.

In general, the hierarchical progressive teaching method has great potential in the simulated practical education of emergency department physicians. It can not only meet the learning needs of different students and improve the teaching effect but also can stimulate the student's interest and enthusiasm in learning. The implementation of a hierarchical progressive teaching method can not only improve the quality of teaching and improve the learning effect of students but also reduce the work burden of teachers and improve work efficiency. However, it should be noted that the hierarchical progressive teaching method is not all-encompassing, so studies need to constantly explore and improve this method in practice, to better apply it in the gastroscopy simulation training education of emergency department doctors.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Study idea conceptualization: Yi Luo

Study experimentation: Yuting Chen

Data analysis: Pengman Chen

Study writing: Pengman Chen

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The Influence of Socioeconomic Factors on Diabetes Management and Its Outcomes

Mehran Khan*, Muhammad Shahbaz, Tooba Waris, Shoaib Yaseen, Iqra Afzal, Emaan Khadim, Sawera Usman, Muhammad Ismail Shah, Sulaiman Aslam, Zafar Iqbal

Bahawalpur College of Pharmacy, BMDC Complex, 63100 Bahawalpur, Punjab, Pakistan

*Corresponding author: Mehran Khan, mehrankhanpharmacist@gmail.com

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Abstract: Diabetes is a growing global issue, with socioeconomic status (SES) influencing diabetes incidence and prevalence. Adults with low incomes are more likely to have diabetes and have higher rates of complications and mortality. Education quality is more important than quantity in SES assessments. High-income individuals are less likely to experience diabetes due to the affordability of balanced diets and medications. Long work hours and illiteracy also contribute to diabetes. Research in Bahawalpur, Pakistan, found that socioeconomic factors significantly influence diabetes patients, with poor economic and diabetic education being more common. Physical activity and lack of life insurance also contribute to diabetes. In Bahawalpur, a cross-sectional study of the influence of socioeconomic factors on diabetes management and outcomes across age and gender groups, involving 374 participants from various social and economic backgrounds was carried out. The questionnaire results show that 60% of the participants were male and 39.39% were female. The participants over the age of 50 make up 66.80% of the total number. Among the 374 participants, 236 (63.10%) were jobless. 41.97% of participants had poor knowledge about diabetes. The participants have poor diabetes management due to poor education, poor economics, and a lack of physical activities, thus having a negative influence on their lives.

Keywords: Diabetes; Socioeconomic factors; Knowledge; Bahawalpur; Pakistan

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1. Introduction

Diabetes is a rapidly increasing global disease impacting human health and affecting social and economic aspects of life. It is predicted that by 2045, there will be 693 million diabetics worldwide, up from 451 million in 2017 ^[1]. Additionally, it is estimated that 49.7% of individuals with type II diabetes are undiagnosed ^[2]. The average life expectancy of patients with type II diabetes is reduced by approximately ten years ^[3]. Most diabetes patients in developing nations are younger than 64, while in developed nations, the majority are older ^[2]. Between 2010 and 2030, the adult population in developing countries is anticipated to have a 69% increase in diabetes, compared to a 20% increase in developed countries ^[3-4].

Pakistan, a developing and low-income nation, is facing a widespread prevalence of diabetes. An

individual's or family's socioeconomic status (SES) is a comprehensive indicator of their financial and social standing ^[5]. Despite variations in socioeconomic status, literacy rates, education levels, cultural norms, and lifestyles, it is crucial to identify the primary factors affecting the lives of diabetic patients ^[6]. Various strategies can be applied to the socioeconomic factors of diabetic patients to achieve better outcomes and management of diabetes.

2. Methodology

This cross-sectional study was conducted from March 18, 2024, to May 30, 2024, at the outpatient and inpatient departments of medicine in the following hospitals: Bahawalpur Victoria Hospital (BVH), Bahawalpur Medical and Dental Hospital (BMDH), Sir Sadiq Abbasi (Civil) Hospital, Bahawalpur, Pakistan. The study also included students from the Islamia University of Bahawalpur (IUB) in the Information and Communication Technology Department and Bahawalpur College of Pharmacy (BCP) Bahawalpur. The inclusion criteria were diabetic patients of both genders and all ages. The exclusion criteria were non-diabetic patients, coma patients, or those unwilling to participate in the study. Data were collected from 374 diabetic patients for this cross-sectional descriptive study. The sample size was determined using the Raosoft calculator software. At the time of enrollment, the following information was recorded: gender, age, employment status, educational status, health insurance, diabetic knowledge, economic and social life of diabetic patients, and its influence on subjects and diabetes.

2.1. Study tool

The standardized questionnaire was employed as a data collection tool for the study. The questionnaire consisted of six types of questions. The first type gathered personal information such as age, gender, qualifications, and other demographic data. The second category included knowledge-based questions about diabetes. The third category gathered information about the economic status of patients. The fourth type gathered information about social factors. The fifth type gathered information about diabetes management. The last type gathered information about the influence of socioeconomic factors on diabetic patients. The study questionnaire is shown below.

Public Healthcare Questionnaire of “The Influence of Socioeconomic Factors on Diabetes Management and Outcomes”

Name: _____ CNIC: _____

- 1) What is your age group?
Under 20
20–50
Over 50
- 2) What is your gender?
Male
Female
Other
- 3) Are you (a) literate _____ or (b) illiterate _____. If (a) then answer the below question;
Up to intermediate level
Undergraduate
Postgraduate

- 4) How would you describe your current employment status?
- Employed full-time
 - Employed part-time
 - Unemployed
- 5) Do you have health insurance?
- Yes, through employer
 - Yes, through the government program
 - No
- 6) How would you rate your household income?
- Low (below average)
 - Average
 - High (above average)
- 7) How often do you check your blood sugar level?
- Daily
 - Weekly
 - Monthly or less
- 8) Do you have access to healthy food options in your area?
- Yes, easily accessible
 - Somewhat accessible
 - Not accessible
- 9) Have you received proper diabetes education?
- Yes, comprehensive education
 - Some education
 - No education
- 10) How often do you engage in physical activity?
- Daily
 - A few times a week
 - Rarely or never
- 11) How many doctor visits related to diabetes do you have per year?
- 1–2 visits
 - 3–5 visits
 - More than 5 visits
- 12) Have you ever skipped medications due to cost?
- Yes, frequently
 - Sometimes
 - No, never
- 13) Do you have a support system for managing your diabetes?
- Yes, strong support
 - Some support
 - No support
- 14) Have you ever had to ration insulin or other diabetes medications?
- Yes, frequently
 - Sometimes
 - No, never

- 15) How would you rate your overall satisfaction with your diabetes management?
- Very satisfied
 - Somewhat satisfied
 - Not satisfied
- 16) Are you aware of community resources available for diabetes management?
- Yes, very aware
 - Somewhat aware
 - Not aware
- 17) Have you ever had to choose between paying for diabetes care and other essentials (e.g., rent, food)?
- Yes, frequently
 - Sometimes
 - No, never
- 18) How often do you experience stress related to managing your diabetes?
- Daily
 - Occasionally
 - Rarely
- 19) How knowledgeable do you feel about managing your diabetes?
- Very knowledgeable
 - Somewhat knowledgeable
 - Not knowledgeable
- 20) Have you ever had to delay or skip medical appointments due to financial constraints?
- Yes, frequently
 - Sometimes
 - No, never
- 21) How would you rate the availability of diabetes care facilities in your area?
- Excellent
 - Adequate
 - Insufficient
- 22) Have you ever participated in a diabetes support group?
- Yes, currently
 - Yes, in the past
 - No
- 23) Do you feel your healthcare provider understands your socioeconomic challenges in managing diabetes?
- Yes, completely
 - Somewhat
 - No, not at all
- 24) How would you rate the affordability of your diabetes medications?
- Affordable
 - Somewhat affordable
 - Not affordable
- 25) How do you perceive the impact of socioeconomic factors on your diabetes management?
- Significant impact
 - Some impact
 - No impact

2.2. Scoring criteria

The evaluation criteria were adapted from standard studies on diabetes in Pakistan. The demographic details of 374 diabetic patients included gender (female and male), educational level, and employment status. Knowledge criteria were classified as poor knowledge (1–2 Yes answers), average knowledge (3 Yes answers), and good knowledge (4 Yes answers). The economic evaluation criteria were classified as poor economic status (1–2 Yes answers), average economic status (3 Yes answers), and good economic status (4–5 Yes answers).

3. Results

Out of a total of 374 patients, 226 (60%) were male, 147 (39.30%) were female, and 1 (0.26%) did not disclose their gender. Regarding age distribution, 27 (7.2%) were under 20 years old, 97 (25.90%) were between 20 and 50 years old, and 250 (66.80%) were over 50 years old. In terms of educational attainment, 231 (61.70%) had education up to intermediate level, 86 (22.90%) were undergraduates, and 57 (15.20%) were postgraduates. Regarding employment status, 96 (25.60%) were employed full-time, 42 (11.22%) were employed part-time, and 236 (63.10%) were unemployed. Among the 374 patients, 19 (5.80%) had employment-based health insurance, 24 (6.41%) had government health insurance, and 331 (88.50%) had no health insurance. The other collected data include diabetes knowledge (Table 1 and Figure 1); economic status (Table 2 and Figure 2); physical activities (Table 3 and Figure 3); availability of diabetes care facilities (Table 4 and Figure 4); number of doctor’s visits (Table 5 and Figure 5); overall management of diabetes (Table 6 and Figure 6); influence of social and economic factors (Table 7 and Figure 7).

Table 1. Diabetes knowledge

Diabetes education	Total	Percentage
Poor	157	41.97%
Average	128	34.22%
Good	89	23.79%

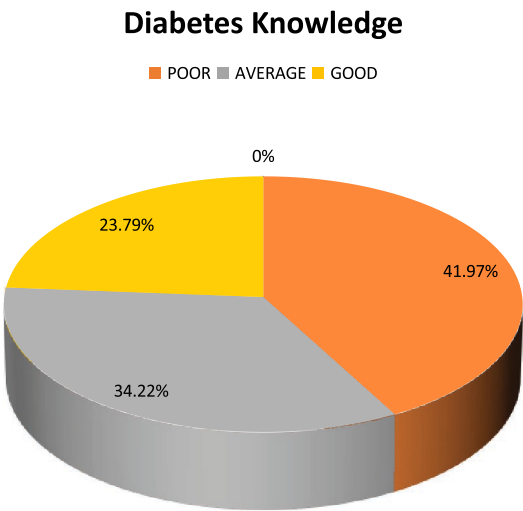


Figure 1. Diabetes knowledge: This figure illustrates the percentage of sample patients’ knowledge of diabetes

Table 2. Economic status of the diabetic patients

Economics	Total	Percentage
Poor	152	40.64%
Average	126	33.68%
Good	96	25.66%

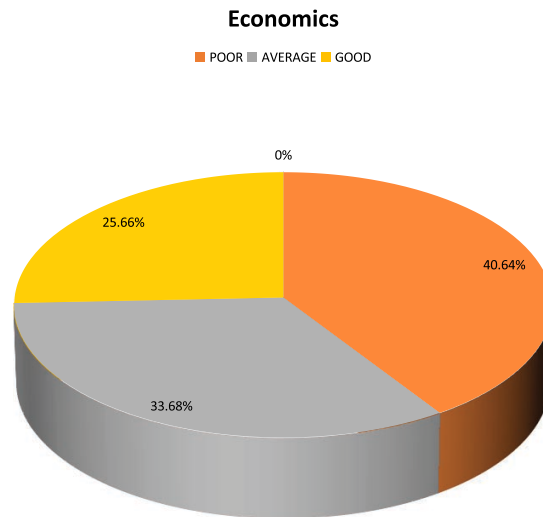


Figure 2. Economics: This figure illustrates the economic status of the total sample of diabetic patients

Table 3. Physical activities of the diabetic patient

Physical activities	Total	Percentage
Daily	54	14.43%
A few times a week	142	37.96%
Rarely	178	47.59%

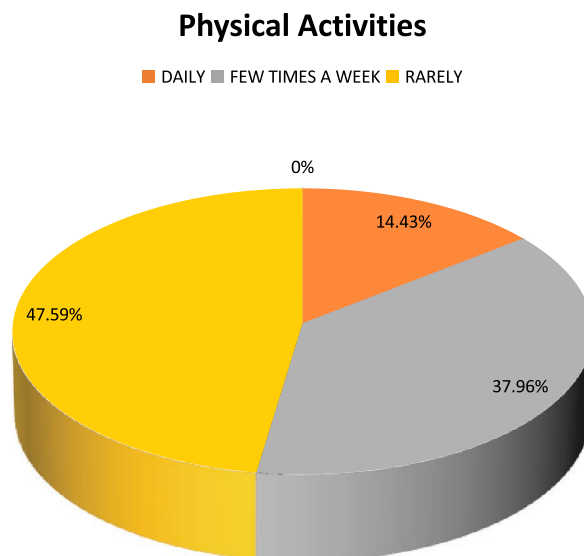


Figure 3. Physical activities of diabetic patients

Table 4. Availability of diabetes care facilities

Availability of diabetes care facilities	Total	Percentage
Excellent	205	54.81%
Adequate	97	25.93%
Insufficient	72	19.25%

Availability of Diabetes Care Facilities

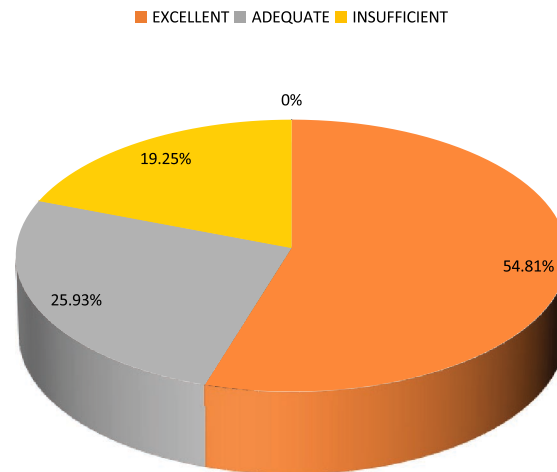


Figure 4. Availability of diabetes care facilities

Table 5. Doctor's visit per year

Doctor's visit per year	Total	Percentage
1 to 2	12	3.20%
3 to 5	39	10.42%
more than 5	323	86.36%

Doctor's Visit Per Year

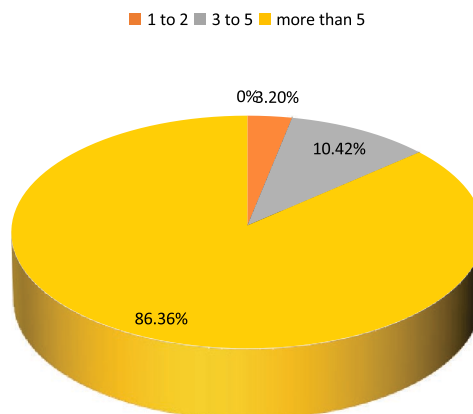


Figure 5. Doctor's visits of the diabetic patient

Table 6. Overall management of diabetes by patients

Overall management	Total	Percentage
Good	77	20.58%
Average	106	28.34%
Poor	191	51.06%

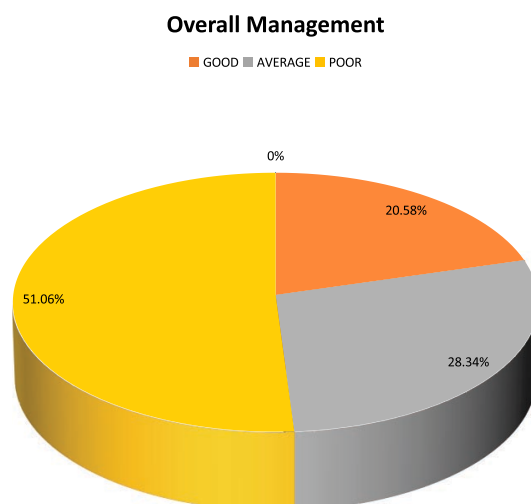


Figure 6. Overall management of diabetes by patients

Table 7. Influence of socioeconomic factors

Socioeconomic factors	Total	Percentage
Positive	84	22.45%
Neutral	143	38.23%
Negative	147	39.30%

Influence of Socioeconomic Factors

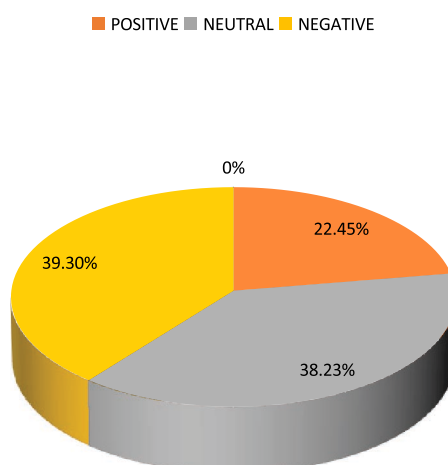


Figure 7. Influence of socioeconomic factors: This figure describes the influence of social and economic factors on diabetic patients, indicating whether the influence is positive, neutral, or negative

4. Discussion

Diabetes is increasingly becoming a serious issue in every nation worldwide. Socioeconomic status (SES) comprises education, occupation, and economic standing. Numerous studies over the years have shown that adults with lower incomes are more likely to have diabetes, along with higher rates of diabetes-related complications and mortality ^[7]. Diabetes incidence and prevalence rates correlate directly with occupation, income, and education levels. Educational attainment can be gauged by counting advanced degrees and years of schooling completed ^[8]. Quality of education is preferred over quantity in SES assessments. The prevalence of diabetes continues to increase as one descends from the highest to the lowest income levels ^[9]. Those with higher incomes are less likely to be affected by diabetes, as they can afford a balanced diet and medications. A meta-analysis by Kivimäki et al. found that individuals with low SES who work long hours (≥ 55 hours per week) are more prone to diabetes compared to those with regular work hours (35–40 hours per week), independent of high SES individuals ^[10]. A U.S. population-based survey reported higher diabetes prevalence among transportation workers compared to physicians ^[11]. Diabetes is not gender-specific; individuals with higher BMI are more susceptible to diabetes, and illiteracy also significantly affects poor glycemic control ^[6].

Research conducted in specific areas of Bahawalpur, Pakistan examined the impact of socioeconomic factors on diabetes patients. Findings revealed a significant influence of socioeconomic factors on diabetic patients. Diabetes is more prevalent among individuals with poorer economic and diabetic education compared to those with better economic and diabetic education. Physical activity is associated with a lower likelihood of diabetes. Individuals without life insurance are more likely to have diabetes than those with insurance. Moreover, socioeconomic factors exert a predominantly negative influence on diabetes.

