Black Sea Journal of Health Science

Volume 7 | Issue 6

ISSN: 2619 - 9041

BS Journals

BLACK SEA JOURNAL OF HEALTH SCIENCE
(BSJ HEALTH SCI)

Black Sea Journal of Health Science (BSJ Health Sci) is double-blind peer-reviewed, open-access international journal published electronically 6 times (January, March, May, July, September, and November) in a year since January 2018. BSJ Health Sci publishes, in English and Turkish full-length original research articles, innovative papers, reviews, mini-reviews, conference papers, case report, rapid communications or technical note by the scientists on technical and clinical studies related to all health sciences.

ISSN: 2619-9041

Phone: +90 362 408 25 15

Fax: +90 362 408 25 15

Email: bsjhealthsci@blackseapublishers.com

Web site: http://dergipark.gov.tr/bshealthscience

Sort of Publication: Periodically 6 times in a year (January, March, May, July, September, and November)

Publication Date and Place: November 15, 2024 - Samsun, TÜRKİYE

Publishing Kind: Electronically

REVIEWERS OF THE ISSUE*

Prof. Dr. Epy Muhammad LUQMAN, Airlangga University, Department of Veterinary Anatomy, Anatomy, INDONESIA

Prof. Dr. Önder İDİL, Amasya University, Department of Basic Education, Biotechnology, TÜRKİYE

Prof. Dr. Sibel KARACA SİVRİKAYA, Balıkesir University, Department of Nursery, Nurse Education, TÜRKİYE

Assoc. Prof. Aybala TAZEOĞLU, Osmaniye Korkut Ata University, Department of Nutrition and Dietetics, Nutritional Epidemiology, TÜRKİYE

Assoc. Prof. Büşra AYHAN, Gazi University, Department of Nutrition and Dietetics, Nutritional Epidemiology, TÜRKİYE

Assoc. Prof. Çiğdem ER ÇALIŞKAN, Kırşehir Ahi Evran University, Department of Field Crops, Analytical Chemistry, TÜRKİYE

Assist. Prof. Dr. Emel YILDIZ, Kütahya Health Science University, Department of Anesthesiology and Reanimation, Anesthesiology, TÜRKİYE

Assist. Prof. Dr. Esma GÖKÇE, Toros University, Department of Nursery, Surgical Diseases Nursing, TÜRKİYE

Assist. Prof. Dr. Hatice AZİZOĞLU, Van Yüzüncü Yıl University, Department of Nursery, Surgical Diseases Nursing, TÜRKİYE

Assist. Prof. Dr. Hatice POLAT, Atatürk University, Department of Internal Medicine Nursing, Nursing, TÜRKİYE

Assist. Prof. Dr. Kadirhan DOĞAN, Kapadokya University, Department of Therapy and Rehabilitation, Anatomy, TÜRKİYE

Assist. Prof. Dr. Muhammet DEĞERMENCİ, Ordu University, Department of Anatomy, Anatomy, TÜRKİYE

Assist. Prof. Dr. Neşe ERDEM, Adnan Menderes University, Department of Nursery, Internal Diseases Nursing, TÜRKİYE

Specialist Kenan DOĞAN, Kocaeli University, Department of Pediatric Nephrology, Pediatric Nephrology, TÜRKİYE

Specialist Kübra ŞAHİN, Üsküdar University, Department of Nutrition and Dietetics, Nutritional Epidemiology, TÜRKİYE

Specialist Muhammet Furkan KORKMAZ, Bursa Training and Research Hospital, Department of Pediatrics, Internal Diseases, TÜRKİYE

Specialist Şengül ÖZMERT, Ankara City Hospital, Department of Anesthesiology and Reanimation, Anesthesiology, TÜRKİYE

Dr. Burcu BAYYURT, Sivas Cumhuriyet University, Department of Medical Biology, Molecular Genetics, TÜRKİYE

Dr. Neslihan YÜCE, Atatürk University, Department of Medical Biochemistry, Medical Biochemistry, TÜRKİYE

* The ranking is arranged alphabetically within the academic title

Volume 7, Issue 6 (2024)

Table of Contents

Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1465505

Open Access Journal
e-ISSN: 2619 – 9041

Research Article
Volume 7 - Issue 6: 226-230 / November 2024

THE EFFECT OF THE PARENT'S PRESENCE DURING THE DRESSING PROCESS ON THE SEVERITY OF THE CHILD'S PAIN

Dudu ALPTEKİN[1]*, Fatma ETİ ASLAN[2], Hamide ŞİŞMAN[1], Refiye AKPOLAT[3]

[1]*Çukurova University, Abdi Sütçü Vocational School of Health Services, 01250, Adana, Türkiye*
[2]*Bahçeşehir University, Faculty of Health Sciences, 34353, İstanbul, Türkiye*
[3]*Cyprus International University, Faculty of Health Sciences, Nicosia, TRNC*

Abstract: This research was carried out to determine the effect of the parent's presence near the child during the dressing process on the severity of pain caused by the dressing. The sample of the descriptive comparative study consisted of 60 children. Ethics committee and study permission were obtained from the relevant institutions. Data were collected by observation and face-to-face interviews using the "Individual Characteristics Form" and the YBATT (facial expression, legs, activity, crying, and being able to be consoled) pain assessment scale. In the examination of the way parents supported their children during the painful procedure, it was observed that 13 (43.4%) of them used remote monitoring approach. The mean dressing time of the children showed a significant difference according to the parent variable; it was determined that the dressing time of the children with a parent present (7.5 min) was higher than the dressing time of the children without a parent present (6.3 min). In this study, it was seen that the presence of the parent with the child during the dressing did not affect the severity of the pain, the presence of the parent extended the dressing time, and the parents were in the approach of remote monitoring as a way of supporting the child during the procedure.

Keywords: Dressing procedure, Pain severity, Child, Parent

***Corresponding author:** Çukurova University, Abdi Sütçü Vocational School of Health Services, 01250, Adana, Türkiye
E mail: dudubaysal@hotmail.com (D. ALPTEKİN)
Dudu ALPTEKİN https://orcid.org/0000-0003-2612-7379
Fatma ETİ ARSLAN https://orcid.org/0000-0003-0965-1443
Hamide ŞİŞMAN https://orcid.org/0000-0001-6867-9054
Refiye AKPOLAT https://orcid.org/0000-0001-8907-0651

Received: April 05, 2024
Accepted: October 10, 2024
Published: November 15, 2024

Cite as: Alptekin D, Eti Arslan F, Şişman H, Akpolat R. 2024. The effect of the parent's presence during the dressing process on the severity of the child's pain. BSJ Health Sci, 7(6): 226-230.

1. Introduction

While post-operative pain was perceived as a natural process that patients who underwent surgical intervention had to endure in the recent past, it is pointed out that today post-operative pain is a problem that needs to be solved by revealing its negative effects in every aspect of the patient's life.