5. Conclusion

This study aimed to explore the influence of socioeconomic factors on diabetic patients, irrespective of gender and age, in Bahawalpur. The findings conclude that socioeconomic status significantly impacts diabetic patients. Factors such as education, income, employment, and social status exert a notable influence on the prevalence and outcomes of diabetes. The findings suggest that patients from lower socioeconomic backgrounds are more likely to develop diabetes compared to those with higher socioeconomic status. Individuals with less knowledge about diabetes are particularly vulnerable to the disease. While diabetes is not gender-specific, socioeconomic status negatively impacts diabetes management. Future research should validate these findings through clinical assessments.

Disclosure statement

The authors declare no conflict of interest.

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Clinical and Biological Impact of KRAS Overexpression in Stomach Adenocarcinoma

Syed Hussain Raza^{1*}, Akbar Ali²

¹Department of Biochemistry and Biotechnology, the Islamia University of Bahawalpur, Bahawalpur, Pakistan

²Nishtar Medical University, Multan, Pakistan

*Corresponding author: Syed Hussain Raza, hussainrbukhari@gmail.com

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Abstract: This study analyzes Kirsten rat sarcoma viral oncogene (KRAS) expression heterogeneity, and biological and clinical relevance in stomach adenocarcinoma (STAD). The study utilized various tools including UALCAN, GEPIA2, Kaplan-Meier (KM) plotter, cBioPortal, STRING, DAVID, and TIMER 2.0 to conduct this analysis. The results illustrated overexpression of KRAS in STAD and the analysis based on various clinicopathological parameters also verified overexpression of KRAS in STAD. Eventually, this overexpression was linked to poor overall survival (OS) of STAD patients. These results suggested the role of KRAS is involved in the development and progression of STAD. The study also assessed several significant correlations of KRAS expression with promoter methylation tumor purity and immune cell infiltration. Genetic alteration of KRAS revealed to have a strong role in STAD initiation. Gene enrichment analysis highlighted the enrichment of KRAS with various pathways. In conclusion, the findings illustrated the potential of KRAS as a diagnostic, prognostic, and therapeutic biomarker in STAD.

Keywords: KRAS; STAD; Biomarker; Prognosis; Expression variations

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1. Introduction

Cancer is a major devastating disease, leading to millions of deaths annually worldwide. There are above 100 subtypes of cancer based on biological pathways ^[1-2]. Stomach cancer is the fifth most widespread cancer with 968,350 cases and 659,853 deaths worldwide in 2021 ^[3]. Adenocarcinoma accounts for roughly more than 90% of all stomach cancer cases. Stomach cancer adenocarcinoma (STAD) has two types which are histologically categorized as diffuse and intestinal, which show variance in epidemiological traits ^[4-5]. Smoking, alcohol consumption, ethnicity, genetic factors, increasing age, and *Helicobacter pylori* infection are major risk factors for STAD ^[6-9]. The incidence of STAD varies geographically in the world, with over 50% of cases reported in developing countries. In 2020, the highest number of STAD cases were registered in Asia, and the least were registered in Africa. The incidence rate of STAD is increasing in adults, and males have two times higher risk of developing STAD than females. Surgery, chemotherapy, chemoradiation, and adjuvant therapy are treatments used in STAD. The 5-year survival rate is less than 20% in Asia and varies from 10% to 30% in Europe ^[10-16]. STAD

diagnosed at higher stages has limited treatment options available, which results in a high mortality rate for STAD. Therefore, it is crucial to evaluate potential diagnostic, therapeutic, and prognostic biomarkers for STAD.

Kirsten rat sarcoma viral oncogene (KRAS) is a member of the RAS family that codes Kirsten rat sarcoma viral oncogene homolog (KRAS) protein. KRAS has a role in various cellular signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway and regulation of cell proliferation. KRAS is highly interactive to GTP because it lacks small molecular binding sites and this results in activation of KRAS. Cell proliferation, cell differentiation, apoptosis, and cellular migration are affected by KRAS, as it initiates the release of signaling molecules facilitating the relay of signals from the cell surface to the nucleus^[17–21]. KRAS has a high mutation rate in cancer and mutations are mainly present in, lung adenocarcinoma, colorectal cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, and urogenital cancer^[22–23]. KRAS expression is associated with poor prognosis in colorectal cancer and lung cancer^[24–25]. Moreover, KRAS mutations are associated with pancreatic cancer, lung cancer, colorectal cancer, and stomach cancer^[26–28]. All these data underscore the potential of KRAS as a therapeutic, prognostic, and diagnostic biomarker in many cancers.

This study aimed to conduct a comprehensive analysis of the KRAS gene as a potential biomarker in STAD, as no such analysis has been performed. The study employed different bioinformatics tools to analyze expression, methylation level, mutation, gene enrichment pattern, and prognostic links of KRAS in STAD.

2. Material and method

2.1. UALCAN

UALCAN is a web-based resource utilized for comprehensive cancer OMICS data analysis^[29]. The study employed the UALCAN database to analyze KRAS expression in STAD samples. The study investigated promoter methylation OF KRAS and its correlation with expression using the TCGA module of UALCAN. The analysis was based on sample type as well as on different pathological parameters.

2.2. Kaplan-Meier Plotter

Kaplan-Meier (KM) Plotter is an online tool to evaluate the overall survival (OS) of cancer patients based on gene expression^[30]. The impact of 54,675 genes on the overall survival of 21 cancers can be evaluated using a KM plotter. The study evaluated the impact of KRAS on the OS of STAD employing a KM plotter. *P* value < 0.05 is considered significant and the hazard ratio was calculated.

2.3. GEPIA2

Gene expression profiling interactive analysis 2 (GEPIA2) is an online tool that can evaluate gene expression in 84 subtypes of cancer based on GTEx and TCGA databases^[31]. GEPIA2 is used to validate the KRAS expression in STAD based on sample types and pathological stages. The prognostic value of KMAS in STAD was also evaluated using GEPIA2.

2.4. cBioPortal

cBioPortal is a public cancer genomic tool intended for interactive investigation of multi-omic cancer datasets^[32]. The study employed cBioPortal to evaluate KRAS genetic variation in STAD. The examined information included alteration prevalence, mutation categorization, and copy number variations (CNAs).

2.5. Protein-protein interaction (PPI)

The Search Tool for the Retrieval of Interacting Genes (STRING) is a database that is used for proteomics

analysis^[33]. The study employed the STRING database to construct the PPI network of KRAS to observe functional relationships. A P value < 0.05 is considered statistically significant.

2.6. Gene enrichment analysis

The Database for Annotation, Visualization, and Integrated Discovery (DAVID) is a web-based comprehensive tool used to elucidate biological functions^[34]. The study performed gene ontology (GO) and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway enrichment analysis of KRAS utilizing the DAVID tool.

2.7. KRAS expression, tumor purity, and immune cell infiltration

The association of gene expression, tumor purity, and immune cell infiltration is analyzed utilizing an online resource TIMER 2.0^[35]. In the current study, the association between KRAS expression, tumor purity, and CD8+ T immune cells is analyzed in STAD using TIMER 2.0. A P value < 0.05 is considered statistically significant.

3. Results

3.1. KRAS expression in STAD and normal samples

The study utilized the UALCAN database to analyze the KRAS expression in STAD and normal samples. The analysis demonstrated that KRAS expression was significantly higher in STAD samples in contrast with normal samples (**Figure 1**). The observed P value $1.09079967280934E-10$ is less than 0.05 which indicates there is a significant difference. This higher expression suggests the role of KRAS in the progression of STAD.

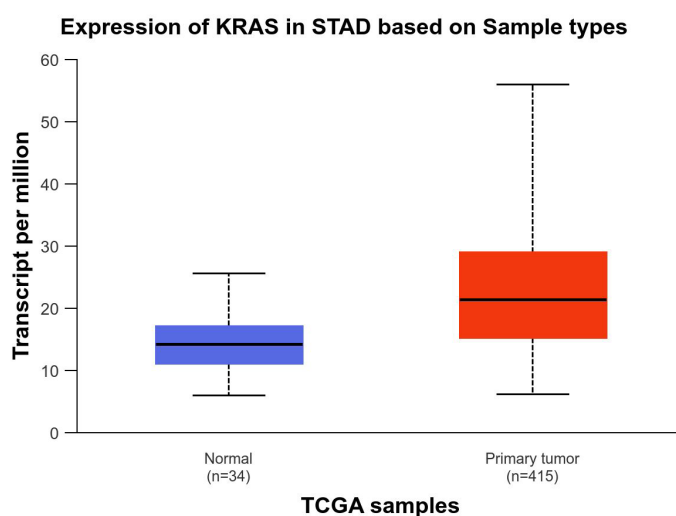


Figure 1: Expression analysis of KRAS in STAD samples and normal samples using UALCAN

3.2. Expression analysis of KRAS in STAD categorized according to various attributes

Simultaneously, the study conducted an analysis of KRAS expression in STAD categorized according to various attributes such as patient's gender, age, race, and pathological stages. First, the study examined expression based on pathological stages and observed that KRAS was statistically up-regulated (P value < 0.05) in cancer stages in contrast with the normal sample (**Figure 2A**). Afterward, analysis based on gender revealed that KRAS expression was significantly up-regulated (P value < 0.05) in STAD samples as compared to normal samples (**Figure 2B**). Next, up-regulated expression of KRAS was assessed in STAD patient samples of various races (**Figure 2C**). Furthermore, investigation based on STAD patients' age group revealed up-regulation but variation in KRAS expression (**Figure 2D**). KRAS was highly expressed in STAD patient samples of the age

group of 21–40 as compared to the age group of 81–100.

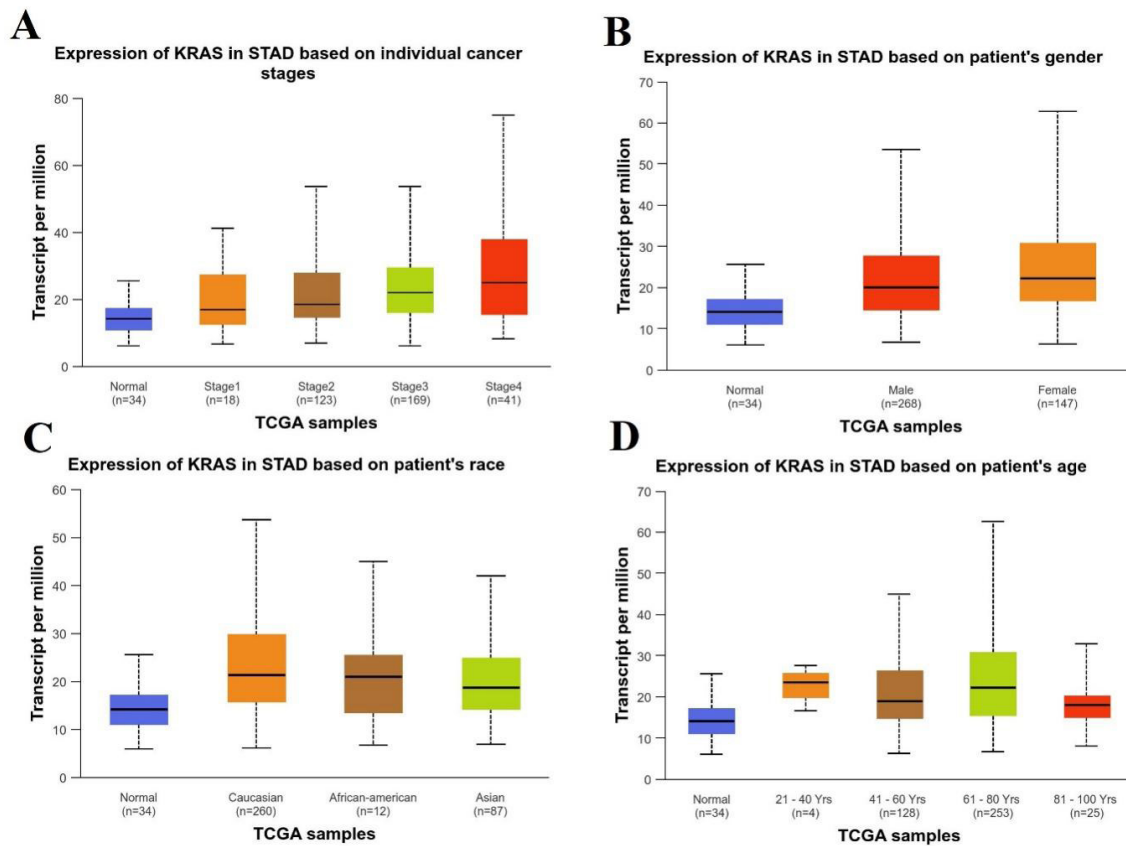


Figure 2. Analysis of KRAS expression in STAD categorized according to various attributes using UALCAN. (A) Analysis of KRAS expression in STAD categorized according to pathological stages. (B) Analysis of KRAS expression in STAD categorized according to the patient's gender. (C) Analysis of KRAS expression in STAD categorized according to the patient's race. (D) Analysis of KRAS expression in STAD categorized according to the patient's age.

3.3. Promoter methylation level of KRAS in STAD and normal

According to prior research, there is an inverse association between expression and promoter methylation. Based on this, the study examined the promoter methylation level of KRAS in STAD using UALCAN^[36]. The result highlighted that KRAS was significantly hypomethylated (P value < 0.05) in STAD samples as compared to normal samples (**Figure 3**). This hypomethylation validates the up-regulation of KRAS expression in STAD and reveals that methylation regulates KRAS expression. This investigation indicates the role of KRAS in the progression of STAD.

3.4. Promoter methylation level of KRAS in STAD categorized according to various variables

The analysis of KRAS promoter methylation level in STAD samples was assessed and categorized according to various variables such as patient's age, race, gender, and cancer stages. Assessment based on STAD individual cancer stages revealed that KRAS is significantly (P value < 0.05) hypomethylated in these stages as compared to normal samples (**Figure 4A**). Next, investigation based on gender indicated variation but hypomethylation of KRAS methylation level in STAD. KRAS was highly hypomethylated in STAD male samples in contrast with female samples and vice versa (**Figure 4B**). Furthermore, the analysis revealed that KRAS is significantly

hypomethylated (P value < 0.05) in STAD patient samples of different races (**Figure 4C**). Moreover, analysis of KRAS methylation levels in STAD based on patient's age demonstrated variation. KRAS was significantly hypermethylated (P value < 0.05) in samples of age group 21–80 and significantly hypomethylated in samples of the remaining age group (**Figure 4D**). This complexity suggests various factors influence the methylation level of KRAS in STAD patient's age samples.

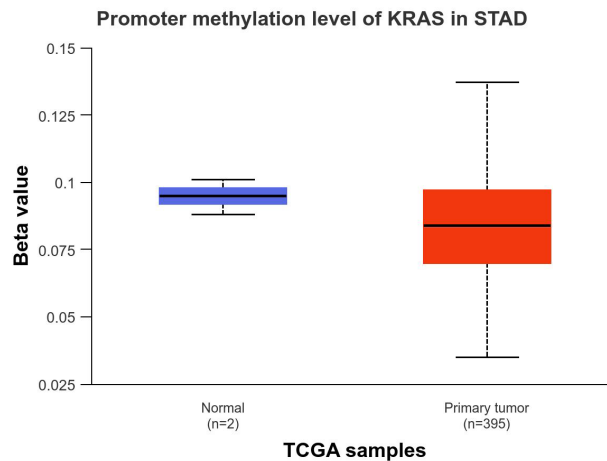


Figure 3. Investigation of the promoter methylation level of the KRAS gene in STAD using the UALCAN database

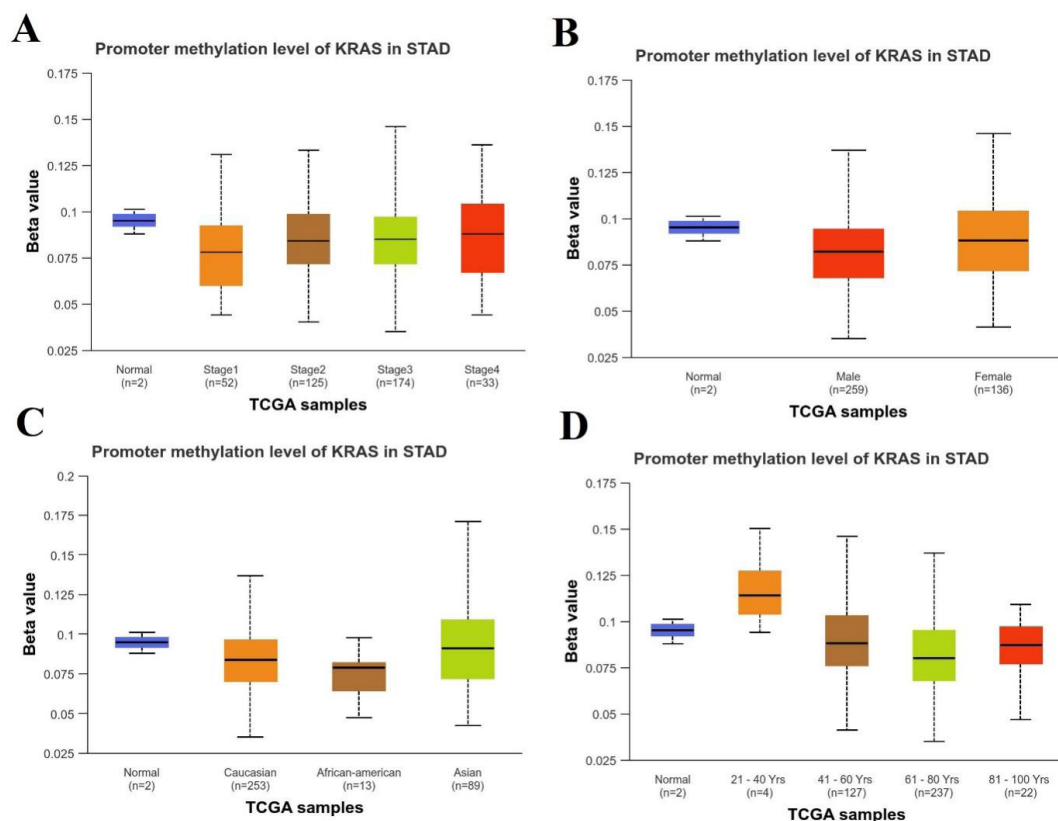


Figure 4. Analysis of KRAS promoter methylation level in STAD categorized according to various attributes using UALCAN. (A) Analysis of KRAS promoter methylation level in STAD categorized according to pathological stages. (B) Analysis of KRAS promoter methylation level in STAD categorized according to patient's gender. (C) Analysis of KRAS promoter methylation level in STAD categorized according to patient's race. (D) Analysis of KRAS promoter methylation level in STAD categorized according to patient's age.

3.5. Prognostic value of KRAS in STAD

The study utilized the KM plotter to examine the impact of KRAS expression on the overall survival (OS) of STAD patients. The investigation indicated that STAD patients with overexpressed KRAS have a low survival rate while patients with lower expressed KRAS have a better survival rate (**Figure 5**). The logrank $P = 0.032$ demonstrates that there is a significant difference and patients with higher KRAS expression have 30% less survival rate hazard ratio $HR = 0.7$ ($0.5-0.97$) indicates. Altogether, the results highlight the role of KRAS in the development and proliferation of STAD.

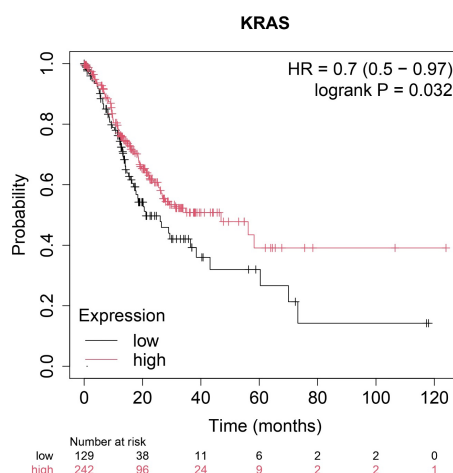


Figure 5. Analysis of the prognostic rate of KRAS in STAD using KM plotter

3.6. Expression and survival analysis using GEPIA2

Simultaneously, GEPIA2 was used to conduct the expression and survival analysis of KRAS in STAD to validate the previous findings. The investigation of KRAS's impact on OS of STAD patients using GEPIA2 demonstrated that there is no significant difference in the prognostic rate of patients with low and high expression (**Figure 6**). The logrank $P = 0.9$ and $HR = 1$ suggested no difference.

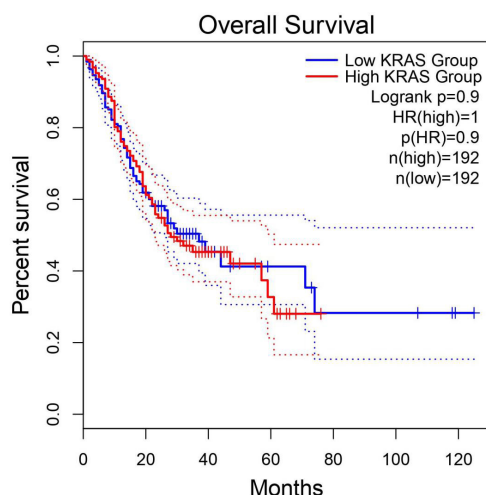


Figure 6. Survival analysis of KRAS in STAD using GEPIA2

The study evaluated the expression of KRAS in STAD in contrast with normal samples using the box plot module of GEPIA2. The study assessed that KRAS was highly expressed in STAD samples compared to normal

samples, but the difference was not significant (**Figure 7A**). Furthermore, the study utilized a stage plot module of GEPIA2 to analyze KRAS expression in STAD pathological stages. The investigation explains that the shape and width of the violin plot are similar, indicating that KRAS expression is equally distributed across these stages (**Figure 7B**). The difference between the KRAS expression is not significant as the P value = 0.283.

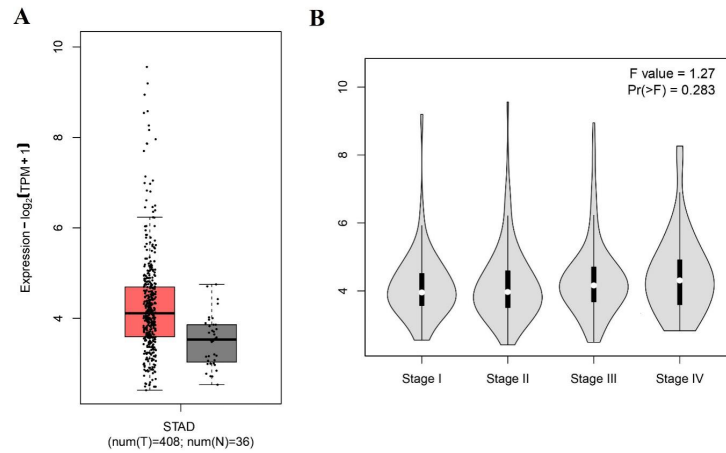


Figure 7. (A) expression analysis of KRAS in STAD using GEPIA2. (B) Expression analysis of KRAS in STAD based on pathological stage using GEPIA2.

3.7. Gene enrichment analysis

The study performed gene enrichment analysis to understand the biological function of KRAS. The study primarily constructed a PPI network using STRING software and assessed 10 strongly associated proteins with KRAS. This explains the diverse association of the KRAS gene and explains its complexity in biological processes (**Figure 8**). Subsequently, employing DAVID software, the study conducted GO and KEGG analysis, evaluating the first four terms for biological process (BP), cellular component (CC), molecular function (MF), and KEGG pathways (**Table 1**).

In GO analysis, the study observed pathways associated with BP, CC, and MF are Ras protein signal transduction, epidermal growth factor receptor signaling pathway, insulin-like growth factor receptor signaling pathway, insulin receptor signaling pathway, cytoplasm, myosin II complex, plasma membrane, cytosol, enzyme regulator activity, calcium ion binding, MAP kinase kinase kinase activity, and protein serine kinase activity. In KEGG analysis, the identified processes are Glioma, neurotrophin signaling pathway, insulin signaling pathway, and Rap1 signaling pathway.

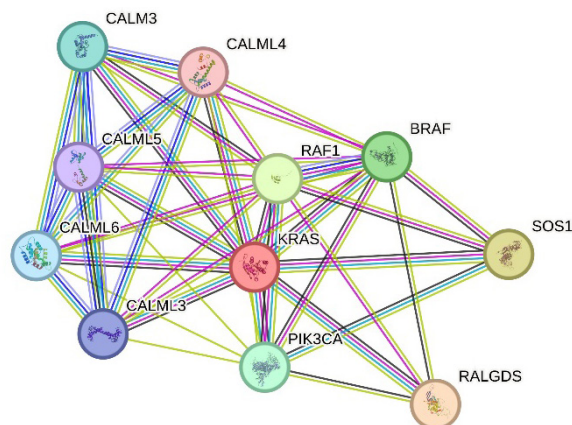


Figure 8. PPI construction of KRAS gene using STRING database

Table 1. GO and KEGG analysis on biological process (BP), cellular component (CC), molecular function (MF), and KEGG pathways

Gene term	Count	Gene	P value
BP			
GO:0007265~Ras protein signal transduction	5	BRAF, KRAS, RAF1, SOS1, RALGDS	4.7867092655479335E-8
GO:0007173~epidermal growth factor receptor signaling pathway	4	PIK3CA, BRAF, KRAS, SOS1	1.8957134610072728E-6
GO:0048009~insulin-like growth factor receptor signaling pathway	3	PIK3CA, RAF1, SOS1	9.105920236010638E-5
GO:0008286~insulin receptor signaling pathway	3	PIK3CA, RAF1, SOS1	4.5202316281570294E-4
CC			
GO:0005737~cytoplasm	8	PIK3CA, CALML6, BRAF, KRAS, CALM3, CALML3, RAF1, SOS1	0.002495574955179402
GO:0016460~myosin II complex	2	CALML6, CALM3	0.014132528548431004
GO:0005886~plasma membrane	7	PIK3CA, BRAF, KRAS, CALM3, RAF1, SOS1, RALGDS	0.014211972791745705
GO:0005829~cytosol	7	PIK3CA, BRAF, KRAS, CALM3, RAF1, SOS1, RALGDS	0.014969131029062653
MF			
GO:0030234~enzyme regulator activity	4	CALML5, CALML6, CALM3, CALML3	2.5450179866138044E-7
GO:0005509~calcium ion binding	5	CALML5, CALML6, BRAF, CALM3, CALML3	2.3862462406048352E-4
GO:0004709~MAP kinase kinase activity	2	BRAF, RAF1	0.009750233042020853
GO:0106310~protein serine kinase activity	3	PIK3CA, BRAF, RAF1	0.011817435270777117
KEGG			
hsa05214:Glioma	9	PIK3CA, CALML5, CALML6, BRAF, KRAS, CALM3, CALML3, RAF1, SOS1	1.8264638958926261E-16
hsa04722:Neurotrophin signaling pathway	9	PIK3CA, CALML5, CALML6, BRAF, KRAS, CALM3, CALML3, RAF1, SOS1	8.098283893995263E-15
hsa04910:Insulin signaling pathway	9	PIK3CA, CALML5, CALML6, BRAF, KRAS, CALM3, CALML3, RAF1, SOS1	2.551728046806132E-14
hsa04015:Rap1 signaling pathway	9	PIK3CA, CALML5, CALML6, BRAF, KRAS, CALM3, CALML3, RAF1, RALGDS	8.46507455081279E-13

3.8. Infiltration level of CD8+ T and tumor purity analysis of KRAS

It was proposed that variation in KRAS expression may have an association with infiltration level of CD8+ T and tumor purity, as KRAS regulates various pathways like the epidermal growth factor receptor signaling pathway and insulin signaling pathway. Therefore, the study assessed the correlation among infiltration level of CD8+ T, tumor purity, and KRAS expression within STAD using TIMER 2.0. In the left plot, the investigation of tumor purity demonstrated a weak negative correlation ($Rho = 0.035$, $P = 0.493$). This reveals that tumor purity and KRAS expression have no significant correlation. However, in the right plot, the assessment of CD8+ T highlighted a weak positive correlation as calculated values were $Rho = 0.117$ and $P = 0.00223$. This

reveals a significant correlation between up-regulated KRAS expression and the infiltration level of CD8+ T (Figure 9). These findings illustrated the potential role of KRAS expression in immune cell infiltrations.

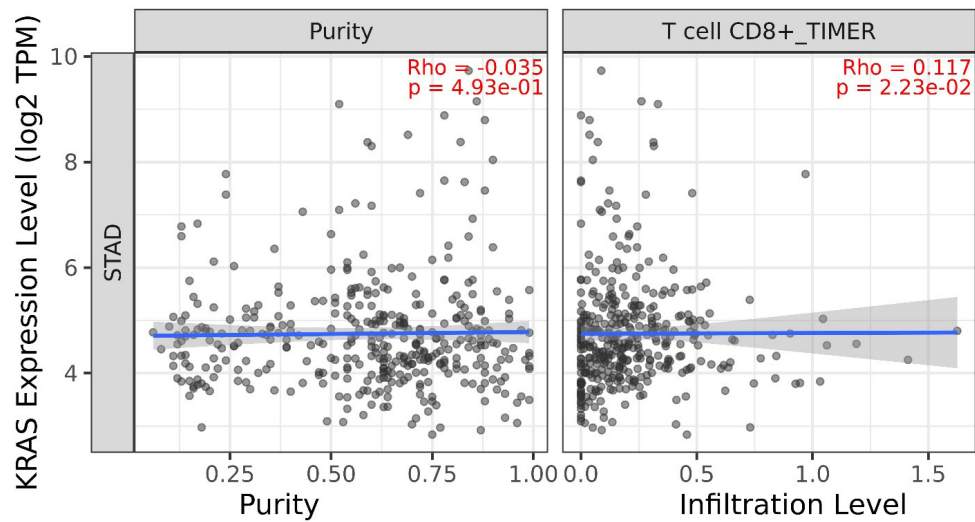


Figure 9. Analysis of correlation of infiltration level of CD8+ T and tumor purity between KRAS expression in STAD using TIMER 2.0

3.9. Genetic alteration of KRAS in STAD

In the study, the assessment of genetic alteration of KRAS in STAD was evaluated using cBioPortal. The analysis revealed that in 16% of genetic mutations of the KRAS gene in STAD, amplification, missense mutation (unknown significance), and missense mutation (putative driver) are observed mutations (Figure 10). This suggested that KRAS genetic mutation has a role in the progression and development of STAD.

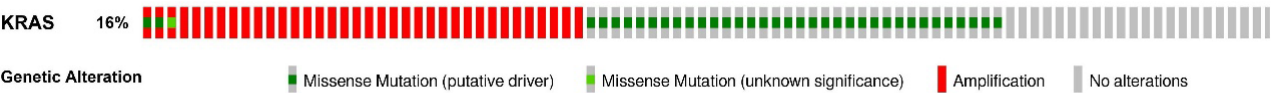


Figure 10. Genetic mutation of KRAS gene in STAD employing cBioPortal

4. Discussion

Cancer is a major threat with millions of mortalities worldwide [37]. Over 90% of stomach cancers are adenocarcinoma and account for thousands of deaths worldwide. It is the cancer with the fifth highest mortality worldwide. STAD is diagnosed at later stages and limited treatments are available. Therefore, the five-year survival rate is just 10%–30% [38–39]. Thus, there is an urgent need to identify useful diagnostic, therapeutic, and prognostic biomarkers of STAD. KRAS is an oncogene and encodes GTPase transductor protein. KRAS protein can become inactive and vice versa and has a role in cell division [40–41]. KRAS is a highly mutated gene in cancers and is linked with many cancers including pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and non-small-cell lung cancer (NSCLC).

The current study started an investigation to evaluate the role of KRAS as a potential biomarker in STAD. The analysis illustrated the up-regulation of KRAS expression in STAD and revealed that the overexpression

is significant (P value = 0.05). Overexpression of KRAS was also determined to be associated with poor OS of STAD patients. Collectively, these findings suggested the role of KRAS in the development and progression of STAD. Furthermore, the study examined the expression of KRAS in STAD based on different clinicopathological parameters and overexpression was evaluated.

Furthermore, the study performed an analysis of promoter methylation and genetic alteration as these factors have an impact on the expression of KRAS. The analysis of KRAS promoter methylation using UALCAN revealed a negative correlation with KRAS overexpression, as KRAS was hypomethylated in STAD. Moreover, 16% of KRAS genetic alteration was assessed in STAD by using cBioPortal. This suggested that mutation strongly regulates KRAS expression and has a role in the progression of STAD. Altogether these results suggested that promoter hypomethylation and genetic alteration have a strong role in the overexpression of KRAS in STAD. The study utilized GEPIA2 to analyze KRAS expression in STAD and analyzed that KRAS was overexpressed. This analysis validates that overexpression of KRAS leads to progression of STAD. In recent years, several studies have identified STAD-related biomarkers such as MAGEA11, FASTKD1, IRF7, CHAC1, NOX4, and HIF1A^[42–44]. However, to our knowledge, up until now neither these nor other biomarkers have been applied to STAD patients with diverse clinicopathological profiles. This study analyzed significant (P value = 0.05) overexpression of KRAS in STAD based on different clinicopathological variables such as patient's age, gender, race, and individual cancer stages. Moreover, KRAS promoter methylation, progression value, and genetic alteration also validate its usefulness as a potential diagnostic, therapeutic, and prognostic biomarker.

Furthermore, the analysis of KRAS's relation with the infiltration level of CD8+ T and tumor purity revealed a significant (P value < 0.05) positive correlation with the infiltration level of CD8+ T and a weak negative correlation with tumor purity. These findings highlight the tumor microenvironment of STAD. Moreover, the PPI network illustrated the association of KRAS with 10 other different genes and this explains the diversity of the KRAS gene. Next, enrichment analysis revealed the linked pathways of KRAS and associated genes. Ras protein signal transduction, epidermal growth factor receptor signaling pathway and enzyme regulator activity are some associated pathways. In KEGG analysis, the identified processes are glioma, neurotrophin signaling pathway, insulin signaling pathway, and Rap1 signaling pathway. Some of these pathways such as Ras protein signal transduction, epidermal growth factor receptor signaling pathway, and Rap1 signaling pathway have been associated with various biological functions including cell cycle, cell proliferation, survival, and immunity^[45–47]. Dysregulation of these processes is one of the main reasons for cancer progression. Thus, these results highlight the role of KRAS in STAD progression.

5. Conclusion

The present study comprehensively analyzed KRAS expression and the association of expression with different variables in STAD utilizing various bioinformatics tools. The advantages of this in silico study include wide-ranging study samples, cost efficiency, and expansion abilities for comprehensive functional and genomic analysis. The findings highlighted the potential of KRAS as a prognostic, diagnostic, and therapeutic biomarker of STAD. However, further testing is needed before it can be used in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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Overview of Skin Cancer and Risk Factors

Muhammad Abubakar*

Department of Biosciences, Comsats University Islamabad, Park Rd, Islamabad Capital Territory 45550, Pakistan

*Corresponding author: Muhammad Abubakar, abubakarbbt3@gmail.com

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Abstract: Skin cancer is a complex and serious health condition with high metastatic abilities and comprises two types including melanoma, the most dangerous type, and non-melanoma skin cancer, such as basal cell carcinoma and squamous cell carcinoma. Skin cancer has a high prevalence ratio and millions of mortalities worldwide. Multiple risk factors account for the initiation, development, progression, and metastasis of skin cancer such as ultraviolet radiations, X-rays, immunocompromised situations, skin lesions, and alteration in genetic makeup. *CEP55*, *FOXM1b*, and *HELLS* genes play critical roles in the progression of the cell cycle, cell proliferation, cell division, DNA replication, and repair system. The overexpression of these genes involves complex molecular mechanisms and is linked with the development and progression of multiple cancers including skin cancer. This review article summarized the history and recent advancement of risk factors for skin tumorigenesis development and progression.

Keywords: Skin cancer; Overexpression; Risk factors; HELLS; CEP55; FOXM1b

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1. Introduction

Skin is the outer covering and largest organ of the human body. It is like a barrier that prevents the body from UV light and other toxic substances to balance the temperature of the human body. The skin consists of three layers dermis, epidermis, and hypodermis^[1]. The outer layer of the skin is the epidermis, the dermis is the skin's inner layer and the deep layer of fat is the hypodermis. The skin protects organs from microbes and regulates the temperature of the body^[2]. There are three layers of skin epidermis which is the outermost layer, beneath the epidermis the layer is dermis and the third layer is hypodermis. Mostly all of the human skin is coated with hair follicles while some can appear hairless. Generally, there are two kinds of skin, hairy and hairless. The epidermis is composed of three systems of cells which are keratinocytes and Langerhans, cells in the Malpighian layer, and melanocytes in the basal layer^[3]. The function of the keratinocyte cells is to synthesize keratin, a thread-like protein with a very protective role. The variation in the layer's thickness depends on the region of the body. For example, the epidermis layer in the eyelid has a thinnest less than 0.1 mm whereas the thickest layer presents in the sole and palm of feet measuring up to 1.5 mm^[4].

The dermis is the middle layer that is beneath the epidermis and is made up of collagen protein which is fibril in structure. The dermis layer is present on the subcutaneous tissue which consists of little projections of fat cells called

lipocytes. The dermis comprises three different cells: mast cells, macrophages, and fibroblasts ^[5]. Hypodermis lies beneath the dermis and is also called subcutaneous tissue. The purpose of its attachment to skin is to underline muscle and bone and supply through nerve and blood vessels. This layer consists of elastin and loose connective tissue. They consist of different cells adipocytes, fibroblasts, and macrophages. The hypodermis layer consists of about 50% of fats and fats serve as a protection and insulator for the body. A hormone produced by lipocytes called leptin regulates body weight ^[6].