However, despite the developments in pain, postoperative pain in children continues to be both a medical and social problem, and children still suffer from pain in the postoperative period (Khan and Weisman, 2007). In the study conducted by ZiskRony et al. (2010), it was reported that 51% of children who underwent surgery experienced an average of sub-intensity pain on the first day after surgery. In another study, in which children were evaluated for pain after lower extremity surgery, it was determined that approximately 75% of children experienced pain in various degrees (Shrestha and Manias, 2010).

In the postoperative period, children not only experience pain due to surgery but also experience pain due to interventional practices during their hospital stay (Shrestha and Manias, 2010; Babl et al., 2012). In this context, the already traumatic disease process in children turns into an even more traumatic process with pain. For this reason, it is important to use non-pharmacological methods and pharmacological methods to relieve pain in improving the process, especially to comply with atraumatic care principles in all applications, and to include parents in care in terms of family-centered care principles.

There are many non-drug methods used to reduce interventional pain in children based on these principles (Lago et al., 2009; Wente et al., 2013). In addition to these non-drug methods, one of the methods that help children cope with pain is the presence of the parent with the child during the procedure. However, although it is reported in the literature that the presence of the parent with the child is an important factor in increasing the child's pain tolerance in coping with pain, it has been found in some literature that this intervention does not affect the pain tolerance of children and that children are affected by the stress of their families and studies on this subject are quite limited (Wente et al., 2013). Pain management during procedures is among the important responsibilities of the health care team. The nurse has a very important place in this team (Çöçelli et al., 2008).

Since many procedures performed on hospitalized children cause pain, the best method to reduce pain should be chosen. Data are needed to determine the

effectiveness of these methods. Since there are no adequate and comprehensive studies on the effect of parental presence on pain intensity during the procedure in our country, this study aimed to provide basic data. In line with this purpose, the study was conducted to determine the effect of parental presence on pain intensity during dressing. The main research questions sought to be answered within the scope of the study are as follows:

1. Does the presence of the parent with the child during the painful procedure reduce the severity of pain?
2. Does the presence of the parent with the child affect the duration of the procedure?
3. How was the parent's approach during the painful procedure?

2. Materials and Methods

The research was of descriptive type. The study population consisted of Çukurova University Balcalı Hospital and Adana Numune Hospital. Patients Hospitalized in the Pediatric Surgery Clinic of Training and Research Hospital children. The sample size was determined by considering the data obtained from a similar study (Voepel et al., 2010). A total of 60 patients, 30 in at least two groups, all of whom had undergone surgery on abdominal organs.

Inclusion criteria:

- Abdominal surgery
- Dressing the child
- The child is between 3-6 years old
- The willingness of the child and his/her family to participate in the study
- The child and/or family does not have speech, hearing or perception problems.

2.1. Data

Individual characteristics form and Facial expression, Legs, Activity, Crying, Cons, and ability (FLACC) pain severity assessment form were collected. There were 12 questions in the form. Seven of these were open-ended questions. The questions in the data form; the child's name-surname, age, gender, medical diagnosis, type of surgery, dressing area, duration, and the number of times the dressing was applied. There was also a section where verbal and behavioral expressions of parents and their observations of support were recorded.

Pain is assessed according to the child's age and cooperation using personal expression, behavioral observation, or physiological measurements. It is more difficult to define pain especially in children aged 0-7 years and in the post-operative care unit in the intensive care unit. There are many methods for assessing pain.

These are based on an observer's assessment or measurement of some characteristics or changes in the patient, or the patient's self-assessment of pain. Method selection should be made according to the child's general condition, age, and, level of pain recognition (Şenaylı et al., 2006).

With the FLACC (Face, Legs, Activity, Crying, Consolability) pain assessment scale developed by Merkel et al. in 1997, five behavioral categories (Face, Legs, Activity, Crying, Consolability) evaluation is done (Güdücü Tüfekci and Erci, 2007).

In this study, the effect of the parent's presence with the child during the dressing process on the severity of pain was investigated; dressing area, dressing time and pain intensity are dependent variables. The independent variables are the child's age, gender, length of hospital stay, medical diagnosis, type and duration of the surgical procedure, how many times the dressing was performed, and the presence of a parent during the dressing.

2.2. Data Collection Stages

While collecting data; two groups were created. During the dressing process, the parent was asked whether he wanted to stay with the child and it was determined which group he would be in. In this direction, pain severity was evaluated in those whose parents were present or not during the dressing application. Data were completed for each child after obtaining the consent of the legal guardian with the Informed Consent Form.

1. Group

The first group included children who underwent postoperative abdominal surgery and received their first dressing. The dressing was performed by the surgeon who performed the surgery at the child's bedside. The parent was allowed to be with the child during the dressing, but where and how to stand was not intervened. In the first part, individual characteristics of the child and the family were questioned. In the second part, pain intensity was measured using the Face, Leg Mobility, Activity, Crying, Consolation (FLACC) pain scale. The obtained pain intensity score was summarized. Verbal and behavioral support (such as holding the hand, hugging) of the parent during the procedure was recorded.

2. Group

It was randomized that the parent was not present with the child during the dressing procedure. The dressing was performed at the child's bedside and by the surgeon who performed the surgery. In the first part, individual characteristics of the child were questioned. In the second part, pain intensity was measured using the Face, Leg Mobility, Activity, Crying, Consolation (FBAAT) pain scale.

2.3. Data Analysis

While evaluating the findings obtained in the study, Statistical Package for the Social Science (SPSS) 21 statistical package program was used. Pearson Chi Square test and Fisher Exact test was used. In the case of two groups in the comparison of quantitative data, Mann-Whitney U test was used for comparison of parameters between groups.

3. Results

The findings of the research are discussed in two parts below. In the section; on individual characteristics and medical data of 60 children included in the study. In the section; Data on the assessment of pain severity of children and parental support were included.

Between children with and without accompanying parents, significant differences in terms of age and gender, respectively (χ^2=6.133; P=0.105>0.05; χ^2=0.071; P=0.500>0.05) were not found (Table 1). In both groups, appendectomy was performed in the majority of children in parallel with their medical diagnosis (Table 2). The difference between the mean dressing times of children is statistically significant. (Mann Whitney U=316.000; P=0.043<0.05). Dressing time for children with a parent (7.5 min), and children without a parent was higher than the dressing time of children (6.3 min) (Table 3).

Children's mean pain intensity according to whether they have a parent or not there was no statistically significant difference (Table 4). Of the parents who were with their child, 13 (43.4%) received dressing during the study, it was determined that they preferred remote monitoring (Table 5).

Table 1. Distribution of individual characteristics (n=60)

Feature		With Parent (n=30)		Non-Parent (n=30)		
		n	%	n	%	P
Age	3	4	13.3	0	0	χ^2=6.133 P=0.105
	4	6	20	3	10	
	5	8	26.7	12	40	
	6	12	40	15	50	
Gender	Female	12	40	11	36.7	χ^2=0.071 P=0.791
	Male	18	60	19	63	

Table 2. Distribution of surgical treatment types applied to children (n=60)

Type of Surgical Treatment	With Parent (n=30)		Non-Parent (n=30)	
	n	%	n	%
Apendektomi	20	66.8	20	66.8
Abscess	1	3.3	0	0
Excision	0	0	1	3.3
Cholecystectomy	1	3.3	1	3.3
Stoma	0	0	2	6.7
Laparoscopy	4	13.3	2	6.7
Nephrectomy	1	3.3	0	0
Primary repair	1	3.3	2	6.7
Pyeloplasty	2	6.7	0	0
Splenectomy	0	0	2	6.7

Table 3. Comparison of the mean dressing duration of children (n=60)

Type of Surgical Treatment	With Parent (n=30)		Non-Parent (n=30)			
	Mean	SD	Mean	SD	MW	Statistical Analysis
Dressing Time (Minute)	7.500	3.330	6.300	4.542	316	0.043

Table 4. Comparison of children's pain severity (n=60)

	With Parent (n=30)		Non-Parent (n=30)			
	Mean	SD	Mean	SD	MW	Statistical Analysis
Pain Intensity	3.300	2.984	2.970	2.553	431.000	0.775

Table 5. Maternal approach (n=30)

Parents Approach	n	%
Hug	7	23.3
Don't Hold Your Hand	6	20
Verbal Suggestion	4	13.3
Remote Monitoring	13	43.4
Total	30	100

4. Discussion

The individual characteristics of both groups of children examined in this study were similar. These Results showed that the groups were homogeneous. This was also observed in pain studies. Pain is a subjective perception and age, gender, and past can be influenced by many factors such as experiences and the environment. These results are also important for the reliability of the results obtained.

The subjective nature of pain is an important factor that makes it difficult to assess and treat. Therefore, despite the advances in pain management today, 85% of patients with pain are pain-free, while 15% of patients with other types of pain continue to suffer from pain. These results suggest that non-pharmacologic methods for pain relief should be examined in depth. Family-centered care is care that best meets the needs and expectations of parents and children model. Family-centered care practices, the benefits and importance of which have been determined by research, painful procedures the parent should be there for the child during the supporting the child. Parents can be with their children during painful procedures is extremely important (Boztepe, 2012). Based on this necessity, this study aims to create a safe environment for children. The mother/parent, who is considered as the mother/parent, is with the child during the painful application. Was found to not affect perceived pain intensity. These results were found to be compatible with the literature. Because Güdücü Tüfekci and Erci (2007) the presence of the parent in the child's presence during the child's pain tolerance in the child did not affect the pain. Again, Broome and Endsley (1989) and Doctor (1994) the presence of parents with the children during the procedures to prevent pain in children reported that it had little effect on tolerance alone. On the other hand, some studies have shown that parental presence plays an important role in coping with pain. This increases children's pain tolerance, calms and children tolerate procedural pain better (Merritt et al., 1990; Naber et al., 2001). The importance of parental presence, as well as parental behavior in the presence of the child, among non-drug methods, is still under investigation. Accordingly, this study analyzed how parents supported their children; parents preferred to watch their children remotely during dressing. This result was inconsistent with the literature. Because O'Keeffe argues that children's coping with pain is influenced by parents' behavior, parents sometimes try to comfort their children and distract them, reported that they used diversion methods (O'Keefe, 2001).

Studies have shown that children are more likely to hear their parents' verbal or physical reactions during painful procedures. Parents should try to help their children during painful procedures by talking to them in a soft voice, holding their hands while supporting them, patting their heads and making eye contact with them (Naber et al., 2001). In this study, it was found that parents preferred to watch from a distance during dressing.

5. Conclusion

When the answers to the research questions were analyzed; It was observed that the presence of a parent during a painful procedure did not affect the intensity of pain, that there was a difference in the duration of the procedure between children with and without their parents present, and that the children with their parents present appeared to have a longer procedure time, and that the parent preferred remote suggestion as a form of support during the procedure. Based on the results from the study; Pain tolerance in painful procedures, parental presence, procedure duration and work to support the child's development in other childhood years. It is recommended to be comprehensive.

Limitations

The limitations of the study are that it was conducted in one region and two centers, and that it was limited in number.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	D.A.	F.E.A.	H.Ş.	R.A.
C	30	30	10	30
D	100			
S		100		
DCP	60		20	20
DAI	60		20	20
L	80	20		
W	40	20	20	20
CR	40	20	20	20
SR	40	20	20	20
PM	40	20	20	20
FA	40	20	20	20

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Approval/Informed Consent

This study was approved by Ethics Committee of Çukurova University (approval date: May 08, 2015, protocol code: 24). Cukurova University Balcalı hospital management and the Ministry of Health, Public Hospitals Authority of Türkiye Permission to work from Adana Public Hospitals Union General Secretariat. Academic Board decisions were taken from all departments where the research was conducted. The research was conducted according to the principles of the Declaration of Helsinki, revised in 2008.

References

Babl FE, Crellin D, Cheng J, Sullivan TP, O'Sullivan R, Hutchinson A. 2012. The use of the faces, legs, activity, cry and consolability scale to assess procedural pain and distress in young children. Pediat Emer Care, 28(12): 1281-1296.

Boztepe H. 2012. Pediatri hemşirelerinin ağrılı işlemler sırasında ebeveynlerin bulunması hakkında görüşleri. Ağrı Derg, 24(4): 171-179.

Broome M, Endsley R. 1989. Maternal presence, children practices, and child response to an ejection. Res Nurs Health, 12: 229-235.

Çöçelli LP, Bacaksız BD, Ovayolu N. 2008. Nurse's role in pain management. Gaziantep Medic J, 14: 53-58.

Doctor M. 1994. Parent participation during painful wound care procedures. J Burn Care Rehab, 3: 288-292.

Güdücü Tüfekci F, Erci B. 2007. The effect of parental presence during painful procedures and some factors on children's pain tolerance. J Atatürk Univ School Nurs, 10(2): 30-40.

Khan KA, Weisman SJ. 2007. Nonpharmacologic pain management strategies in the pediatric emergency department. Clin Ped Emerg Medic, 8: 240-247.

Lago P, Garetti E, Merazzi D, Pieragostini L, Ancora G, Pirelli A, Bellieni CV. 2009. Guidelines for procedural pain in the newborn. Acta Pædiatrica, 98: 932-939.

Merritt KA, Sargent JR, Osborn LM. 1990. Attitudes regarding parental presence during medical procedures. AJDC, 144: 270-271.

Naber D, Moritz S, Lambert M, Pajonk FG, Holzbach R, Mass R, Andresen B. 2001. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res, 50(1-2):79-88.

O'Keefe N. 2001. Pain and children. World Irish Nurs, 9(10): 34-36.

Şenaylı Y, Özkan F, Şenaylı A, Bıçakçı Ü. 2006. Evaluation of postoperative pain in children with (FLACC) pain scale. Turkiye Klin J Anest Reanim, 4(1): 1-4.

Shrestha-Ranjit JM, Manias E. 2010. Pain assessment and management practices in children following surgery of the lower limb. J Clin Nurs, 19: 118-128.

Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. 2010. Reliability and validty of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. Amer J Crit Care, 19(1): 55-61.