Skin cancer was discovered by a French physician Theophile Hyacinthe Laennec (1781–1825), in the 1800s and he was also the inventor of the stethoscope. For the first time, he described autonomous diseases known as black tumors. An old woman was affected by “Cancer Anthracine” at the age of 52 years and a small black spot appeared which bigger with time. The patients later produced metastasis on the skin and due to the tumor, the women died. Like this, different special cases can be proved by English and German authors ^[7]. The cancer that arises from the skin is called skin cancer and it arises due to the invasion of abnormal cells to other regions of the body ^[8]. Non-melanoma are then categorized into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). NMSC grows slowly and can destroy the tissues near it and cannot spread into another region. However, melanoma is the most invading and aggressive skin cancer. More than 90% of skin cancers are caused by UV light, as exposure to UV light increases the risk of skin cancer ^[9].

The incidence rate of skin cancer varies by age and histological type. The most common skin cancers are melanoma and non-melanoma consisting of basal cell carcinoma and squamous cell carcinoma. Melanoma is the 19th and non-melanoma is the 5th most common cancer in the world ^[10]. Skin cancer is more common in fair-skinned people and the occurrence of skin cancer is associated with skin color and geographical zone. In whites, melanoma is more common than in other ethnic people. The developing rate of melanoma is 2.4% in Caucasians, 0.5% in Hispanics, and 0.1% in blacks ^[11]. Melanoma is more common in males than in females. Malignant melanoma presents more in females as compared to males after age 50 but overall melanomas are more common in men. At the age of 15–29, melanomas are increasing faster in females than males ^[12]. The sum of all data showed a continuous increase in the incidence of skin cancer in Europe, Canada, and the USA during the last decades. In New Zealand, the highest incidence rate has been reported with 50 cases within 100,000 persons, 48 cases per 100,000 persons in Australia, followed by 48 cases per 100,000 in the US, and 13.2 cases per 100,000 in Europe ^[13–14]. In Asia, skin cancer is approximately 2 to 4 percent of all cancers. The frequency of skin cancer is very low in the Pakistani population as compared to the Western world. However non-melanoma skin cancer is increasing in the Asian population including Pakistan ^[15]. Skin cancer will double in the next 30 years in the Asian population. Among the 80,000 deaths that occurred in 2010 due to skin cancer, 49,000 were due to melanoma while 31,000 were due to non-melanoma skin cancer ^[16].

BCC occurs mostly on open regions of the body like the neck or face and it appears as a waxy bump, a brown or fleshed-colored scar-like lesion, and a bleeding sore that heals and reappears. SCC also occurs in sun-exposed areas and most likely in dark-skinned people. It may appear as a firm, red nodule and a flat lesion with a scaly, crusted surface. Melanoma can grow in any place on the body, in any case, typical skin or in a current mole that gets malignant ^[17]. Melanoma frequently shows up on the face of influenced men. In females, this sort of malignant growth frequently occurs on the lower legs. It may appear as a brownish spot with black dots, a mole that changes in color and size, a small lesion with an irregular border, a painful lesion that itches or burns, and dark lesions on palms, soles, fingertips, or toes ^[18].

2. Grades of skin cancer

Skin cancer is categorized into stages like other cancers. The World Health Organization (WHO) specified

the grading criteria for skin cancer and it is graded from I to IV ^[19]. Some of the main characteristics of these tumors are listed below in **Table 1**.

Table 1. Main characteristics of skin tumors (Grade I to IV)

Grade	Characteristics
I	They mostly look like normal cells/tissues and are considered low-graded tumors and are called well-differentiated.
II	These tumors have a slightly abnormal appearance and are called moderately differentiated.
III	These tissues look very abnormal and poorly differentiated. Grade 3 is considered a high grade.
IV	They look more abnormal than other cells and tissues. They are higher grades and spread faster than other lower grades.

3. Types of skin cancer

Skin cancer is grouped into malignant melanoma and nonmalignant skin cancers. Non-melanoma consists of basal cell carcinoma and squamous cell carcinoma. Research estimates have shown that BCC and SCC affect more than 3 million Americans a year ^[20]. Some of the common groups of skin cancer are shown in **Table 2**.

Table 2. Major types of skin cancer

Cancer types	Description	Appearance	Severity	Occurrence
Basal cell carcinoma	Develop in the basal cell of the skin epidermis	Non-lethal, open sour, small pink growth	Less severe than other types	Most widely occurred cancer
Squamous cell carcinoma	Develop in the squamous cells of the skin	Just like wart scaly patches, pen sores	More severe than the BCC	Less occur than BCC
Melanoma	Develop in the skin cell called melanocyte	Multi-colored, asymmetrical, size may reach 6mm	The most severe type termed a deadly skin cancer	It occurs rarely

BCC is the most common type of skin cancer and is also known as basal-cell cancer. BCC has a slow-growing rate and infects the tissue near it, but not spread to other areas. Globally, BCC represents 32% of all cancers and 80% of all skin cancers. It is considered that BCC originated from trichoblasts which are follicle-sebaceous-apocrine germ. On the other hand, one contention is that basal-cell carcinoma is trichoblastic carcinoma ^[21]. DNA damage due to exposure to the sun results in the formation of dimer. Most mutated regions are removed during the DNA repair mechanism but not all crosslink-caused mutation. More than 99% of people with BCC are White, and more than 95% are aged over 40 years old. Half of BCC patients are men ^[22].

The 2nd most common skin cancer is squamous cell carcinoma, which is also called cutaneous cell carcinoma and makes up about 20% of NMSC. SCC has more spreading ability than BCC to distinct regions. When limited to the peripheral layer of the skin, a precancerous or in situ type of SCC is known as Bowen's sickness ^[23]. They are created from the flat squamous cells that make up a lot of the epidermis, the peripheral layer of the skin. This sort of skin malignant growth is generally found on territories of the skin that have been exposed to the sun, for example, the neck, ears, face, or the back of the hand. However, they may be created in different regions, for example, in scars, skin ulcers, or the genital region. According to the 2015 GBD report about 2.2 million people have SCC and about 51,900 deaths occurred globally ^[24]. Melanoma is a type of skin cancer that develops from a pigment-containing cell known as melanocytes. Melanoma is also called malignant melanoma. They commonly occur on the legs in females and on the back in males. Approximately 25% of

melanoma develops from moles. Changes that occur in mole such as an increase in size, color changes, irregular edges, and itchiness indicate melanoma. Melanoma is caused by UV light exposure and low pigment levels ^[25].

4. Risk factors

Multiple factors are responsible for skin cancer such as UV exposure, hereditary factors, and environmental risk factors. Skin cancer is also caused due to genetic polymorphisms. Skin cancer is more common in older than young people. Mostly non-melanoma skin cancer appears after 50 years of age. In recent years, skin cancer dramatically increased in people after 65 years of age. After 70 years of age, Merkel cell cancer is most common. Skin cancer also develops in younger people, when they have fair skin ^[26]. In humans, the most exposed organ to ultraviolet radiation (UVR) is the skin. DNA damage, a mutation that occurs in genes, and other factors that play a role in the photoaging of skin are affected by ultraviolet radiation ^[27-28]. UVR reaching the surface of the earth is influenced by several factors like altitude, latitude, weather conditions, and UV light elevation. There are two main types of ultraviolet rays UVA and UVB. Rays that are passed into the skin deeper are UVA than UVB such as elastosis. There is indirect damage from UVA rays to DNA, mediating the formation of free radicals and damage to cellular membranes. Erythema or sunburn is caused due to UVB rays ^[29]. DNA damage will occur even on low exposure to UVA/UVB. Before the age of 20, most skin damage was from UV light, but the effects will only appear many years later. People who work outdoors have a higher risk of developing skin cancer because of more exposure to the sun. UV rays directly affect the p53 suppressor gene, which is found mutated in melanoma ^[30]. The incidence of melanoma correlates with the annual average amount of UV radiation. The intensity of UV will be greater on and near the equator. Latitude shows a direct relationship with the incidence of melanoma. Melanoma will be greater in those individuals who are living in high-altitude regions due to greater UV influences ^[31]. In women, melanoma is found frequently on the legs and commonly on the back of men due to UV exposure. People living in the high UV radiation of Australia have a higher risk of melanoma than those who are living in Northern Europe and migrated there at 10 years of age or older ^[32].

Every stage of carcinogenesis is affected by UV exposure so it is a complete carcinogen. After high exposure to UV, apoptosis of keratinocytes led by the pathway p53/p21/bax/BCL-2 followed by a hyperproliferative phase, resulting in epidermal hyperplasia. Exposure to solar radiation which is nonionizing specifically UVB and UVA is an important risk factor in the pathogenesis of BCC ^[33]. UV radiation of keratinocytes increases the production of the gene proopiomelanocortin (POMC) and α -melanocyte-stimulating hormone (α MSH), which is highly involved in pigmentation of skin whether skin produces red-yellow pigment (pheomelanin) or brown-black pigment (eumelanin) ^[34]. UV radiation not only damages the DNA directly but also indirectly by producing UV-induced immunosuppression and free radicals. UV radiation affects Langerhans cells (LCs) which result in the loss of dendritic network form in the epidermis ^[35]. LCs are damaged by UV which induces regulatory T cells (Tregs) to produce IL-10, an immune-suppressive cytokine. Dermal fibroblasts and keratinocytes produced IL-33 which is why mast cells (MCs) in the skin increase response to UV radiation ^[36]. Proteoglycan (PGs) are formed from GAG strains and protein scaffolds. PGs take part in the structuring of collagen fiber, and it affects the formation and separation of extracellular matrix. Heparan sulfate proteoglycans (HSPG) play a role in the extracellular matrix ^[37]. Proteoglycan strain cleaves by heparanase which increases the tumor cell growth, resulting in the formation of oligosaccharides that enhance angiogenesis and growth factors production, causing inflammation and cell proliferation ^[38]. Therefore, heparanase is involved in the formation of BCC and SCC. Discontinued UV exposure might be associated with melanoma and BCC appearance and continuous UV exposure is related to SCC. UV exposure affects the expression of p53 which changes in both SCC and AKs ^[39].

Different studies have shown that X-rays also affect the pathogenesis of NMSC. A study reported that the skin cancer risk is increased due to therapeutic ionizing radiations (IRs), like X-rays. It has been reported that radiation therapy for acne can increase the risk of new BCC [40]. Those who received radiation therapy at an early age have a higher risk of NMSC [16]. The dormancy period between the development of NMSC and first exposure is at least 20 years, although the dormancy effect differs based on treatment age and therapy types received [41]. Production of radicals or bond-breaking is due to the ionizing radiation absorption that leads to damage in cellular molecules. Double (DSBs) or single bond breaks are produced due to IR exposure. Cell death is caused by double-stranded breaks [42]. After DSBs, H2AX histone is converted to a γ -H2AX phosphorylated form in the involved region to repair the damage. Different studies have shown that cellular mass could be increased after cellular damage due to P53 accumulation. Apoptosis, DNA repair, or arrest of the cell cycle results in P53 accumulation [43].

Gamma, beta, and alpha are different types of cutaneous human papillomavirus (HPV). In immunosuppressed patients, beta-HPV plays a role as a cofactor in SCC. Different studies have shown that in SCC lesions DNA is detected in multiple beta-HPV types [15]. Beta-papilloma virus plays a role in tumorigenesis of SCC, changing cell cycle progression, repairing DNA, and surveillance of the immune system resulting in the expansion of keratinocytes [44]. Different studies have shown that some alpha-HPV is identified in SCC. HPV77 is detected in cutaneous lesions of immunosuppressed patients. However, in SCC, the exact role of HPV remains unclear because, in normal skin samples of SCC patients, the DNA of HPV has also been found [45]. In the rise of skin cancer, the involvement of HPV infection was described by Lutz and Lewandowsky based on Epidermodysplasia verruciformis (EV) for the first time. EV is a heritable disease characterized by specific types of HPV, called EV-HPV types, which are now termed β -HPV types [46]. The risk of causing SCC is likewise expanded by exposure to cancer-causing chemicals, overall arsenic. In vitro arsenic exposure results in an increase in the expression of many proteins, such as keratin 7 and keratin 9. On the other hand, the involucrin production is reduced. Inflammatory pathways were associated with these proteins which affect the growth of skin neoplastic, such as nuclear factor (NF)- κ B and tumor necrosis factor (TNF)- α [47]. Previous studies have shown that a member of the transmembrane 4 superfamily CD151, increases the carcinogenesis of skin and induces SCC development. Therefore, it has been concluded that inflammation causes an increase in carcinogenesis by testing animal models with chemicals [48].

In carcinogenesis, immunosuppression plays the main role in NMSC development. Earlier studies have shown in immunosuppressed patients, that many class I and II of (human leukocyte antigen) HLA allele groups were related to SCC. However, many studies have not proved this association. A study has observed that there is no association between SCC and HLA-A*11 [49]. It has been reported that there is no association found between SCC and HLA-DRB1/01 in immunosuppressed patients, opposite to the association found positive in immunosuppressed patients [50]. It has been reported that in SCC, the heterogeneous expression of protein class I HLA may also explain why immunosuppression raises the risk of BCC to 10-fold, but SCC up to 65-fold. Indeed the pathogenesis of SCC may be better controlled by immune surveillance because of the partial expression of protein I HLA, in comparison to BCC, wherein BCC the protein class I HLA is completely absent [51]. Therefore, this lost insusceptible observation shows that immunosuppression would influence SCC pathogenesis more than that of BCC. In this way, research suggested that the unusual expression of the HLA-G protein on the outside of SCC malignant growth cells in immunosuppressed patients was taken into consideration. The immunomodulatory impacts of HLA-G under ordinary physiological conditions are very much reported [52]. HLA-G in early-stage tissues, grown-up resistant special organs, and hematopoietic cells give inhibitory signs to natural killer cells (NKC) and T cells. Subsequently, HLA-G articulation on SCC tumors

could permit tumoral cells to contrarily manage NK and T lymphocyte-interceded obliteration. Moreover, it has been accounted for that HLA-G articulation was available in different malignant growths (melanoma, colon, breast, lung, and renal), and that melanoma cell lines communicating HLA-G isoforms had repressed cytotoxic reactions from NK and T-cells ^[53]. Besides, UV radiation has suppressive effects on skin immunity. It has been reported that lesions such as cyclobutane pyrimidine dimers (CPDs) are immune-suppressive and are induced by UV radiation ^[54]. Furthermore, other molecules are stimulated by UV radiation with immunosuppressive characters like prostaglandins, platelet-activating factors, reactive species of oxygen (ROS), and IL-10. Moreover, memory T cells, cytotoxic T cells, and mast cells are inhibited by UV radiation and activated by the natural killer cells, T lymphocytes, and regulatory B lymphocytes. All these findings highlight sharply the clear relationship between UV radiation and immunosuppression ^[55–56].

Changes occur in DNA that affect gene expression through acetylation, methylation, and phosphorylation. These changes play an important role in apoptosis, cell division, cell proliferation, growth, and tumorigenesis ^[57]. There are several epigenetic risk factors for skin cancer. Changes occur in some genes increasing the risk of skin cancer. Cyclin Dependent Kinase Inhibitor 2A (CDKN2A) also called P16 is the best-known gene that associates the higher risk of melanoma. There are other genes like MC1R, MITF, and TERT genes that are associated with a higher risk of skin cancer ^[58]. About 5%–10% of skin cancer cases are inherited. There are 50/50 chances of skin cancer if the patient has a defined genetic mutation. One type of melanoma caused by hereditary are called familial atypical mole-melanoma syndrome (FAM-M syndrome), caused by an alteration in the CDKN2A gene on chromosome 9. Mutations in p16 result in unregulated cell growth and have an increased lifetime risk of developing melanoma ^[59–60].

5. Role of CEP55, FOXM1b, and HELLS genes in skin cancer

Centrosomal protein 55 (*CEP55*) is a gene that encodes the protein *CEP55* and plays an important role in cytokinesis. The upregulation or downregulation of *CEP55* has resulted in cytokinesis problems and increasing multinucleated cells. The growth of cancer cells has been increased due to overexpression of *CEP55* ^[61]. The *CEP55* gene is located on chromosome 10q23.33, extents 32.5kb of genetics distance, and forms 70-kDa proteins comprising 464 amino acids which are translated by 9 exons. As for the cytogenetic location of *CEP55*, it is a member of the centrosome and mid-body associated protein family, and it takes part in the cytokinesis process. Much evidence has shown that *CEP55* was overexpressed in multiple tumors ^[62]. Overexpression of *CEP55* may increase the migration, invasion, and proliferation of tumor cells. In different oncogenic processes the main role played by the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway, includes apoptosis, differentiation, cell proliferation, invasion, epithelial-mesenchymal transition (EMT), and migration ^[63]. Different studies have shown that there is an interaction of other molecules to signal the PI3K/Akt pathway that may regulate the biological behavior of cancerous cells. Previous research demonstrated that in ESCC, *CEP55* is overexpressed. They showed that *CEP55 increases the proliferation of cells* in-vivo and in vitro, regulates migration and invasion of cells, and induces ESCC cells to undergo EMT via the PI3K/Akt pathway ^[64]. The knockdown of *CEP55* can significantly inhibit viability and tumor cell proliferation and result in tumor cell death. It has been determined that EP55 is an antigen related to tumors as well as a cancer-testis antigen. Testis-specific proteins that are typically expressed mostly in the testes but become additionally expressed in malignancy are known as cancer-testis antigens ^[65]. According to some current studies, CEP55 influences the PI3K/AKT signaling pathway and promotes cancer. An increasing body of research shows a link between CEP55 overexpression and the onset and spread of several malignant tumors, such as lung,

stomach, and breast cancers. When CEP55 is knocked down, tumor cells may experience severe viability and proliferation inhibition or possibly die. It has been shown that liver patients with overexpression of CEP55 may have a poor prognosis ^[66].

Forkhead box M1b (*FOXM1b*) gene is present on chromosome 12p13.13 and is made up of 10 exons. Due to the splicing of Exon Va and VIIa, *FOXM1* gives rise to 3 isoforms which are *FOXM1a*, *FOXM1b*, and *FOXM1c*. *FOXM1a* contains both Va and VIIa which is why *FOXM1a* lacks transactivational activity ^[67]. Both *FOXM1b* (which lacks either exon) and *FOXM1c* are transcriptionally active. It has been suggested that *FOXM1b* is present in cancer cells and has a high transforming potential. *FOXM1b* is involved in transcriptional activation and is expressed in the testes and skin. The expression of *FoxM1* in primary breast cancer, basal cell carcinomas, and hepatocellular carcinoma is up-regulated ^[68–70].

There are three major domains of *FOXM1b*, consisting of the N-terminal repressor domain (NRD), FKH domain, and Transactivation domain (TAD). FKH plays a role in the activity of DNA binding whereas NRD helps in *FOXM1b* auto-regulatory activity. The structure of FKH domain of *FOXM1b* containing three α -strands (S1, S2, S3), three β -helices (H1, H2, H3), and two loops or wings (W1, W2) and arranged them in H1–S1–H2–turn–H3–S2–W1–S3–W2 order. In three alternatively spliced exons, FKH consists of two spliced exons. The absence or presences of these exons affect the specificity of DNA binding ^[71]. In humans, *FOXM1a*, *b*, and *c* are the variants. *FOXM1b* (also known as HFH-11B, FKHL16, Trident, Win, MPP2, MPM2) contains no additional exons. *FOXM1b* is transcriptionally active. The binding affinity of DNA in *FOXM1b* is higher than other variants ^[72]. The only isoform that was found showing cell cycle-dependent mRNA expression pattern in two different human cell lines is *FOXM1b*. It is expressed in B and T lymphoid, erythroid cell lines, myeloid cell lines, and different carcinoma cell lines. The function of *FOXM1b* is to regulate the expression of genes in the cell cycle. *FOXM1b* is expressed during the G1 phase and keeps an invariant transcript and level of protein during the G2, S, and M phases ^[73]. Cell proliferation is controlled by *FOXM1b* through inhibiting factors that repress the entry of phases M and S, like cyclin-dependent kinase inhibitors (CKI), p21 CIP1/WAF1 and p27Kip and by cyclin-dependent kinases (CDK) activators, like cyclin A/CDK2 for S-phase entry ^[74]. In addition, it also plays a crucial role in executing mitosis properly as evident from the development of pleiotropic mitotic defects such as aneuploidy and polyploidy, chromosome segregation anomalies, and defects in mitotic spindle formation in *FOXM1* deficient cells ^[75].

According to a significant amount of evidence, *FOXM1* is a transcription element related to proliferation. The thymus, testis, small intestine, and colon of adult mice exhibited elevated levels of *FOXM1*, while in vivo expression experiments in mouse embryos revealed significant levels of expression in all organs ^[72]. However, since the ovary, spleen, and lung have fewer dividing cells than other organs, the levels were noticeably lower there. Additionally, it has been discovered that *FOXM1* is expressed in erythroid, myeloid, and B and T lymphoid cell lines as well as several cancer cell lines; however, it lacks expression in inactive or terminally differentiated cells ^[76]. The main role of *FOXM1* is to control how cell cycle genes are expressed. It expresses itself in the G1 phase and continues to be represented at the same transcript and protein level in the S, G2, and M phases. *FOXM1* primarily regulates cell proliferation in mammalian cells by stimulating cyclins or cyclin-dependent kinases (CDK) activators, such as cyclin A/CDK2, for S-phase entrance, and by preventing elements that suppress S and M-phase entrance, such as cyclin-dependent kinase inhibitors (CKI), p21 CIP1/WAF1, and p27Kip ^[77]. The specificity subunits of the Skp1-Cullin1-F-box (SCF), Skp2, and Cks1, whose transcription has been linked to *FOXM1* regulation, are crucial for controlling CDKI degradation during the G1/S transition. Furthermore, as demonstrated by the emergence of pleiotropic mitotic problems in *FOXM1* defective cells, including aneuploidy and polyploidy, chromosomal segregation abnormalities, and difficulties in mitotic spindle

growth, it is essential for the efficient execution of mitosis ^[78]. Microarray, chromatin immunoprecipitation (ChIP), and, more recently, ChIP-seq studies have demonstrated that *FOXM1* regulates the expression of G2 phase genes, which include crucial mitotic regulators such as CCNB1 (Cyclin B1), Cyclin A, AURKB, Survivin, Plk1, Cdc25B (cell cycle progression and mitotic entry); CENPA, CENPB, CENPF (essential for mitotic spindle checkpoint integrity), and MYC (c-Myc) studies. Genes controlled by *FOXM1* control the cell cycle and other biological processes ^[79]. Additionally, FOXM1 prevents early cellular death. The characteristics of FOXM1 deficient MEFs and FOXM1 knockout MEFs showed early senescence. Through overexpression research, the traits were reversed by raising the expression of *FOXM1*, and a similar outcome was obtained using c-Myc to induce the polycomb protein Bmi-1 ^[80].

A growing body of proof indicates that *FOXM1* plays a critical role in maintaining genomic integrity and responding to DNA damage. This idea was supported by the abnormalities that *FOXM1*-deficient MEFs showed, including polyploidy, aneuploidy, cytokinesis problems, chromosome missegregation, and a high frequency of DNA breaks ^[76]. When osteosarcoma cells were given a FOXM1 knockdown, similar outcomes were observed. According to research reports, FOXM1 overexpression reduces the buildup of double-strand DNA breaks in MCF-7 cells, indicating that it primarily plays an essential function in homologous recombination. Five HR genes are among the most significant FOXM1 target genes (*brca2*, *xrcc2*, *exo1*, *rad51*, *brip1*). In response to genotoxic stress, FOXM1 also promotes the expression of the DNA repair genes XRCC1 (X-ray cross-completing group 1) and BRCA2 (breast cancer-associated gene 2). It was recently discovered that NBS1, an essential part of the DNA damage repair complex, is also a *FOXM1* target gene ^[74]. Their research showed that *FOXM1* overexpression increases ATM phosphorylation and NBS1 expression by adjusting MRN (MRE11/RAD50/NBS1) complex phases, which activates DNA damage healing signaling. Additionally, it was discovered that *FOXM1* interacted with NFκβ in breast cancer cells subjected to doxorubicin to control the activity of DNA repair genes such as EXO1, RFC4, POLE2, and PLK4, thereby shielding the cancer cells from double-strand breaks caused by doxorubicin ^[81]. The balance between cell division, proliferation, and apoptosis is maintained by *FOXM1* signaling, and numerous human malignancies are characterized by aberrant *FOXM1* gene transcription. Several tumors, including head and neck squamous cell carcinomas, pancreatic cancer, lung cancer, stomach cancers, and cervical squamous cell carcinomas, have been linked to the development of the 12p13 chromosomal band encoding the *FOXM1* gene ^[82]. Furthermore, one of the most frequently elevated genes in human solid tumors is *FOXM1*, according to gene expression profiling of malignancies. This finding confirms the connection between *FOXM1* dysregulation and the advancement of cancer. The primary mechanism by which *FOXM1* exhibits oncogenic capability is through transcriptional activation of genes implicated in many aspects of cancer formation. There have been reports of many oncogenic signaling pathways interacting with the *FOXM1* pathway. It has been discovered that the hedgehog signaling pathway increases the expression of the *FOXM1* gene in lung, basal cell, skin cancer, and pancreatic cancers. This signaling pathway's constituent parts are connected to *FOXM1*. For example, it has been noted that Gli1 overexpression occurs in NSCLC, and this is known to activate the transcription of *FOXM1* in basal cell carcinoma ^[67]. Moreover, it has been demonstrated that Gli2 is primarily involved in basal cell and hepatocellular carcinoma. Additionally, notch signaling is essential for the continued existence of prostate cancer cells. It achieves this by downregulating Akt and *FOXM1*, which inhibits cell proliferation and induces death ^[83].

The existence of *FOXM1* interaction motifs in the Caveolin-1 (Cav1) promoter, which is known to be essential for the advancement of pancreatic cancer, and EMT significantly elucidates the involvement of *FOXM1* in the development and severity of pancreatic cancer. Additional research on the *FOXM1*-Cav1 signaling pathway in developing more effective therapeutic strategies to manage this fatal cancer ^[84]. Similar to

FOXMI, COX-2 is also overexpressed in a variety of tumors and has been linked to other illnesses. Lung cancer is caused by the binding and stimulation of COX2 promoter expression by the *FOXMI*-responsive component present in the COX2 promoter ^[85]. *FOXMI* has been linked to tumor angiogenesis, invasion, and metastasis, and it is involved in the initiation and advancement of numerous malignancies. According to the latest findings, downregulating *FOXMI* prevents breast cancer cells from growing, migrating, and invading other cancers such as pancreatic, hepatic, and stomach cancers ^[86]. By preventing the expression of several molecules, including uPA, uPAR, MMP-2, MMP9, and VEGF (vascular endothelial growth factor), which are involved in the breakdown of extracellular matrix and angiogenesis. Along with other genes known to accelerate tumor growth, *FOXMI* is also included in the cluster of genes associated with breast tumor development. Research has demonstrated that *FOXMI* regulates ER α expression in breast cancer cells biologically. In addition to promoting carcinogenesis and hormone insensitivity in breast tumors, ER α regulates *FOXMI* ^[69]. Further data indicates that *FOXMI* expression is negatively regulated by ER α , which in turn plays an anti-proliferative effect in the progression of breast cancer. A HER2-resistant breast tumor may benefit from targeting *FOXMI* as a novel therapeutic target, as indicated by a different study that likewise revealed a favorable association between *FOXMI* expression and HER2 status. Overexpression of *FOXMI* was found to stimulate the promoter of Slug, an EMT-related gene, hence promoting EMT in breast cancer ^[67].

Variation in the expression of genes may result in cancer development. The first proof of *FOXMIb* connected to epigenetic regulation was the knowing of *HELLS*, a chromatin redesigning/DNA helicase, as a downstream target of *FOXMI* in head and neck squamous cell carcinomas (HNSCC) ^[67]. Atypical upregulation of *FOXMIb* was found to reprogram the normal cells by altering its methylation towards those found in malignancy cells, through the enrollment of *HELLS* and two DNA methyltransferases *DNMT1* and *DNMT3B*. Evidence from previous studies has also shown that expression of *FOXMI* with *HELLS* and *CEP55* is a biomarker for early cancer detection. In many cancers, overexpression of *FOXMIb* was detected and it was associated with instability of chromosomes. During mitosis, Phosphorylation of *FOXMIb* occurs and is initiated by Cyclin–Cdk complexes, such as Cdk1, Cdk2, and mitogen-activated protein kinase (*MAPK*) in G1 and continued through the G2 and M-phases of the cell cycle ^[88]. Activation of *FOXMI* may inhibit tumor suppressor proteins P53 and other inhibiting factors such as p21 and p27. This means that over-expression of *FOXMI* is associated with an increase in cancer cells ^[89].

Lymphoid-specific helicase (*HELLS*) gene encodes an enzyme called Lymphoid-specific helicase in humans. The function of helicase included DNA strand separation, replication, repair, recombination, and transcription. *HELLS* are involved in cellular proliferation and play a role in leukemogenesis ^[90]. If downregulation occurs in *HELLS*, then genetic instability increases, and additional effects on DNA methylation could contribute to tumorigenesis. *CEP55* accompanied by other molecules (*FOXMI* and *HELLS*) could be used as a biomarker set for early diagnosis of head and neck squamous cell carcinoma ^[91]. The *HELLS* gene is located on chromosome 10q23.33, and forms 97-kDa proteins comprising 838 amino acids which are translated by 26 exons. *HELLS* protein consists of helicase C-terminal and helicase ATP binding. It also contains a nuclear localization signal ^[92]. *HELLS* is a member of the SNF2 family of chromatin remodeling proteins that use ATP to change the structure of chromatin. These changes together with altering in other epigenetic mechanisms like methylation of DNA, and histone modification change the cellular processes such as mitosis, transcription, DNA repair, and meiosis. *HELLS* is also important for gene control of stem cells, meiosis, DNA repair, and packaging of repetitive DNA ^[93–94]. *HELLS* play an important role in cellular proliferation and mammalian development through methylation of DNA and chromatin-remodeling. Removing of *HELLS* gene caused cellular senescence, premature aging, developmental retardation, gene modification, or upregulation of *HELLS*

causing various cancers including skin cancer ^[95]. In the embryonic stem cell, expression of *HELLS* was identified recently as one of the consent genes. *HELLS* is involved in the control of expression of the p16 tumor suppressor gene through repression, and decreasing *HELLS* caused increasing in the expression of p16 in small lung cancer ^[96]. P16 is also suppressed by *FOXM1b* ^[97]. A study additionally recommended that *HELLS* could control the expression of stem cell genes to induce the proliferation of stem cells and keep up self-renewal by interfacing with two transcriptional factors, E2F3 and MYC. In CRC, *HELLS* incites the expression of TET2 and TET3, which essentially impair metastasis, while in most revealed cases, *HELLS* is considered a positive controller of metastasis ^[98]. It can be hypothesized that the *HELLS* gene's role in DNA repair has potential involvement in skin cancer, particularly considering the role of UV radiation in inducing DNA damage.

6. Conclusion and future dimensions

The intricate interplay between genetic predisposition and environmental factors in the pathogenesis of skin cancer is a complex and multifaceted area of research. While the focus of this review has been on the roles of *CEP55*, *FOXM1b*, and *HELLS* genes, it is imperative to acknowledge the broader spectrum of genetic and environmental risk factors contributing to skin cancer development. Established risk factors such as excessive sun exposure, fair skin type, and immunosuppression undoubtedly play pivotal roles. However, the identification of additional genetic markers and their interactions with environmental stimuli holds the potential to revolutionize the understanding of disease etiology and prevention. Future research should delve deeper into the complex interplay between these genes and other established risk factors. Large-scale population-based studies incorporating both genetic and environmental data are essential to elucidate gene-environment interactions and identify high-risk populations. Furthermore, functional studies aimed at elucidating the precise mechanisms by which these genes contribute to skin cancer pathogenesis are warranted. Ultimately, a comprehensive understanding of the genetic and environmental landscape of skin cancer will enable the development of personalized prevention strategies, early detection methods, and targeted therapeutic interventions. By unraveling the intricate web of factors contributing to skin cancer, researchers can strive towards improving patient outcomes and reducing the global burden of this disease.

Disclosure statement

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Author contribution

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Analysis of the Application Effect of Comprehensive Nursing Intervention in Elderly Patients with Cirrhosis Ascites

Rui Cao*

Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

*Corresponding author: Rui Cao, 254142704@qq.com

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Abstracts: *Objective:* To investigate the effects of comprehensive nursing intervention on the complication rate, nursing satisfaction, and prognosis of elderly patients with cirrhotic ascites. *Methods:* 62 elderly patients with cirrhotic ascites were selected for the study, and the inclusion time was from January 2022 to January 2023. According to the random method, the patients were divided into the reference group and the observation group, and conventional nursing and comprehensive nursing were carried out to compare the nursing effect, respectively. The patient's satisfaction with care and prognosis was investigated. *Results:* The quality of life and satisfaction scores of the observation group were higher than those of the reference group, and the complication rate was lower ($P < 0.05$). *Conclusion:* Comprehensive nursing intervention in patients with cirrhosis ascites can reduce the incidence of complications, and is conducive to improving their quality of life and satisfaction.

Keywords: Comprehensive nursing intervention; Cirrhosis ascites; Effect analysis

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1. Introduction

Cirrhosis is a chronic liver disease with a high recurrence rate and a long duration of illness, which is usually manifested by portal hypertension, liver function damage, and so on, and ascites will be formed in the late stage. Elderly patients with multiple coexisting diseases have a higher chance of complications. If the treatment is not timely enough, it is likely to induce liver failure, and may even pose a threat to the patient's life safety^[1]. Therefore, it is necessary to provide patients with appropriate comprehensive nursing interventions during clinical treatment to improve the therapeutic effect and improve their prognosis^[2]. This paper mainly focuses on the impact of nursing intervention on the incidence of complications, nursing satisfaction, and prognosis of elderly cirrhotic patients with ascites.

2. Information and methods

2.1. General information

62 cases of elderly patients with cirrhosis and ascites were selected for the study, the inclusion time was from January 2022 to January 2023, and the median age of the reference group was 57.06 ± 1.22 years. The patients were divided into two groups according to the random method, with 20 males and 11 females in the reference group, and a median age of 57.06 ± 1.22 years old; and 18 males and 13 females in the observation group, with a median age of 57.42 ± 1.24 years old. The comparison of the general information between the two groups was not statistically significant ($P > 0.05$). All patients were diagnosed with cirrhotic ascites and were aware of this study. Patients with hepatocellular carcinoma and important organ damage were excluded; patients with incomplete basic clinical information were excluded.

2.2. Methods

2.2.1. Reference group

The reference group was given routine nursing care. The patient's blood pressure, pulse rate, mental state, and so on were observed. The nature and color of excreta and vomitus of the patients were observed to adjust the treatment plan. Dietary guidance is carried out according to the situation of the patients to ensure balanced nutrition.

2.2.2. Observation group

The observation group was given comprehensive intervention nursing as follows. (1) Psychological care, elderly patients with chronic diseases are prone to anxiety, guilt, self-blame, and even despair and anorexia. Patients sometimes show depression, do not talk much, and sometimes show irritability. For such patients and their families, nursing staff should emotionally move the patients with deep understanding and sincere kindness. The nursing staff should talk with the patient and help them face reality with the use of successful cases to enlighten them, enhance their psychological capacity, fully mobilize the positive factors of the patient, and take the initiative to cooperate with the treatment. (2) Skincare. Elderly patients have poor nutritional status and poor skin elasticity, so keep the skin clean. For patients with ascites, the abdominal skin is tight, and umbilical hernia incidence is high, so the patients should wear loose clothing. For patients with itchy skin, the nursing staff should tell them to trim their fingernails to prevent scratching the skin, use warm water to wipe the skin or apply glycerin lotion. (3) Dietary guidance. Provide patients with low-fat, high-protein, high-vitamin, and low-salt diets according to their conditions, avoiding stimulating, hard, and rough foods. Strictly follow the basic principle of eating small meals, avoiding overeating, and taking small bites to prevent the risk of upper gastrointestinal bleeding caused by eating rough food that cuts the varicose veins. Strictly control the intake of water and sodium, and do not consume seafood, soy sauce, sodium-containing monosodium glutamate, and so on. No smoking and alcohol, try not to eat easy flatulence food such as leeks, onions, soya beans, and so on. (4) Ascites care. Before the operation, tell the patients and their families about the process, goals, and therapeutic effects of laparotomy, improve their cooperation, and tell the patients to empty their bladders to reduce the risk of accidental injury by the puncture. After the operation, assist the doctor in extracting the ascites, and at the same time, observe the patient's vital signs, state of consciousness, and the amount, color, and condition of ascites, to find and treat any abnormality promptly. After the operation, use an abdominal bandage to bandage the abdomen to observe the oozing situation of the puncture site, and then observe the patient's body. For the oozing situation of the puncture site, if the oozing is excessive, then a gelatin sponge can be applied. The massive release of ascites will cause protein loss and electrolyte disorders to a certain extent, with a high risk of infection, and even cause hepatic encephalopathy in serious cases, so nursing staff should observe in time to

deal with it immediately. If the peritoneal tube is used to release ascites, it should be kept in a fluent state and properly fixed, and the oozing and bleeding of the dressing should be observed at the same time. (5) Postural care. When there is a large amount of ascites, it is necessary to have sufficient rest, which in turn improves hepatic blood flow. Assist the patient in keeping a lying position to achieve diuresis and promote the excretion of sodium and water. If the patient has dyspnoea or palpitation, they can be kept in a semi-recumbent position, turning over during the period of bed rest, and have periodic limb movement to reduce the risk of pulmonary embolism, pressure ulcers, and other risks. Once the patient's clinical symptoms are relieved and the ascites are reduced, they can be instructed to perform activities out of bed.