Wente SJK, Richfield MN. 2013. Nonpharmacologic pediatric pain management in emergency departments: A systematic review of the literature. J Emer Nurs, 39(2): 140-150.

Zisk Rony RY, Fortier MA, Chorney JM, Perret D, Kain ZN. 2010. Management parental postoperative pain management: attitudes, assessment and management. Pediatrics, 125(6): e1372-e1378.

Black Sea J Health Science
doi: 10.19127/bshealthscience.1543889

Open Access Journal
e-ISSN: 2619 – 9041

Research Article
Volume 7 - Issue 6: 231-239 / November 2024

NURSING STUDENTS' HEALTH PERCEPTIONS AND AFFECTING FACTORS

Yasemin ÇELİK[1]*

[1]*Afyonkarahisar Health Sciences University, Faculty of Health Sciences, Department of Nursing, 03030, Afyonkarahisar, Türkiye*

Abstract: This research was conducted to determine the health perception levels of nursing students and the influencing factors. The descriptive cross-sectional study was conducted between August 2023 and September 2023. The sample of the study consisted of 138 students studying in the Nursing Department of the Faculty of Health Sciences in the Aegean region who volunteered to participate in the study. The socio-demographic information (12 questions) questionnaire form and the Health Perception scale (15 questions) developed in line with the literature were used to collect data. The data were evaluated in the SPSS 27.00 package program. As a result of the research, it was determined that the average score that the students got from the health perception scale was 38.99±5.24. When the sub-dimensions of the health perception scale were examined; The Control Center sub-scale average score was determined as 12.82±3.15, the Certainty sub-scale average score as 12.44±2.75, the Importance of Health sub-scale average score as 6.90±1.97, and the Self-awareness sub-scale average score as 6.83±1.70. While there was a significant difference between the students' family type, smoking, financial level, health level, place of residence and family health status and health perception and its subgroups (P<0.05), it was determined that there was no statistically significant difference between age, gender, parental education level, chronic disease and regular medication use (P>0.05). It was concluded that the students' health perception general score and subscale scores were not at the desired level and that various factors negatively affected these scores in general. Various strategies should be planned to strengthen students' health perceptions.

Keywords: Health perception, Nursing, Students, Healthy behavior

***Corresponding author:** Afyonkarahisar Health Sciences University, Faculty of Health Sciences, Department of Nursing, 03030, Afyonkarahisar, Türkiye
E mail: celikyasemin@hotmail.com (Y. ÇELİK)
Yasemin ÇELİK https://orcid.org/0000-0002-8134-3026

Received: September 05, 2024
Accepted: October 11, 2024
Published: November 15, 2024

Cite as: Çelik Y. 2024. Nursing students' health perceptions and affecting factors. BSJ Health Sci, 7(6): 231-239.

1. Introduction

Health perception can be defined as a combination of an individual's feelings, thoughts and expectations about their own health (Ozdelikara et al., 2018). In other words, health perception reveals a person's personal beliefs and explanations about their health status. Health perception is an important data in terms of showing the individual's physical, mental and social well-being, and it also refers to a process that aims to provide, develop and maintain healthy lifestyle behaviors for the individual (Shaw et al., 2012; Dilek and Aydanur, 2017).

Many factors such as the individual's gender, age, and education level, economic, environmental and sociocultural factors shape health perception and are effective in the development of health behaviors (Alkan Ağaçdiken et al., 2017). Students experience the last stage of adolescence with university education. The university period is a period in which some anxious periods such as separation from home and family, making new friends, learning a profession and finding a job are experienced. During this process, students may try to gain an identity and mature, and their health behaviors may also change. This change is especially important in terms of health-related perceptions and behaviors. During this period, students may develop health-enhancing behaviors according to their health perceptions or adopt unhealthy lifestyle behaviors that will harm themselves and society (Hür et al., 2014; Çelik and Soyer, 2022).

The high perception of health of nursing students can positively affect their approach to individuals, families and communities to whom they will provide health services in the future. Therefore, students are expected to develop behaviors that strengthen their health perceptions during their education process (Çilingir and Aydın, 2017; Doğu and Atasoy, 2017). The foundation of a healthy society is formed by individuals who have a high perception of health and have developed healthy lifestyle behaviors based on this perception. Nurses have important roles in developing public health and reinforcing positive health behaviors. The health perceptions of future nurses should be developed from the beginning of their university education-training period and they should be provided with knowledge, skills and attitudes regarding individual and community health, especially themselves (Can et al., 2008; Alkan Ağaçdiken et al., 2017; Çelik and Soyer, 2022). In this context, it is thought that some disease knowledge-

related courses, especially internal medicine and surgical disease nursing, given theoretically and practically in the second year according to the nursing curriculum, can contribute greatly to students' health perception. Therefore, the aim of this study was to examine the health perception level and influencing factors of nursing students, who are the future members of the nursing profession who have direct responsibility for protecting and improving the health of individuals. First, third and fourth year students were not included in the study because the aim of the study was to access data from students who were intensively exposed to disease information for the first time. Therefore, the aim of this study is to examine the health perception levels and influencing factors of nursing students, who are future members of the nursing profession who have direct responsibility for protecting and improving the health of individuals.

2. Materials and Methods

2.1. Purpose and Type of the Study

This study was conducted as a descriptive cross-sectional study to determine the health perception levels of nursing students and the influencing factors.

2.2. Sample of the Study

The universe of the study consisted of students who completed their 2nd year education at the Nursing Department of the Faculty of Health Sciences at Afyonkarahisar Health Sciences University between August 2023 and September 2023. The courses in which information about diseases is given most intensively in the nursing department curriculum (Internal Medicine Nursing, Pathology, Pharmacology, etc.) are held during the 2nd year. The fact that students, who were equipped with information about health and healthy human physiology in the previous process, encountered the disease phenomenon intensively in the 2nd year constituted an important point in the selection of the sample. In the later processes of nursing education, the education received in the 2nd year is expanded according to the fields. The aim of the study was to reach the data of students who encountered disease information intensively for the first time. No sample selection was made in the study, and the study was completed with 138 students who volunteered to participate in the study out of a class of 145. The survey forms were administered online because it was the summer term. The survey was tested with a few people before application and possible errors and deficiencies were corrected. On the other hand, the number of questions was prepared in small numbers so that the answers would not be boring.

2.3. Data Collection Tools

Data were collected using the "Sociodemographic Information" form and the "Health Perception Scale."

Sociodemographic information: was collected with a questionnaire form (12 questions) consisting of questions such as age, gender, family type, mother and father's education status, smoking, financial situation, prepared in line with the literature (Shaw et al., 2012; Dilek and Aydanur, 2017; Ağaçdiken et al., 2017; Ozdelikara et al., 2018).

Health Perception Scale (HPS): The scale developed by Diamond et al. (2007) was adapted to Turkish society by Kadıoğlu and Yıldız (2012). The Cronbach alpha coefficient of the scale was 0.77 for nursing students and 0.70 for their families, and it was found to have a good level of reliability in both groups. Kadıoğlu and Yıldız (2012) conducted the validity and reliability study of the Turkish translation of HPS by applying it to nursing students at two universities in Istanbul and their family members. In the retest, the Pearson correlation value was found to be 0.78 (P=0.000). As a result, the scale was accepted as valid and reliable. HPS is a five-point Likert-type scale consisting of 15 items and four sub-factors. The scale has 15 items and four sub-factors titled "control center", "self-awareness", "certainty" and "importance of health". Items 1, 5, 9, 10, 11 and 14 are positive attitudes, items 2, 3, 4, 6, 7, 8, 12, 13 and 15 are negative statements. Positive statements were scored as "I very much agree = 5", "I agree = 4", "I am undecided = 3", "I do not agree = 2", "I do not agree = 1". Negative statements were reverse scored. The minimum score that can be obtained from the scale is 15, and the maximum score is 75. As the score obtained from the scale increases, the Health Perception score increases positively. The lowest scores that can be obtained from the "center of control", "self-awareness", "certainty", "importance of health" subgroups are 5, 3, 4, 3, and the highest scores are 25, 15, 20, 15, respectively (Kadıoğlu and Yıldız, 2012). In this study, the general Cronbach alpha value of the scale was calculated and was found to be reliable as 0.811.

The control center (CCM) sub-dimension is aimed at determining whether the individual attributes being healthy to factors outside of himself (luck, fate, religious belief, etc.), that is, whether he gathers the control center in himself in being healthy and his self-confidence in changing his health (Kadıoğlu and Yıldız, 2012; Dündar Kurt, 2019; Bıçakcı, 2022).

The self-awareness (SAF) sub-dimension is aimed at determining the level of the individual's self-awareness perception regarding exercise and proper nutrition for being healthy, and the belief that being healthy is in his own hands (Kadıoğlu and Yıldız, 2012; Dündar Kurt, 2019; Bıçakcı, 2022).

The certainty (CES) sub-dimension is aimed at determining whether the individual has a definite idea about what he/she needs to do to stay healthy and be healthier (Kadıoğlu and Yıldız, 2012; Dündar Kurt, 2019; Bıçakcı, 2022).

The importance of health (SGÖ) sub-dimension is aimed at determining the extent to which the individual attaches importance to his/her health, the extent to which he/she makes material sacrifices in this regard, and whether the importance he/she attaches to health is one of the priorities in his/her life (Kadıoğlu and Yıldız,

2012; Dündar Kurt, 2019; Bıçakcı, 2022).

2.4. Statistical Analyses

Data analysis was performed using the SPSS 27 statistical program. For reliability, internal consistency coefficient Cronbach's Alpha test statistics were used, and the reliability coefficient was determined as $0.01 \leq \alpha < 0.40$ (not reliable); $0.40 \leq \alpha < 0.60$ (low reliability); $0.60 \leq \alpha < 0.80$ (highly reliable) and $0.80 \leq \alpha < 1.00$ (highly reliable) (Kalaycı, 2008). Mean and percentage values were calculated, t test and ANOVA (variance analysis) analyses were performed. In parametric tests, when variances were not distributed homogeneously, Welch test results were taken as basis. In multiple comparisons of groups found to be significant as a result of ANOVA test, Tukey or Tamhane test was applied according to variance homogeneity. While interpreting the results, $P<0.05$ was considered as the significance level (Genç and Soysal, 2018).

3. Results

Of the students who participated in the study, 85 (61.59%) were between the ages of 18-21 and 118 (85.51%) were female. 123 (89.13%) of the students lived in a nuclear family, 101 (73.19%) of the mothers had primary school education while 61 (44.20%) of the fathers had primary school education. 115 (83.33%) of the students did not smoke, 99 (71.74%) of them had income equal to expenses and 74 (53.62%) of them considered their health level to be moderate. 100 students (72.46%) lived with their families, 125 (90.58%) did not have a chronic disease, 124 (89.86%) did not use any regular medication and 56 (40.58%) did not have a chronic disease in their families. The total number of participants is 138 (Table 1).

According to the analysis results of HPS and its sub-dimensions, the average HPS total score was 38.99±5.24, which is at a medium level close to weak, the average score of the CCM sub-dimension was 12.82±3.15, which is weak, the average score of the SAF sub-dimension was 6.83±1.70, which is weak, the average score of the CES sub-dimension was 12.44±2.75, which is medium, and the average score of the HPS sub-dimension was 6.90±1.97, which is weak.

Table 1. Descriptive characteristics of students (n=138)

Variable	Category	n	%
Age	18-21	85	61.59
	22-25	53	38.41
Gender	Female	118	85.51
	Male	20	14.49
Family Type	Nuclear Family	123	89.13
	Extended Family	10	7.25
	Divorced	5	3.62
Mother Education Level	Primary School	101	73.19
	High School	26	18.84
	University	11	7.97
Father Education Level	Primary School	61	44.20
	High School	48	34.78
	University	29	21.01
Smoking Status	Yes	23	16.67
	No	115	83.33
Financial Level	Income More Than Expenses	22	15.94
	Income Equals Expenses	99	71.74
	Income Less Than Expenses	17	12.32
Health Level	Good	62	44.93
	Average	74	53.62
	Poor	2	1.45
Place of Residence	State Dormitory	20	14.49
	Private Dormitory	6	4.35
	House with Friends	12	8.70
	Family	100	72.46
Chronic Disease Status	Yes	13	9.42
	No	125	90.58
Medication Status	Yes	14	10.14
	No	124	89.86
Family Health Status	Chronic Patient	36	26.09
	Hospitalization	19	13.77
	Chronic Disease and Hospitalization	27	19.57

No Disease	56	40.58	

Table 2. Mean scores and reliability results of the health perception scale and its sub-dimensions

Variable	Score Range	Mean ±SD	Min.	Max.	Cronbach alfa
Control Center	5-25	12.82±3.15	5.00	25.00	0.782
Self-Awareness	3-15	6.83±1.70	3.00	12.00	0.766
Certainty	4-20	12.44±2.75	6.00	20.00	0.786
Importance of Health	3-15	6.90±1.97	3.00	13.00	0.801
Health Perception Scale	15-75	38.99±5.24	24.00	51.00	0.811

According to the normality and reliability analyses of HPS and its sub-dimensions, the total scores of the CCM, SAF, CES and SGÖ sub-dimensions and the HPS are close to normal distribution according to skewness and kurtosis values, and the reliability coefficients (Cronbach alpha values ranging from 0.766 to 0.811) show that these scales and their sub-dimensions are reliable (Table 2).

According to the obtained data, it was determined that the family types of the students had a significant effect on the HPS and its sub-dimensions. Accordingly, the scores of the students with a divorced family type were higher in the CCM and CES than in other family types, and the scores of the students living in a nuclear family were higher in the SGÖ and SAF than in other family types (P<0.05) (Table 3).

It was determined that the scores of the students who did not smoke were statistically significantly higher than those who did (P<0.05), but smoking status did not have a significant effect on the scores of the CES, SGÖ, SAF and HPS (P>0.05) (Table 3).