2.3. Observation indicators

The quality of life scores of psychological function, physiological function, organic health, and social function of the two groups were compared, and the complication rate and satisfaction of the patients were recorded ^[3].

2.4. Statistical analysis

SPSS 20.0 software was used to analyze the statistical data, (%) describes the count data, and ($\pm s$) describes the measurement data, respectively. Chi-square and *t*-tests were performed, if the value of $P < 0.05$ between the groups, there is statistical significance.

3. Results

3.1. Comparison of the quality of life scores of the two groups

The scores of the reference group were significantly lower than those of the observation group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of the quality of life scores of the two groups [$n (\pm s)$]

Group	Cases	Psychological functions	Physiological functions	Organismal health	Social functions
Reference group	31	1.22 \pm 0.85	3.21 \pm 1.01	2.31 \pm 1.50	1.07 \pm 0.93
Observation group	31	3.21 \pm 1.01	4.75 \pm 1.20	4.30 \pm 1.22	3.52 \pm 1.30
<i>t</i>		8.393	5.786	5.730	8.534
<i>P</i>		0.000	0.000	0.000	0.000

3.2. Comparison of complications and satisfaction between the two groups

Comparing the reference group, the observation group has a lower complication rate and higher satisfaction, with a significant difference ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparing the complications and satisfaction of the two groups [$n (\%)$]

Group	Cases	Complications	Satisfaction
Reference group	31	7 (22.58)	23 (74.19%)
Observation group	31	1 (3.23)	29 (93.55%)
χ^2		5.166	4.292
<i>P</i>		0.023	0.038

4. Discussion

Cirrhosis is a kind of diffuse liver injury, and its complication is most common in ascites, which means that cirrhosis has progressed to an advanced stage ^[4]. Ascites in cirrhosis have a high recurrence rate, a long duration of disease, and a poor prognosis, which can have a serious impact on both the quality of life and the health of patients. Relevant research results have proved that for elderly patients with cirrhosis ascites, strengthening its comprehensive nursing intervention has a very important impact on reducing the occurrence of complications in patients with cirrhosis as well as relieving patients' pain, and can effectively improve the prognosis of patients ^[5].

Comprehensive nursing intervention is extremely critical to promote the recovery of patients' conditions and alleviate their pain. Implementing psychological care in the care of cirrhotic patients with ascites can effectively improve the patients' bad mood, improve the degree of cooperation of the patients, and promote the smooth progress of clinical work ^[6]. Due to the relatively low immunity of patients, the prevention and control of their infections in the clinic can reduce the risk of secondary infections, thus ensuring the health of the patient's organism. Complication care, by closely observing the patient's condition and increasing the frequency of rounds, can take effective measures to deal with the abnormalities when they are found promptly and can delay the deterioration of the condition ^[7].

Analyzing the results of the study, it was found that the quality of life score of the observation group was higher than that of the reference group, and compared with the reference group, the observation group had a higher degree of satisfaction and a lower incidence of complications ($P < 0.05$). This indicates that comprehensive nursing intervention in patients with cirrhosis ascites can reduce the complications of patients, and is conducive to improving their quality of life and satisfaction.

In conclusion, the application of integrated nursing intervention in elderly patients with cirrhotic ascites has a very important role in reducing complications, improving patients' quality of life, and increasing their satisfaction, with obvious application effects.

Disclosure statement

The author declares no conflict of interest.

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The Multifaceted Role of Phafin Proteins in Cancer: A Comprehensive Review of Their Functions, Mechanisms, and Therapeutic Potential Across Various Tumor Types

Yasir Hameed*

Department of Biotechnology, Institute of Biochemistry, Biotechnology, and Bioinformatics, The Islamia University of Bahawalpur, Pakistan

*Corresponding author: Yasir Hameed, yasirhameed2011@gmail.com

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Abstract: Phafin proteins, specifically Phafin1 and Phafin2, have recently emerged as critical players in cancer biology due to their involvement in essential cellular processes such as autophagy, apoptosis, and signal transduction. Phafin1, characterized by its pleckstrin homology (PH) domain and FYVE domain, regulates autophagy and apoptosis, thereby influencing cancer cell survival and proliferation. Dysregulation of Phafin1-mediated autophagy and its interaction with pro-apoptotic proteins like Bax contribute to apoptosis resistance in various cancers, including breast and lung cancer. Phafin2, sharing structural similarities with Phafin1, plays roles in endosomal trafficking and signaling pathways, enhancing cancer cell migration and invasion, particularly in colorectal and gastric cancers. Elevated levels of Phafin proteins correlate with poor prognosis and chemoresistance, underscoring their potential as diagnostic markers and therapeutic targets. Targeting Phafin proteins through small molecule inhibitors or monoclonal antibodies presents a promising therapeutic strategy, aiming to restore the balance between autophagy and apoptosis in cancer cells. This review synthesizes recent research on Phafin proteins, highlighting their molecular mechanisms, roles in specific cancers, and potential clinical applications, providing a comprehensive understanding of their significance in cancer biology and therapy.

Keywords: Phafin proteins; Cancers; Treatment; Diagnosis

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1. Introduction

Phafin proteins are a relatively novel family of proteins that have garnered interest due to their involvement in crucial cellular processes. With the increasing focus on understanding the molecular underpinnings of cancer, Phafin proteins have emerged as significant due to their dual domains that allow interactions with phosphoinositides and other proteins ^[1-2]. Phafin1 and Phafin2, the primary members of this protein family,

contain two critical domains: the pleckstrin homology (PH) domain and the Fab1, YOTB, Vac1, and EEA1 (FYVE) domain. The PH domain allows binding to phosphoinositides, while the FYVE domain facilitates localization to endosomal membranes ^[3-4]. These structural features enable Phafin proteins to participate in a variety of cellular processes ^[5-6].

Phafin1 is particularly involved in autophagy and apoptosis, crucial for cellular homeostasis and stress response ^[7]. Its role in autophagy, a process essential for degrading damaged organelles and proteins, is particularly significant in cancer where autophagy can either suppress or promote tumor growth depending on the context ^[8]. Phafin1 also modulates apoptosis by interacting with pro-apoptotic proteins such as Bax, promoting apoptosis resistance in cancer cells ^[9]. Phafin2, although less studied than Phafin1, shares similar structural features and functions, including roles in endosomal trafficking and cellular signaling pathways ^[10].

2. Structure and function of Phafin proteins

2.1. Structural characteristics

Phafin proteins contain two critical domains: the pleckstrin homology (PH) domain and the Fab1, YOTB, Vac1, and EEA1 (FYVE) domain. The PH domain allows binding to phosphoinositides, while the FYVE domain facilitates localization to endosomal membranes. These structural features enable Phafin proteins to participate in a variety of cellular processes ^[11].

2.2. Functional roles

Phafin1: Phafin1 is involved in autophagy and apoptosis, crucial for cellular homeostasis and stress response. Its role in autophagy, a process essential for degrading damaged organelles and proteins, is particularly significant in cancer where autophagy can either suppress or promote tumor growth depending on the context ^[12].

Phafin2: Less studied than Phafin1, Phafin2 shares similar structural features and functions, including roles in endosomal trafficking and cellular signaling pathways ^[13].

3. Phafin proteins in cancer: Molecular mechanisms

Recent studies have highlighted several mechanisms through which Phafin proteins influence cancer progression as follows.

3.1. Autophagy

Phafin1 has been shown to regulate autophagy, a critical process in cancer. Dysregulation of autophagy can lead to uncontrolled cell growth and cancer development. For instance, Phafin1-mediated autophagy inhibition has been linked to increased survival of cancer cells under stress conditions ^[14]. In breast cancer, Phafin1 modulates autophagy by interacting with Beclin-1 and other autophagy-related proteins, promoting tumor cell survival ^[15].

3.2. Apoptosis

Phafin proteins are also involved in apoptosis, another crucial process in cancer. By modulating apoptotic pathways, Phafin proteins can influence the survival of cancer cells. Phafin1, for example, has been shown to interact with pro-apoptotic proteins such as Bax, promoting apoptosis resistance in cancer cells ^[16].

3.3. Signal transduction

Phafin proteins interact with various signaling pathways, including the PI3K/AKT pathway, known for its role

in cell growth and survival. Dysregulation of this pathway is a common feature in many cancers. Phafin1 has been shown to activate AKT signaling, contributing to increased cell proliferation and survival in lung cancer cells ^[17].

4. Phafin proteins in specific cancers

4.1. Breast cancer

Phafin1 expression has been correlated with poor prognosis in breast cancer patients. Studies suggest that Phafin1 promotes cell survival and proliferation through its role in autophagy and apoptosis inhibition ^[18]. For instance, high levels of Phafin1 have been associated with increased tumor size and metastatic potential in breast cancer models ^[19]. Phafin1-mediated autophagy regulation is critical for breast cancer cell survival, especially under metabolic stress conditions ^[20].

4.2. Lung cancer

In non-small cell lung cancer (NSCLC), Phafin1 has been implicated in resistance to chemotherapy. Its ability to regulate autophagy and apoptosis pathways contributes to the survival of cancer cells despite treatment ^[21]. Phafin1-mediated AKT activation has also been linked to enhanced proliferation and survival of lung cancer cells under chemotherapeutic stress ^[22]. Additionally, Phafin1 expression has been shown to correlate with increased tumor growth and metastatic potential in lung cancer models ^[23].

4.3. Colorectal cancer

Elevated levels of Phafin2 have been observed in colorectal cancer tissues. Phafin2 appears to enhance cancer cell migration and invasion, highlighting its potential as a therapeutic target ^[24]. Studies have shown that Phafin2 interacts with matrix metalloproteinases (MMPs), facilitating extracellular matrix degradation and tumor invasion ^[25]. Moreover, Phafin2's role in modulating the epithelial-mesenchymal transition (EMT) process has been implicated in colorectal cancer progression ^[26].

4.4. Gastric cancer

Both Phafin1 and Phafin2 are overexpressed in gastric cancer, where they contribute to cancer progression by modulating autophagy and apoptosis ^[27]. Phafin1 has been shown to enhance autophagy, supporting cancer cell survival under nutrient-deprived conditions commonly found in the tumor microenvironment ^[28]. Additionally, Phafin2 has been linked to increased cell proliferation and invasion in gastric cancer models ^[29].

4.5. Other cancers

Research has also implicated Phafin proteins in other cancers such as ovarian, pancreatic, and prostate cancers. In ovarian cancer, Phafin1 overexpression has been linked to chemoresistance and poor clinical outcomes ^[30]. In pancreatic cancer, Phafin2 has been shown to promote cell migration and invasion through interactions with the Rho family of GTPases ^[31]. Prostate cancer studies indicate that Phafin1 may play a role in androgen receptor signaling, influencing tumor growth and progression ^[32].

5. Clinical implications and future directions

Understanding the role of Phafin proteins in cancer opens up several avenues for clinical applications as follows.

5.1. Diagnostic markers

Given their differential expression in various cancers, Phafin proteins could serve as biomarkers for early cancer detection and prognosis. For example, elevated Phafin1 levels in serum samples could potentially indicate breast or lung cancer presence and progression^[33–34].

5.2. Therapeutic targets

Targeting Phafin proteins may offer a novel approach to cancer treatment. For example, inhibiting Phafin1 could restore the balance between autophagy and apoptosis, leading to increased cancer cell death. Small molecule inhibitors or monoclonal antibodies against Phafin proteins are being explored as potential therapeutic strategies^[35].

5.3. Drug development

The development of small molecules or antibodies that specifically target Phafin proteins could provide new therapeutic options for cancer patients. High-throughput screening approaches are being used to identify compounds that can modulate Phafin protein activity^[36].

6. Conclusion

Phafin proteins play a crucial role in the regulation of autophagy, apoptosis, and signal transduction pathways in cancer. Recent research has significantly advanced the understanding of these proteins, highlighting their potential as diagnostic markers and therapeutic targets. Continued research is essential to fully elucidate the mechanisms by which Phafin proteins influence cancer and to develop effective strategies for targeting these proteins in cancer therapy.

Disclosure statement

The author declares no conflict of interest.

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Relationship between Psychosomatic Factors and Functional Dyspepsia and Progress in Treatment

Yue Pan^{1*}, Houjun Yang²

¹Gao County People's Hospital, Yibin 645100, Sichuan Province, China

²Yibin Hospital, Children's Hospital of Chongqing Medical University, Yibin 644600, Sichuan Province, China

*Corresponding author: Yue Pan, 1298769854@qq.com

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Abstract: *Objective:* To investigate the relationship between psychosomatic factors and functional indigestion, to provide relevant treatment methods and measures according to the actual situation as a clinical reference. *Methods:* This pilot study was conducted in the hospital from August 2023 to August 2024, and 100 patients who were diagnosed with functional dyspepsia were selected for the study. In this study, the anxiety self-rating scale and depression self-rating scale were applied to assess the psychological conditions of the patients and analyze the relationship between psychological conditions and functional dyspepsia. Subsequently, the patients were divided into two groups, in which one group was given conventional glutamine and other treatments, as the control group, and the other group was given comprehensive treatment, as the experimental group, to compare and analyze the differences in the treatment effects of the patients in the two groups. *Results:* Among the 100 patients in this study, 34 of them were accompanied by anxiety mood disorder, 22 patients were accompanied by depression mood disorder, and 44 patients were accompanied by anxiety and depression mood disorder. The psychosomatic factors were significantly associated with functional dyspepsia. After treatment, both groups of patients have high treatment efficiency of 98.00% and 84.00% respectively, but the difference in data comparison is statistically significant ($P < 0.05$), in which the experimental group has the higher efficiency. At the same time, before treatment, both groups of patients were accompanied by bad mood (SAS and SDS scores are higher than the standard score), and the comparison of data between groups is not significant ($P > 0.05$). After the treatment, the effect was significant, the patients' scores (SAS and SDS) were reduced, meaning the patients in the experimental group had a greater degree of reduction, and the difference between the experimental group and the control group increased ($P < 0.05$), and the improvement of bad mood was better. *Conclusion:* The human body's mental psychological factors usually functional dyspepsia accompanied by correlation, the occurrence of adverse mental psychological problems can lead to functional dyspepsia. Based on this, it is of positive significance to give patients comprehensive treatment, adopt measures such as acid suppression and gastric protection, and at the same time give patients psychological treatment, which is more conducive to improving patients' bad mood and digestive function and promoting patients' recovery.

Keywords: Psychological factors; Functional dyspepsia; Relationship

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1. Introduction

Functional dyspepsia is a common clinical disease, and its incidence rate has continued to increase in recent years due to the influence of people's daily dietary habits and other factors ^[1]. From the actual development situation, after the onset of the disease, the clinical symptoms of the patient are mainly postprandial satiety, epigastric pain, epigastric burning, and early satiety, which has a greater impact on the patient's aphasia and is prone to lead to a variety of complications, which is more threatening to the patient's health. At present, there are many factors leading to the occurrence of this disease in patients, among which living environment, family genetic history, and dietary habits are important factors ^[2]. In recent years, clinical data from several studies have shown that adverse psychological factors are an important cause of functional dyspepsia ^[3]. Based on this, it is particularly important to further analyze the impact of psychosocial factors on functional dyspepsia and give targeted treatment strategies according to the actual situation, and this study is carried out to analyze the specific analyses as follows.

2. Information and methods

2.1. Data analysis

This research work was carried out in the hospital, from July 2023 to July 2024, with a total of 100 patients selected as subjects for the study (all of them with functional dyspepsia). For the subsequent treatment, the patients were divided into two groups to judge the feasibility of the comparative study. In the experimental group, there were 50 patients, 26 males and 24 females, and the mean age of the patients was 45.34 years with a standard deviation of 5.45 (range: 23–77 years). In the control group, there were 28 males and 22 females and the mean age of the patients was 45.28 years with a standard deviation of 6.52 (range: 24–79 years). The data of the two groups of patients were compared and analyzed under the statistical method, and the results indicated that all of them were $P > 0.05$, indicating that this comparative test was valid.

Inclusion criteria: all patients were diagnosed with functional dyspepsia after various examinations (gastroscopy, ultrasound, blood biochemistry examination, and so on); all patients did not have the occurrence of organic lesions with systemic symptoms; and all patients grasped the study process through explanation, indicating that they were voluntarily participating and cooperating.

Exclusion criteria: patients who have major diseases in other organs; patients allergic to the current study drugs; patients who agreed to participate and cooperate with the study, but have poor compliance; patients with mental/consciousness abnormalities.

2.2. Methods

Firstly, the relationship between psychological factors and functional dyspepsia was analyzed. In the implementation, it was necessary to apply the self-assessment scale of anxiety (SAS) and self-depression scale (SDS) to assess the psychological moods of the 100 patients in the study. The scores of the two scales consisted of 20 entries, and the evaluation of each entry was scored with a 5-point scale, with the scores from 0 to 4 indicating the aggravation of the degree, respectively. Afterward, the total score was calculated, and the standard score was 50 and 53 points, respectively. Exceeding the standard score was classified as accompanied by anxiety and depression, and as the score increased, the patient's negative emotions worsened. Subsequently, the correlation between bad mood and functional dyspepsia was determined.

The patients were then divided into two groups, in which 50 patients in the control group were given conventional treatment, mainly glutathione and vitamin B. The dosage of the drugs was 10 mg and 20 mg, respectively, and the frequency of use was three times a day. The patients in the experimental group were

given the same treatment, with a comprehensive treatment method added. The patients were given the standard treatment of acid inhibitors, gastrokinetic drugs, and anti-*Helicobacter pylori* treatment. At the same time, the patients were given psychological treatment mainly based on cognitive therapy. The nursing staff strengthened communication with patients, clarified the causes of patients' negative emotions, and then gave targeted counseling to explain disease knowledge to patients and guide patients to understand the impact of negative emotions on the disease. The nursing staff guides patients to master the implementation strategies of mindfulness-based stress reduction and so on to improve their negative emotions. At the same time, increase the traditional Chinese medicine treatment, the application of Pinellia and Magnolia bark decoction, including *Poria cocos*, Magnolia bark, Perilla leaf, Magnolia bark, ginger, and Pinellia. The medicine is boiled in water and the decoction is given, 1 dose per day, divided into 2 doses.