When the financial levels of the students were examined, the scores of those whose income was higher than their expenses were found to be lower in terms of the SGÖ than those whose income was lower than their expenses; and the scores of those whose income was higher than their expenses were found to be lower in terms of the HPS than those whose income was equal to their expenses (P<0.05). On the other hand, it was revealed that the scores of the CCM, CES and SAF did not show a significant difference according to financial levels (P>0.05) (Table 3).

The students who perceived their health level as poor health had higher scores in terms of SGÖ than those who perceived their health level as good and moderate health level (P<0.05), but it was determined that the scores of CCM, CES, SAF and HPS did not show significant differences according to health levels (P>0.05) (Table 3).

It was determined that the CCM, CES and SAF sub-dimensions showed significant differences according to the place of residence (P<0.05). In terms of place of residence, students staying in state dormitories had higher CCM scores than those staying with their families, while those staying in state dormitories had lower scores than those staying with their friends in terms of CES, and those staying in state dormitories had lower scores than those staying with their families in terms of SAF (P<0.05). On the other hand, it was concluded that the SGÖ and HPS scores did not show significant differences related to the place of residence (P>0.05) (Table 3).

The HPS scores of students with a family history of chronic illness were found to be higher than those with a family history of hospitalization (P<0.05), but it was observed that the sub-dimensions of the CCM, SAF, CES and SGÖ did not show a significant difference in terms of the health status of the family (P>0.05) (Table 3).

The obtained data revealed that the HPS and its sub-dimensions (CCM, SAF, CES and SGÖ) did not show a significant difference in terms of age, gender, mother's education level, father's education level, the student's chronic disease status and medication use status. (P>0.05) (Table 3).

4. Discussion

Health perception is effected by various factors such as education, social, cultural and economic status and is related to how the individual perceives his/her own health. An individual may feel healthy when he/she is sick or sick when he/she is healthy. Therefore, healthy behavior requires knowing health perception first for a healthy lifestyle. The World Health Organization points to nurses as the basic human power in health protection and development activities. Nurses, who play an important role in health services, need to understand and emphasize the importance of health development and be a guide and model in gaining these behaviors (Aristizabal Castano and San Martin Rodriguez, 1998; Whitehead, 2005). One of the main purposes of professional education in nursing is to provide nursing students with the knowledge, skills and attitudes that will enable them to protect and develop both their own and individuals' health. Nursing students are expected to understand the importance of developing their health from their student years. The purpose of examining the health perception and affecting factors of nursing students is to determine and evaluate the goals related to health development in nursing education curricula and to contribute to the literature on health perception and affecting factors.

In the study, it was determined that the students' HPS average score was 38.86±5.11 and it was seen that it was at a moderate level close to weak. In similar studies on health perception (Zaybak and Fadıloğlu, 2004; Can et al., 2008; Dilek and Aydanur, 2017), it was stated that the health perception scores of nursing students were at a moderate level. This result shows that the students' health perceptions were not at the desired level, but they could control their behaviors that could affect their

health and their health responsibility was at a moderate level.

Table 3. Comparison of the students' descriptive characteristics and HPS and sub-dimension score averages (n=138)

	HPS Mean±SD	CCM Mean±SD	SAF Mean±SD	CES Mean±SD	SGÖ Mean±SD
Age					
18-21	38.86±5.11	12.84±3.23	6.75±1.76	12.33±2.72	6.94±2.07
22-25	39.21±5.48	12.79±3.06	6.96±1.60	12.62±2.82	6.83±1.82
Test / P	t= -0.379/ 0.705	t= 0.077/ 0.938	t= -0.703/ 0.483	t= -0.608/ 0.544	t=0.321/ 0.749
Gender					
Female	39.07±5.15	12.81±3.22	6.77±1.68	12.58±2.74	6.90±1.93
Male	38.55±5.88	12.85±2.81	7.20±1.82	11.60±2.72	6.90±2.25
Test / P	t= 0.407 / 0.684	t= -0.048 / 0.962	t= -1.044 / 0.298	t= 1.487 / 0.139	t= -0.004 / 0.997
Family Type					
Nuclear Family(1)	39.12±5.10	12.78±2.82	6.95±1.65	12.34±2.67	7.05±1.93
Extended Family(2)	35.50±4.25	11.60±2.55	6.30±1.77	12.10±2.28	5.50±0.85
Divorced(3)	42.80±7.66	16.20±8.04	5.00±1.87	15.60±4.04	6.00±3.32
Test / P	F=3.722/0.027*	F=3.777/0.025*	F=3.857/0.023*	F=3.587/0.030*	F=3.531/0.032
Difference	3>1	3>1.3>2	1>3	3>1.3>2	* 1>2
Mother Education Level					
Primary School(1)	38.81±5.17	12.46±2.62	6.86±1.70	12.40±2.53	7.10±1.98
High School(2)	39.77±5.22	13.65±4.22	6.65±1.79	12.92±3.14	6.54±2.00
University(3)	38.82±6.23	14.18±4.24	7.00±1.55	11.73±3.74	5.91±1.45
Test / P	F=0.348 / 0.706	F=2.673 / 0.073	F=0.209 / 0.811	F=0.781 / 0.461	F=2.398 / .095
Difference	-	-	-	-	-
Father Education Level					
Primary School(1)	38.49±5.24	12.54±2.46	6.97±1.74	12.08±2.80	6.90±2.04
High School(2)	39.83±5.79	13.29±4.01	6.63±1.86	12.94±2.77	6.98±2.10
University(3)	38.66±4.15	12.62±2.86	6.90±1.29	12.38±2.57	6.76±1.62
Test / P	F=0.956 / 0.387	F=0.831 / 0.438	F=0.567 / 0.568	F=1.316 / 0.272	F=0.112/0.894
Difference	-	-	-	-	-
Smoking Status					
Yes	38.00±5.93	11.17±3.30	6.57±2.09	13.00±2.56	7.26±1.66
No	39.19±5.10	13.15±3.03	6.89±1.62	12.33±2.78	6.83±2.02
Test / P	t= -0.995 / 0.321	t= -2.808 / 0.006*	t= -0.828 / 0.409	t= 1.066 / 0.288	t= 0.967 / 0.335
Financial Level					
Income More Than Expenses(1)	36.45±4.38	11.68±1.91	6.73±1.35	12.00±2.67	6.05±1.40
Income Equals Expenses(2)	39.66±5.28	13.14±3.39	6.86±1.83	12.68±2.80	6.98±1.96
Income Less Than Expenses(3)	38.41±5.22	12.41±2.72	6.82±1.33	11.65±2.47	7.53±2.35
Test / P	F= 3.613/0.030*	F= 2.124 /0.124	F= 0.053/ 0.948	F= 1.362 /0.261	F=3.118/0.047
Difference	1<2	-	-	-	* 1<3
Health Level					
Good(1)	38.94±5.94	12.87±3.45	6.94±2.00	12.34±3.08	6.79±2.10
Average(2)	38.89±4.60	12.78±2.95	6.69±1.37	12.58±2.48	6.84±1.64
Poor(3)	44.50±2.12	12.50±0.71	9.00±1.41	10.50±0.71	12.50±0.71
Test / P	F= 1.124 /0.328	F= 0.023 /0.977	F= 2.037 /0.134	F= 0.634 /0.532	F= 9.218 /0.001*
Difference	-	-	-	-	3>1.3>2