2.3. Observation indexes

Statistically analyze the correlation between psychosomatic factors and functional dyspepsia.

Comparison of the treatment effect of the two groups of patients, mainly based on the evaluation of the improvement of the patient's symptoms, including the three indicators of significant effect, effective and ineffective, the evaluation criteria for significant effect: after treatment, the patient's symptoms (epigastric pain, postprandial satiety) disappeared. Effective evaluation criteria: after treatment, the patient's symptoms (epigastric pain, postprandial fullness) significantly improved, occasionally. Ineffective evaluation criteria: after treatment, the patient's symptoms (epigastric pain, postprandial fullness) still exist, or even aggravated. Afterward, the total effective rate of the patients was calculated (the sum after excluding the ineffective rate).

Calculate the psychological mood changes of the patients after treatment, still applying the anxiety self-assessment scale and depression self-assessment scale, with higher scores meaning the worse the moods of the patients.

2.4. Statistical methods

Calculations were performed with the help of SPSS 26.0 software. (mean ± SD) indicates the mean and standard deviation of the measurement data. In the process of data processing, the data between different groups were mainly calculated and compared, and the *t*-value was used to verify the difference in the data. If the calculated results show a *P*-value less than 0.05, it is considered that there is a significant difference between the two groups.

3. Results

3.1. Correlation analysis

Among the 100 patients in this study, 34 of them were accompanied by anxiety mood disorders, 22 were accompanied by depression mood disorders, and 44 were accompanied by anxiety and depression mood disorders. The psychological factors are significantly associated with functional dyspepsia, as shown in **Table 1**.

Table 1. Correlation between psychosomatic factors and functional dyspepsia [*n* (%)]

Factors	β	95% CI	OR	Wald value	<i>P</i>
Anxious mood disorders	0.327	1.076–1.776	0.983	4.767	<0.05
Depressive mood disorder	0.388	1.055–2.032	0.814	6.789	<0.05
Anxiety, depressive mood disorder	0.943	1.105–5.546	0.914	11.467	<0.05

3.2. Effective rate of treatment

Although both groups of patients have a high treatment effectiveness rate, with 98.00% and 84.00% respectively, the difference in data comparison is statistically significant ($P < 0.05$), in which the experimental group has a higher effectiveness rate (Table 2).

Table 2. Comparison of patients' therapeutic effects [n(%)]

Groups	Significant	Effective	Ineffective	Total effective rate
Experimental group (n = 50)	37 (74.00)	12 (24.00)	1 (2.00)	49 (98.00)
Control group (n = 50)	25 (50.00)	17 (34.00)	8 (16.00)	42 (84.00)
χ^2				5.983
P				0.014

3.3. Mood improvement

Before treatment, both groups of patients were accompanied by adverse emotions (SAS and SDS scores were higher than the standard score), and the comparison of data between groups was not meaningful ($P > 0.05$). After treatment, the effect is significant and the patients' scores (SAS and SDS) are reduced. The experimental group patients' scores reduced to a greater extent, and the difference with the control group increased ($P < 0.05$), indicating improvement of bad mood is better. The specific comparison is shown in Table 3.

Table 3. Comparison of patient's mood changes (mean \pm SD)

Groups	SAS (points)		SDS (points)	
	Before treatment	After treatment	Before treatment	After treatment
Experimental group (n = 50)	53.45 \pm 5.45	42.65 \pm 6.56	55.67 \pm 6.56	44.39 \pm 6.34
Control group (n = 50)	53.67 \pm 5.28	46.67 \pm 6.04	55.78 \pm 6.23	47.98 \pm 6.19
χ^2	0.205	3.188	0.086	2.865
P	0.838	0.002	0.932	0.005

4. Discussion

Functional dyspepsia is a common clinical disease. The occurrence of this disease is usually related to non-organic diseases, which leads to gastrointestinal motility disorders in patients. In recent years, the incidence of this disease has gradually increased, and the clinical awareness of the prevention and treatment of this disease has also been continuously improved [4]. From the actual development situation, to prevent and treat this disease, first need to analyze the pathogenic factors that cause this disease. At present, there are relatively many studies on the pathogenic factors of the disease, among which many theories believe that anxiety, depression, and other adverse mental and psychological problems lead to the occurrence and development of this disease. However, it is not perfect and further research and analysis are needed [5].

In the present study, after taking the functional dyspepsia patients selected from the hospital as an example, the results show that there is a significant correlation between psychological factors and functional dyspepsia. The analysis of research results showed that it was related to the following aspects. Firstly, when mental psychological disorders occur in the human body, it usually breaks the balance between the limbic system of the

brain and the hypothalamus, which affects the contraction force of the patient's circular muscle and adversely affects the vagus nerve tension, which affects the patient's stomach and causes delayed gastric emptying, and causes a series of dyspeptic reactions to occur ^[6]. At the same time, when mental and psychological abnormalities occur, it will have an impact on the transmission of the brain-intestinal axis, thus disrupting the balance of the hypothalamus and its limbic system. This situation not only reduces the contraction conduction speed of the human stomach and intestines but also has an impact on the efficiency of its conduction efficiency, which is prone to triggering the obstruction of gastric emptying, thus leading to the occurrence of abdominal pain, abdominal distension and other functional dyspepsia symptoms in the human body ^[7]. In addition, mental and psychological abnormalities will also affect the function of the human autonomic nervous system, making it unable to effectively regulate the distal colon, limiting intestinal motility, triggering the occurrence of gastrointestinal immune dysfunction and other adverse conditions, so that the patient suffers from dyspepsia and other uncomfortable symptoms.

In this case, it is particularly important to treat patients with functional dyspepsia by improving their anxiety and depression and giving psychological treatment ^[8]. Among them, conventional therapeutic drugs can improve the gastrointestinal function of patients, promote the recovery of gastrointestinal dynamics, and alleviate the symptoms of functional dyspepsia in patients. At the same time, according to clinical research data, traditional Chinese medicine has a positive significance on the improvement of patients' anxiety, depression, and other adverse emotions. Among them, the effect of Pinellia and Magnolia decoction is remarkable. This method is a kind of traditional medicine that can promote the improvement of gastric emptying of patients while improving the gastrointestinal function of patients and improving the dyspepsia of patients. In addition, there is 90% ethanol extract in this prescription, which is similar to the effect of fluoxetine in Western medicine, and both of them can achieve the antidepressant effect. Therefore, this drug has a significant effect on the improvement of the patient's bad mood, dyspepsia, and other conditions ^[9]. Psychotherapy can help patients understand their disease from their subjective consciousness, and point out that emotions and mental state are important factors affecting the regression and occurrence of functional dyspepsia, thereby improving patients' understanding, promoting patients to actively regulate their emotions, and improving treatment compliance. This can alleviate the severity of the disease, improve the symptoms of functional dyspepsia, and facilitate the recovery of patients ^[10].

In summary, functional dyspepsia is a serious disease, in which psychological factors have a significant correlation with the occurrence and development of the disease. Therefore, it is necessary to pay attention to the degree of clinical importance, strengthen the process of treatment of this disease, and increase the utilization of traditional Chinese medicine and psychotherapy to improve the patient's bad mood and promote the recovery of the patient. The result of this study is significant so it is worthwhile to promote and publicize clinically, providing a guarantee for the health and recovery of patients with functional dyspepsia.

Disclosure statement

The authors declare no conflict of interest.

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Analysis of the Changing Trend of the Burden of Rheumatic Heart Disease in China from 1990 to 2021

Yanli Yang^{1,2}, Shiliang Xi^{1,3*}, Ying Li^{1,2}

¹The First Clinical Medical College of Three Gorges University, Yichang 443003, Hubei Province, China

²Department of Electrocardiogram (ECG) Diagnostic, Yichang Central People's Hospital, Yichang 443003, Hubei Province China

³Department of Pain, Yichang City Central People's Hospital, Yichang 443003, Hubei Province, China

*Corresponding author: Shiliang Xi, ooooooctor@outlook.com

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Abstract: *Objective:* This study aims to provide an accurate quantitative analysis of the burden of rheumatic heart disease in China, and to provide a scientific basis for the formulation of effective prevention and control strategies. *Methods:* Based on the latest public database 2021 Global Burden of Diseases (GBD2021), the characteristics and trends of incidence, prevalence, mortality, and attributable risk factors of rheumatic heart disease in the Chinese population from 1990 to 2021 were quantitatively analyzed. *Results:* From 1990 to 2021, the incidence of rheumatic heart disease in China decreased from 620,195 to 445,472, with an average annual decrease rate of 1.07%. The incidence rate decreased from 52.72/100,000 to 31.31/100,000 with an average annual decrease rate of 1.65%, while the age-standardized incidence rate decreased from 48.92/100,000 to 39.86/100,000 with an average annual decrease rate of 0.46%. The number of cases increased slightly from 8,923,639 to 9,073,096, with an average annual growth rate of 0.28%, and the prevalence decreased from 758.75/100,000 to 637.72/100,000 with an average annual decrease rate of 0.31%. The age-standardized prevalence decreased from 708.27/100,000 to 619.85/100,000 with an average annual decrease rate of 0.21%. The number of deaths decreased from 134,208 to 78,910, with an average annual decrease rate of 1.98%, and the mortality rate decreased from 11.41/100,000 to 5.51/100,000 with an average annual decrease rate of 2.55%. The age-standardized mortality rate decreased significantly from 19.07/100,000 to 5.00/100,000 with an average annual decrease rate of 5.00%. These data show that although the number of cases increased slightly, the incidence rate, prevalence rate, mortality rate, and age-standardized rates all showed a downward trend. *Conclusion:* From 1990 to 2021, the burden of rheumatic heart disease in China has undergone significant changes. Although the number of cases increased slightly, the incidence rate, prevalence rate, mortality rate, and age-standardized rates all showed a downward trend. Specifically, the incidence rate decreased from 52.72/100,000 to 31.31/100,000, indicating a significant decrease in the number of new cases of rheumatic heart disease per 100,000 people. The decrease in prevalence rate, from 758.75/100,000 to 637.72/100,000, reflects a decrease in the proportion of the population with rheumatic heart disease. The most significant decrease is in the mortality rate, from 11.41/100,000 to 5.51/100,000, indicating a substantial reduction in the risk of death from rheumatic heart disease. These changes may be attributed to the continuous progress in healthcare services, implementation of public health policies, and increased population health awareness in China. In addition, advances in medical technology, improvements in emergency systems, and optimization of cardiovascular disease management have also played an important role in reducing mortality rates. However, the slight increase in the number of cases suggests that despite significant progress, rheumatic heart disease

remains an important challenge in the field of public health in China, requiring continuous attention and intervention.

Keywords: Rheumatic heart disease; Disease burden; Attributable risk factors; China

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1. Introduction

Rheumatic heart disease (RHD), a sequela of rheumatic fever, remains a significant public health challenge, particularly in regions with limited access to healthcare and inadequate preventive measures ^[1]. The Global Burden of Disease (GBD) study provides a comprehensive and systematic assessment of the global, regional, and national disease burden, offering invaluable insights into the epidemiological patterns of RHD ^[2]. This study aims to analyze the disease burden of RHD among the Chinese population from 1990 to 2021, utilizing the GBD database. The analysis will encompass the incidence, prevalence, and mortality rates, as well as the disability-adjusted life years (DALYs), to assess the temporal trends and the impact of RHD on public health in China ^[3].

Furthermore, the study will explore the attributable risk factors for RHD, which are crucial for informing targeted interventions ^[4]. The GBD data allows for the quantification of the contribution of various risk factors, such as socio-economic status, environmental exposures, and healthcare access, to the overall disease burden ^[5]. By identifying the predominant risk factors, this research will contribute to a more nuanced understanding of the multifaceted determinants of RHD in China. The findings are expected to guide policy-making and resource allocation for effective RHD prevention and control strategies, ultimately reducing the disease burden and improving the quality of life for affected individuals ^[6]. This research is not only timely but also essential for advancing the global health agenda, especially in the context of non-communicable diseases, which have been increasingly recognized as a major challenge in the 21st century.

2. Materials and methods

2.1. Data

The data for this study are derived from the latest Global Burden of Diseases study (GBD2021) database, which provides detailed epidemiological data on rheumatic heart disease in China from 1990 to 2021, including incidence, prevalence, and disease burden indicators by age, gender, and region. GBD2021 comprehensively analyzes and estimates the disease burden of 369 diseases or injuries in 204 countries (regions) globally using a unified and comparable approach, and systematically outlines the attributable disease burden of 87 risk factors. It is currently the most comprehensive database globally. This study screened the GBD2021 data, selecting the region as “China”, disease as “Rheumatic heart disease”, and risk factors as “Select only level 3 risks”, all years from 1990–2021, all ages, and both genders. The definition of rheumatic heart disease follows the International Classification of Diseases tenth edition (ICD-10) coding.

2.2. Indicator selection

This study uses the incidence number, prevalence number, death number, incidence rate, prevalence rate, mortality rate, and age-standardized rate (ASR) of incidence, prevalence, and mortality to evaluate the epidemiological trends and disease burden of rheumatic myocarditis in China. The above data can be directly obtained from the GBD official website (<https://www.healthdata.org/gbd>).

2.3. Statistical methods

All statistical analyses were performed using R software (version 4.2.1) and SAS software (version 9.4) to ensure the accuracy and reliability of the analysis. The significance level was set at $P < 0.05$ to evaluate the statistical significance of the results.

3. Results

3.1. Incidence rate of rheumatic heart disease in the Chinese population

From 1990 to 2021, the incidence of rheumatic heart disease in the Chinese population showed a gradually decreasing trend (**Table 1**). The number of cases decreased from 620,195 in 1990 to 445,472 in 2021, with an average annual reduction rate of 1.07%. The incidence rate decreased from 52.72/100,000 in 1990 to 31.31/100,000 in 2021, with an average annual reduction rate of 1.65%. The age-standardized incidence rate decreased from 48.92/100,000 in 1990 to 39.86/100,000 in 2021, with an average annual reduction rate of 0.46%. These data indicate that the incidence and number of cases of rheumatic heart disease in China are significantly decreasing. This trend may be attributed to improved medical conditions, widespread public health interventions, and effective prevention and control measures for rheumatic fever and related diseases. However, despite the overall downward trend, rheumatic heart disease remains an important public health issue that requires attention. Continued strengthening of prevention and control measures and health education is crucial for further reducing the incidence rate.

Table 1. Incidence of rheumatic heart disease in the Chinese population from 1990 to 2021

Years	Incidence number	Incidence rate (Per 100,000)	Age-standardized incidence rate (Per 100,000)
1990	620195.60(484500.11–778535.74)	52.72(41.18–66.18)	48.92(38.62–60.36)
1991	615784.22(484122.84–774227.18)	51.62(40.59–64.91)	48.09(38.18–59.09)
1992	609474.47(482535.87–763760.82)	50.53(40.00–63.32)	47.23(37.62–57.94)
1993	601436.24(477024.93–750850.33)	49.41(39.19–61.68)	46.35(36.99–56.69)
1994	591866.58(470048.97–738523.85)	48.26(38.33–60.22)	45.49(36.42–55.62)
1995	582150.11(462744.51–725773.39)	47.19(37.51–58.83)	44.67(35.82–54.81)
1996	570501.72(453818.63–710014.05)	46.01(36.60–57.27)	43.81(35.14–53.86)
1997	556718.65(443871.04–691780.26)	44.72(35.65–55.57)	42.84(34.42–52.78)
1998	542486.35(433462.37–672855.02)	43.41(34.69–53.85)	41.88(33.62–51.71)
1999	529428.22(423320.92–655520.98)	42.21(33.75–52.27)	41.04(32.91–50.78)
2000	519608.28(414850.04–641468.67)	41.27(32.95–50.95)	40.45(32.34–50.17)
2001	513543.57(411300.46–634578.46)	40.60(32.52–50.17)	40.21(32.12–49.73)
2002	509902.04(407768.26–631266.55)	40.11(32.08–49.66)	40.25(32.11–49.62)
2003	507230.22(404827.78–629674.65)	39.69(31.67–49.27)	40.44(32.24–49.87)
2004	504466.13(401684.85–627168.59)	39.25(31.25–48.80)	40.66(32.40–50.04)
2005	501006.20(399127.07–624758.39)	38.75(30.87–48.32)	40.79(32.43–50.32)
2006	498879.44(397365.36–620242.96)	38.34(30.54–47.66)	40.96(32.64–50.67)
2007	498889.63(397571.36–619428.65)	38.07(30.34–47.27)	41.28(32.86–51.17)

Table 1 (Continued)

Years	Incidence number	Incidence rate (Per 100,000)	Age-standardized incidence rate (Per 100,000)
2008	499129.77(397736.57–616420.68)	37.82(30.13–46.70)	41.62(33.09–51.68)
2009	497989.27(397053.38–612984.16)	37.47(29.88–46.13)	41.88(33.24–52.07)
2010	494001.74(394802.72–605666.52)	36.95(29.53–45.30)	41.93(33.27–52.24)
2011	487247.11(390396.28–596932.72)	36.26(29.05–44.42)	41.77(33.14–52.16)
2012	479243.24(385050.06–588036.45)	35.47(28.50–43.52)	41.52(32.94–51.93)
2013	470941.70(379123.41–577355.43)	34.64(27.89–42.47)	41.22(32.69–51.60)
2014	463477.01(374494.75–567561.59)	33.88(27.38–41.49)	40.94(32.41–51.31)
2015	457748.92(370984.54–560822.51)	33.23(26.93–40.72)	40.73(32.20–51.13)
2016	453696.88(368077.61–556315.66)	32.69(26.52–40.09)	40.60(32.13–50.93)
2017	451193.26(365805.57–552444.16)	32.27(26.16–39.51)	40.47(32.09–50.77)
2018	449922.08(365449.83–551149.51)	31.97(25.97–39.17)	40.35(32.02–50.57)
2019	448973.26(364290.91–549646.80)	31.74(25.76–38.86)	40.22(31.93–50.35)
2020	445682.97(361603.38–546084.91)	31.40(25.47–38.47)	39.92(31.62–49.88)
2021	445472.95(360393.94–544036.99)	31.31(25.33–38.24)	39.86(31.52–49.65)
Estimate annual percentage change (%)	-1.07(-1.16–-0.98)	-1.65(-1.73–-1.56)	-0.46(-0.61–-0.32)

3.2. Prevalence of rheumatic heart disease among the Chinese population

The number of cases, incidence rate, and age-standardized incidence rate of rheumatic heart disease in the Chinese population have remained stable with a slight decrease from 1990 to 2021 (**Table 2**). The number of cases increased from 8,923,639 in 1990 to 9,073,096 in 2021, with an average annual growth rate of 0.28%. The incidence rate decreased from 758.75/100,000 in 1990 to 637.72/100,000 in 2021, with an average annual decrease rate of 0.31%. Meanwhile, the age-standardized incidence rate decreased from 708.27/100,000 in 1990 to 619.85/100,000 in 2021, with an average annual decrease rate of 0.21%. These data indicate that although the number of cases has slightly increased, the incidence rate and age-standardized incidence rate have decreased due to the growth of the population base. This shows that China has achieved certain achievements in the prevention and control of rheumatic heart disease, and the disease burden is relatively stable and has been reduced. However, rheumatic heart disease remains a public health issue that requires continuous attention and the strengthening of prevention, control, and management measures.