Table 3. Comparison of the students' descriptive characteristics and HPS and sub-dimension score averages (n=138) (continue)

	HPS Mean±SD	CCM Mean±SD	SAF Mean±SD	CES Mean±SD	SGÖ Mean±SD
Place of Residence					
State Dormitory(1)	39.15±6.35	14.70±4.92	6.20±1.91	12.05±3.94	6.20±2.21
Private Dormitory(2)	38.33±6.56	12.83±4.22	5.83±0.75	13.67±3.39	6.00±1.79
House with Friends(3)	39.42±3.50	12.42±1.88	6.33±0.49	14.33±1.97	6.33±1.50
Family(4)	38.95±5.16	12.49±2.64	7.08±1.73	12.22±2.42	7.16±1.94
Test / P Difference	F= 0.065/ 0.978 -	F= 2.917/ 0.037* 1>4	F= .774/0.044* 1<4	F= .742/0.046* 1<3	F= 2.234/ 0.087 -
Chronic Disease Status					
Yes	39.54±4.58	12.85±3.36	7.00±1.83	12.08±2.02	7.62±1.89
No	38.94±5.32	12.82±3.15	6.82±1.69	12.48±2.82	6.82±1.97
Test / P	t= 0.393 / 0.695	t= 0.033 / 0.974	t= 0.371 / 0.712	t= -0.502 / 0.617	t= 1.385 / 0.168
Medication Status					
Yes	39.71±4.60	13.07±3.20	7.00±1.75	12.43±2.10	7.21±1.58
No	38.91±5.32	12.79±3.16	6.81±1.70	12.44±2.82	6.86±2.01
Test / P	t= 0.542 / 0.589	t= 0.315 / 0.753	t= 0.386 / 0.701	t= -0.019 / 0.985	t= 0.632 / 0.529
Family Health Status					
Chronic Patient(1)	41.14±4.55	13.47±3.95	7.31±1.72	13.31±2.59	7.06±2.24
Hospitalization(2)	36.89±5.71	11.74±3.96	6.42±1.50	12.11±3.07	6.63±1.86
Chronic Disease and Hospitalization(3)	38.56±4.23	12.30±2.49	6.48±1.31	12.52±2.06	7.26±2.23
No Disease(4)	38.54±5.59	13.02±2.44	6.84±1.87	11.96±2.95	6.71±1.68
Test / P Difference	F= 3.404 / 0.020* 1>2	F= 1.603 / 0.192 -	F= 1.714 / 0.167 -	F= 1.884 / 0.135 -	F= 0.654 / 0.582 -

*P<0.05, F=ANOVA test, Difference=Tukey test, t=independent samples t test.

When the health perception scale sub-dimensions were examined, it was observed that the CES sub-dimension mean score (12.44±2.75) was at a moderate level and similar studies (Çilingir and Aydın, 2017; Deleş and Kaytez, 2020; Demir et al., 2021) supported the literature. When the obtained result is examined based on the definition of certainty, it shows that students have a moderately certain idea about what they need to do to stay healthy and be healthier.

It was determined that the CCM sub-dimension mean score (12.82±3.15) was weak, and the study by Özsoy and Şentürk (2021) supports the obtained result. According to this result, it is seen that the students participating in the study attribute being healthy to factors outside of themselves (luck, fate, religious belief, etc.) and have low self-confidence in changing their health. From this perspective, it is thought that students are inadequate in taking responsibility for their health and paying attention to positive behaviors related to health.

The mean score of the SAF sub-dimension (6.83±1.70) was found to be at a weak level, similar to some literature (Lee and Loke, 2005; Nacar et al., 2014). This result shows that the students' self-awareness perceptions regarding exercise and proper nutrition related to being healthy and their beliefs about whether being healthy is in their own hands are weak.

The mean score of the SGÖ sub-dimension (6.90±1.97) was found to be at a weak level and some similar literatures on this subject (Alkan Ağaçdiken et al., 2017; Çilingir and Aydın, 2017) support the obtained result. This situation reveals the view that the students do not attach much importance to health, do not make financial sacrifices for their health and that the importance they give to health is not a priority in their lives.

The weak perception mostly seen in HPS and its sub-dimensions (CCM, SAF, CES and SGÖ) suggests that students who encounter disease information intensively for the first time in the 2nd grade do not fully acquire positive health perception, or even if they do, they cannot implement it, or this situation may be related to factors outside of education.

Students with divorced family types had higher CCM and CES scores than other family types, and students living in nuclear families had higher SAF and SGÖ scores than other family types (P<0.05). No literature was found

directly related to sub-dimension scores, but Şimşek et al. (2012)'s study is similar in terms of general health perception. The obtained result can be explained by the fact that students are significantly affected by family structure and dynamics, and parents' attitudes and behaviors regarding health have a direct effect on children.

It was determined that the CCM scores of the non-smokers were significantly higher than the smokers (P<0.05), and similar literature (Lee, 2019; Solak, 2022) supports the result obtained. This suggests that the students are aware of the health hazards of smoking and that this awareness positively affects the control center sub-dimension score.

When the financial status of the students is examined, the scores of those whose income is higher than their expenses are found to be lower than those whose income is lower than their expenses in terms of SGÖ; and the scores of those whose income is higher than their expenses are found to be lower than those whose income is equal to their expenses in terms of HPS (P<0.05). Most of the literature that affects the financial status of the students and their health perceptions and general health behaviors (Özbaşaran et al., 2004; Cihangiroğlu and Deveci, 2011; Çilingir and Aydın, 2017) shows the opposite of the study result. Financial status is one of the important factors that affect individuals' access to health services, eating habits and stress levels, and therefore their health perceptions. The obtained result can be explained by the fact that the financial status perceptions of the students are lower than expected and that their socioeconomic status may limit their access to factors that improve their health perception (access to health services, healthy nutrition, gym membership, etc.).

The scores of the students who perceived their health level as poor were found to be higher in terms of SGÖ than those who perceived their health level as good and moderate (P<0.05). Similar literature (Sentell et al., 2013; Çilingir and Aydın, 2017; Doğan and Çetinkaya, 2019; Kerkez and Şahin, 2023) indicates that the total mean scores of the health perception scale of the students who perceived their health as good were found to be low. The findings suggest that students who evaluated their health status as poor may become more conscious of issues such as increased awareness of health problems, personal experiences, motivation and health literacy, and give more importance to health-related issues.

It was determined that the CCM, CES and SAF sub-dimensions showed significant differences according to the place of residence (P<0.05). In terms of place of residence, students staying in state dormitories had higher CCM scores than those staying with their families, while those staying in state dormitories had lower scores than those staying with their friends in terms of CES, and those staying in state dormitories had lower scores than those staying with their families in terms of SAF (P<0.05). Various studies conducted on the subject show different findings regarding the place of residence not having an effect on HPS (Lee, 2019; Dündar Kurt, 2019) and having an effect (Ünalan et al., 2007; Tuğut and Bekar, 2008; Şimşek et al., 2012). Based on this situation, the obtained result can be interpreted as students living in clean, safe and well-equipped environments perceive their health more positively, while students living in crowded and unhygienic environments may negatively affect their health perceptions.