Table 2. Prevalence of rheumatic heart disease among the Chinese population from 1990 to 2021

Years	Prevalence number	Prevalence rate (Per 100,000)	Age-standardized prevalence rate (Per 100,000)
1990	8926339.61(6909494.23–11186049.91)	758.75(587.31–950.82)	708.27(558.87–875.81)
1991	8909723.96(6940742.62–11089930.60)	746.95(581.88–929.73)	698.02(552.14–859.49)
1992	8873528.27(6896089.93–11024845.06)	735.64(571.70–913.98)	687.41(543.75–844.91)
1993	8826660.09(6857054.27–10941132.85)	725.13(563.33–898.84)	676.67(534.10–829.01)

Table 2 (Continued)

Years	Prevalence number	Prevalence rate (Per 100,000)	Age-standardized prevalence rate (Per 100,000)
1994	8770579.50(6815716.80–10854257.55)	715.20(555.79–885.12)	665.77(525.46–814.46)
1995	8713837.81(6773062.91–10740948.06)	706.29(548.98–870.60)	654.90(516.91–800.04)
1996	8632514.70(6707178.33–10630492.77)	696.25(540.97–857.40)	643.00(507.71–785.55)
1997	8526980.00(6621487.47–10496371.65)	684.90(531.85–843.09)	629.96(497.41–770.09)
1998	8425193.94(6555988.71–10391935.76)	674.23(524.64–831.62)	617.50(487.39–755.01)
1999	8350206.41(6509949.41–10312505.10)	665.80(519.07–822.27)	607.15(478.87–742.31)
2000	8333762.90(6512748.89–10298732.67)	661.89(517.26–817.95)	600.65(473.39–734.11)
2001	8375537.36(6561641.10–10315075.27)	662.18(518.77–815.52)	598.80(472.25–730.81)
2002	8453835.47(6646036.28–10402777.02)	664.98(522.78–818.28)	600.22(473.80–731.59)
2003	8551970.36(6746514.79–10502002.48)	669.11(527.85–821.68)	603.45(476.84–737.89)
2004	8650600.06(6845121.11–10611072.88)	673.08(532.60–825.62)	606.99(480.06–745.29)
2005	8738853.22(6932017.06–10738676.92)	675.93(536.18–830.62)	609.48(482.13–749.69)
2006	8855255.98(7038780.46–10847393.96)	680.48(540.89–833.56)	613.87(485.59–754.48)
2007	9024876.13(7191569.22–11037552.10)	688.64(548.75–842.21)	621.93(491.90–764.05)
2008	9203432.01(7354488.33–11252138.78)	697.27(557.19–852.48)	630.75(498.91–773.70)
2009	9345979.12(7479206.91–11422269.83)	703.25(562.79–859.49)	637.54(504.36–780.87)
2010	9411269.24(7533929.61–11508486.25)	703.94(563.52–860.81)	639.64(506.15–782.65)
2011	9409321.64(7528742.22–11503993.82)	700.17(560.23–856.04)	638.16(504.96–781.35)
2012	9388410.18(7506034.23–11471557.35)	694.82(555.51–849.00)	636.05(503.16–779.28)
2013	9354235.04(7482880.43–11419040.33)	688.14(550.47–840.04)	633.58(501.00–776.71)
2014	9313525.46(7457707.20–11352242.82)	680.85(545.19–829.89)	631.06(498.79–774.00)
2015	9276255.78(7441681.68–11292264.08)	673.48(540.29–819.85)	628.96(496.91–771.74)
2016	9246990.94(7442456.79–11248922.44)	666.29(536.26–810.53)	627.71(496.36–770.78)
2017	9226186.92(7450183.11–11215438.57)	659.88(532.86–802.16)	626.98(496.82–770.23)
2018	9207244.24(7458147.49–11160697.13)	654.31(530.01–793.13)	626.24(497.22–769.14)
2019	9180723.88(7457306.28–11108643.43)	649.10(527.25–785.41)	625.08(497.08–767.46)
2020	9110475.29(7409807.16–11056409.17)	641.82(522.01–778.90)	621.63(494.56–765.36)
2021	9073096.05(7393885.70–10994319.08)	637.72(519.69–772.75)	619.85(492.05–763.74)
Estimate annual percentage change (%)	0.28(0.16–0.40)	-0.31(-0.43–0.19)	-0.21(-0.36–0.06)

3.3. The mortality of rheumatic heart disease in the Chinese population

Between 1990 and 2021, the number of deaths, death rate, and age-standardized death rate of rheumatic heart disease in the Chinese population have all shown a decreasing trend (**Table 3**). The number of deaths decreased from 134,208 in 1990 to 78,910 in 2021, with an average annual reduction rate of 1.98%. The death rate decreased from 11.41 per 100,000 in 1990 to 5.51 per 100,000 in 2021, with an average annual reduction rate

of 2.55%. At the same time, the age-standardized death rate significantly decreased from 19.07 per 100,000 in 1990 to 5.00 per 100,000 in 2021, with an average annual reduction rate of 5.00%. These data reflect that over the past 30 years, China has achieved significant progress in the prevention and control of rheumatic heart disease, leading to a significant reduction in the burden of disease-related deaths. The downward trend may be attributed to improvements in public health measures, better quality medical services, and the effectiveness of early intervention and management of the disease. These results indicate that continued investment and intervention are still necessary for further reducing the number of deaths and death rates related to rheumatic heart disease.

Table 3. The mortality of rheumatic heart disease in the Chinese population from 1990 to 2021

Years	Death number	Death rate (Per 100,000)	Age-standardized death rate (Per 100,000)
1990	134208.87(109948.62–157944.08)	11.41(9.35–13.43)	19.07(15.78–22.57)
1991	134352.59(113664.36–156305.06)	11.26(9.53–13.10)	18.55(15.80–21.56)
1992	132491.45(112943.06–153826.36)	10.98(9.36–12.75)	17.78(15.30–20.61)
1993	128658.83(111690.32–147737.39)	10.57(9.18–12.14)	16.84(14.62–19.51)
1994	125154.26(110900.70–141816.91)	10.21(9.04–11.56)	15.99(14.07–18.05)
1995	120701.22(106346.57–134375.12)	9.78(8.62–10.89)	15.05(13.25–16.83)
1996	115973.51(104873.38–131309.42)	9.35(8.46–10.59)	14.12(12.74–16.03)
1997	111108.81(101209.59–122899.73)	8.92(8.13–9.87)	13.21(12.05–14.62)
1998	108245.57(97583.81–122113.97)	8.66(7.81–9.77)	12.56(11.35–14.15)
1999	107238.32(97168.60–119221.94)	8.55(7.75–9.51)	12.12(10.98–13.57)
2000	106736.04(97302.01–118865.85)	8.48(7.73–9.44)	11.78(10.71–13.13)
2001	105707.96(94821.98–119187.42)	8.36(7.50–9.42)	11.41(10.27–12.83)
2002	104399.73(93781.33–116231.38)	8.21(7.38–9.14)	10.96(9.78–12.26)
2003	105351.16(94560.11–118888.26)	8.24(7.40–9.30)	10.81(9.72–12.17)
2004	105448.60(95455.25–117106.60)	8.20(7.43–9.11)	10.55(9.49–11.82)
2005	101470.21(92222.47–112316.04)	7.85(7.13–8.69)	9.87(8.95–10.94)
2006	94463.99(85135.31–103549.57)	7.26(6.54–7.96)	8.82(7.91–9.71)
2007	90156.50(82096.00–99238.48)	6.88(6.26–7.57)	8.12(7.30–8.95)
2008	89421.03(81192.32–97468.05)	6.77(6.15–7.38)	7.81(7.07–8.56)
2009	87668.79(79682.48–95512.95)	6.60(6.00–7.19)	7.42(6.69–8.06)
2010	85575.68(76768.56–93886.60)	6.40(5.74–7.02)	7.00(6.29–7.70)
2011	83078.58(74661.97–90688.75)	6.18(5.56–6.75)	6.54(5.84–7.16)
2012	80305.55(71040.61–88874.03)	5.94(5.26–6.58)	6.06(5.35–6.68)
2013	78841.88(70308.92–87845.94)	5.80(5.17–6.46)	5.74(5.08–6.39)
2014	77768.00(68123.39–86973.98)	5.69(4.98–6.36)	5.45(4.74–6.09)
2015	77148.66(67292.67–87696.72)	5.60(4.89–6.37)	5.20(4.51–5.91)
2016	78101.79(66177.47–89342.51)	5.63(4.77–6.44)	5.06(4.27–5.79)

Table 2 (Continued)

Years	Death number	Death rate (Per 100,000)	Age-standardized death rate (Per 100,000)
2017	77521.27(65773.78–91472.31)	5.54(4.70–6.54)	4.83(4.11–5.67)
2018	77134.34(63991.10–92069.26)	5.48(4.55–6.54)	4.62(3.84–5.52)
2019	77458.33(63037.67–93931.74)	5.48(4.46–6.64)	4.46(3.60–5.40)
2020	78240.76(62612.70–95617.76)	5.51(4.41–6.74)	4.34(3.49–5.27)
2021	78910.64(61703.40–100717.52)	5.55(4.34–7.08)	4.21(3.30–5.37)
Estimate annual percentage change (%)	-1.98(-2.14–-1.82)	-2.55(-2.71–-2.39)	-5.00(-5.14–-4.86)

3.4. Change trends in the disease burden of rheumatic heart disease among different genders in the Chinese population

From 1990 to 2021, the incidence, prevalence, and mortality rates of rheumatic heart disease among the Chinese population showed an overall decreasing trend, with significant differences between genders (**Figure 1**). Overall, the incidence rates in all age groups and age-standardized rates have gradually decreased from a peak. The incidence and prevalence rates have continuously decreased in both males and females since 1990, with similar decreasing trends but higher absolute values in females. Meanwhile, the mortality rate also significantly decreased, especially rapidly since the early 1990s, and remained low thereafter. The age-standardized incidence and prevalence rates have also shown a decreasing trend, indicating a significant reduction in the burden of rheumatic heart disease since 1990 in both total and age-adjusted views. Nevertheless, females still significantly exceed males in all indicators, suggesting the need for more interventions and disease management measures targeting females. Overall, the improvement of public health measures and medical conditions has played a positive role in reducing the burden of rheumatic heart disease.

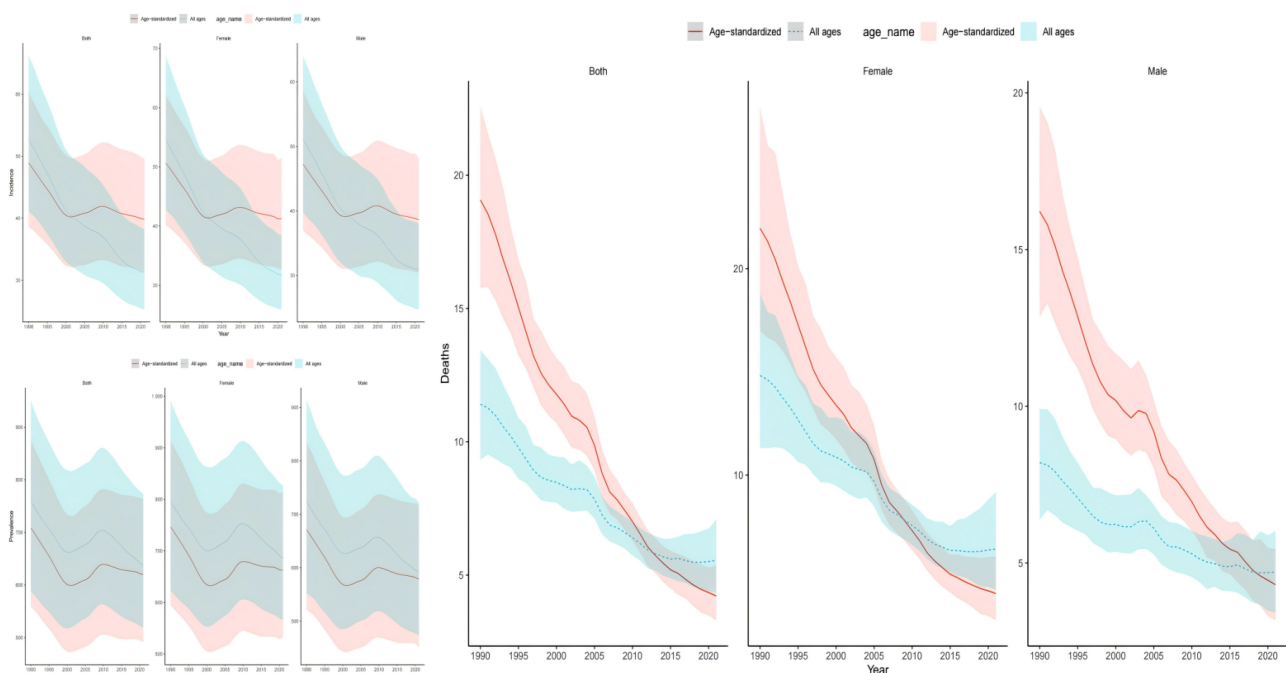


Figure 1. Change in trends in the disease burden of rheumatic heart disease among different genders in the Chinese population from 1990 to 2021

4. Discussion

Over the past few decades, China has undergone rapid socio-economic development and changes in population structure, which have had profound impacts on the field of public health. Based on the Global Burden of Disease (GBD) database, this study systematically analyzed the trends of disease burden of Rheumatic Heart Disease (RHD) in China from 1990 to 2021 and explored the differences in disease burden by gender. The results show that although the incidence, prevalence, and mortality of RHD are overall declining, this disease remains an important challenge in the field of public health in China ^[7].

Firstly, from the perspective of incidence rate, the annual average reduction rates of rheumatic heart disease in China are 1.07%, 1.65%, and 0.46% respectively, indicating significant progress in the prevention and treatment of rheumatic heart disease over the past thirty years ^[8]. This may be attributed to the improvement of healthcare services, implementation of public health policies, and increased awareness of population health. However, it is worth noting that despite the decreasing incidence rate, the number of rheumatic heart disease patients has shown a slight increase, which may be related to population aging and improved disease diagnosis rates ^[9].

The downward trends in the incidence and mortality rates indicate that China has achieved certain effectiveness in the long-term management of rheumatic heart disease ^[9]. The decrease in incidence may be related to early diagnosis and effective treatment, while the significant reduction in mortality rates may be associated with advances in medical technology, improvements in emergency medical systems, and optimization of cardiovascular disease management ^[10]. Furthermore, the declining age-standardized incidence and mortality rates further confirm the alleviation of the disease burden of rheumatic heart disease, demonstrating success in controlling disease risk factors.

In terms of gender differences, this study found that women have higher incidence, prevalence, and mortality rates of rheumatic heart disease than men, which may be related to biological differences, gender-specific social-behavioral factors, and unequal access to medical resources ^[11]. For example, women may be more susceptible to hormonal changes, which may increase the risk of cardiovascular diseases ^[12]. Additionally, women may face more obstacles in accessing medical resources and health information, which may affect their understanding and management of the disease. Therefore, future public health strategies need to pay special attention to women to reduce gender differences and improve overall health levels.

In addition, this study also found that, although the overall trend is declining, there may be differences in the disease burden of rheumatic heart disease among different regions and different socioeconomic groups ^[13]. This suggests that more targeted intervention measures are needed to address the health needs of specific groups. For example, in resource-poor areas, it may be necessary to strengthen infrastructure construction and improve the accessibility and quality of medical services. For groups with lower socioeconomic status, it may be necessary to provide more health education and economic support to promote the formation and maintenance of healthy behaviors.

The findings of this study emphasize the importance of continued investment in cardiovascular disease prevention and control measures. Despite some progress, rheumatic heart disease remains one of the leading causes of death and disability. Therefore, sustained public health efforts are needed, including health promotion, disease prevention, early diagnosis, and effective treatment. In addition, interdisciplinary research needs to be strengthened to better understand the complex causes and factors influencing rheumatic heart disease, and to provide scientific evidence for the development of more effective intervention strategies.

Based on the Global Burden of Disease (GBD) database, this study conducted a systematic analysis of the changing trend of rheumatic heart disease (RHD) burden in China from 1990 to 2021 and explored the differences in disease burden between different genders ^[4]. Although the study provided valuable insights, there were some limitations. The study mainly focused on indicators such as incidence, prevalence, and mortality rates, but the disease burden of rheumatic heart disease may also be affected by other factors, such as the impact of the disease on patients' quality of life, the economic burden caused by the disease, and patient's satisfaction with medical services ^[10]. Future research could consider incorporating these factors into the analysis to obtain a more comprehensive assessment of disease burden. Furthermore, although this study revealed gender differences, it did not delve into the specific reasons behind these differences. Gender differences may be related to various factors such as biology, socio-cultural factors, economic status, and access to medical resources ^[14]. Future research could use qualitative methods to analyze how these factors affect the disease burden of rheumatic heart disease in different gender populations.

In conclusion, this study provides a comprehensive analysis of the changing trends in the disease burden of rheumatic heart disease in China and reveals differences in disease burden between different genders. These findings are of great significance for guiding future public health policies and the allocation of medical resources. By implementing comprehensive prevention and control measures, it is hoped that the disease burden of rheumatic heart disease can be further reduced, improving the overall health level of the Chinese population.

Disclosure statement

The authors declare no conflict of interest.

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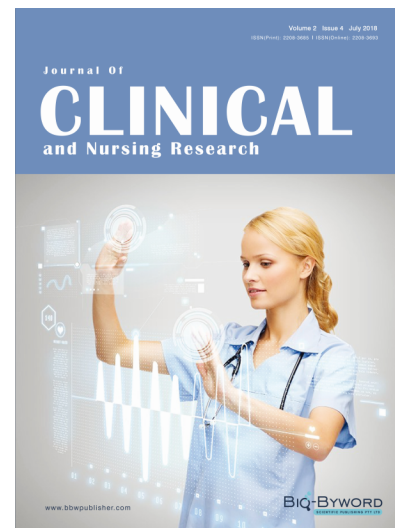
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