The HPS scores of students with a family history of chronic disease were found to be higher than those of students with a family history of hospitalization (P<0.05). When the literature was examined, no study was found explaining the relationship between chronic diseases, hospitalization history and health perception in family members. The obtained result can be explained by the fact that family members with chronic diseases regularly apply to health services and closely follow the treatment processes, and this long-term observation may have helped students better understand the importance of health services and increase their health perception more than students with only a family history of hospitalization.

5. Conclusion

It was determined that the students' average score on SAS was at a medium level close to weak. When the HPS sub-dimensions were examined; the CCM sub-scale average score was weak, the CES sub-scale average score was medium, the SGÖ sub-scale average score was weak, the SAF sub-scale average score was weak and it was seen that the average scores were not at the desired level. While there was a significant difference between the students' family type, smoking, financial level, health level, place of residence and family health status and health perception and sub-groups (P<0.05), it was determined that there was no statistically significant difference between age, gender, parental education level, chronic disease and regular medication use (P>0.05).

In line with these results:

- It is recommended that assessments be made during vocational training to reveal students' attitudes not only on the health of the patients they care for but also on their own health, that responsibilities be given to develop these attitudes positively and that they be supported to transform them into behavior,
- In order for students to make the right decisions about their own health and create a control mechanism, the curriculum should be supported with the necessary training in this field, that comprehensive information be provided on the importance and sustainability of health, and that cross-sectional studies be conducted to determine the effect of the basic training to be given on students' health perceptions,
- It is recommended that the findings regarding the students' poor perception of health in general

should be emphasized in the curriculum, especially in courses with a lot of lecture hours, such as Internal and Surgical Diseases Nursing, which is taught in the second year of the education period, and that the objectives related to this subject in the curriculum should be evaluated.

Limitation of the Study

The limitation of the study is that the study was conducted only with students who completed their 2nd year education at the Nursing Department of the Faculty of Health Sciences at Afyonkarahisar Health Sciences University and that there was no similar group studying in a department not related to health. Therefore, the results of the study do not reflect the general results.

Author Contributions

The percentage of the author contributions is presented below. The author reviewed and approved the final version of the manuscript.

	Y.Ç.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100
PM	100

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management.

Conflict of Interest

The author declared that there is no conflict of interest.

Ethical Approval/Informed Consent

Participants were informed that participation in the study was voluntary, and verbal and written permissions were obtained from the participants and from the institution. Permission was obtained from the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Approval date: March 03, 2023, protocol code: 2023/3) for the conduct of the study.

Acknowledgments

The author would like to thank the students and faculty administrators who contributed to the realization of this study.

References

Alkan Ağaçdiken S, Özdelikara A, Boğa NM. 2017. Hemşirelik öğrencilerinin sağlık algılarının belirlenmesi. Gümüşhane Üniv Sağlık Bil Derg, 6(2): 11-21.

Aristizabal Castano I, San Martin Rodriguez L. 1998. Health habits of health professionals. Rev Enferm, 21(237): 15-18.

Bıçakcı HS. 2022. Bir Üniversite hastanesi sağlık personelinin Covid 19 pandemi sürecinde sağlık algısı ve beslenme alışkanlıklarının değerlendirilmesi. Uzmanlık Tezi, Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi Aile Hekimliği Anabilim Dalı, Konya, Türkiye, pp: 78.

Can G, Ozdilli K, Erol O, Unsar S, Tulek Z, Savaser S, Ozcan S, Durna Z. 2008. Comparison of the health-promoting lifestyles of nursing and non-nursing students in Istanbul, Turkey. Nurs Health Sci, 10(4): 273-280. https://doi.org/10.1111/j.1442-2018.2008.00405.x

Çelik Y, Soyer Er Ö. 2022. Sağlık bilimleri alanları hemşirelik mesleğini nasıl algılıyor? Selçuk Sağlık Derg, 3(2): 117-128.

Cihangiroğlu Z, Deveci SE. 2011. Healthy life style behaviours and related influencing factors of the students of Elazig High School of Health Sciences of Firat University. Firat Medic J, 16(2): 78-83.

Çilingir D, Aydın A. 2017. Hemşirelik bölümünde öğrenim gören öğrencilerin sağlık algısı. Florence Nightingale Hemş Derg, 25(3): 167-176. https://doi.org/10.17672/fnjn.343254

Deleş B, Kaytez N. 2020. Çocuk Gelişimi lisans öğrencilerinin stres düzeylerinin sağlık algısı üzerine etkisinin incelenmesi. Gümüşhane Üniv Sağlık Bil Derg, 9(4): 365-373.

Demir G, Özen B, Savaş M. 2021. Hemşirelik birinci sınıf öğrencilerinde sağlık algısı. Sağlık Bil Derg, 30(3): 295-300.

Diamond JJ, Becker JA, Arenson CA, Chambers CV, Rosenthal MP. 2007. Development of a scale to measure adults' perceptions of health: Preliminary findings. J Community Psychol, 35(5): 557-561.

Dilek Ç, Aydanur A. 2017. Hemşirelik bölümünde öğrenim gören öğrencilerin sağlık algısı. Florence Nightingale Hemş Derg, 25(3): 167-176.

Doğan M, Çetinkaya F. 2019. The level of health literacy of academicians and factors affecting it. Hacettepe J Health Administ, 22(2): 389-400.

Doğu Ö, Atasoy I. 2017. Hemşirelik lisans öğrencilerinde sağlık algısına cinsiyet ve diğer faktörlerin etkisi. J Nursing Sci, 9(2):107-113

Dündar Kurt G. 2019. Çıraklık eğitimi gören adölesanların sağlık algısı ve stresle başa çıkma tarzları. Yüksek Lisans Tezi, Marmara Üniversitesi, Sağlık Bilimleri Enstitüsü, İstanbul, Türkiye, pp: 87.

Genç S, Soysal Mİ. 2018. Parametric and nonparametric post hoc tests. BSJ Eng Sci, 1(1): 18-27.

Hür SD, Andsoy II, Şahin AO, Kayhan M, Eren S, Zünbül N, İnanmaz N. 2014. Karabük üniversitesi sağlık yüksekokulu öğrencilerinde depresif belirtiler. J Psychiat Nurs, 5(2): 72-6.

Kadıoğlu H, Yıldız A. 2012. Sağlık algısı ölçeğinin Türkçe çevriminin geçerlilik ve güvenilirliği. Türkiye Klin J Med Sci, 32: 47-53.

Kalaycı S. 2008. SPSS uygulamalı çok degiskenli istatistik teknikleri. Asil Yayın Dağıtım Ltd. Sti, 3rd. ed., Ankara, Türkiye, ss: 120.

Kerkez N, Şahin T. 2023. A study on investigation of the relationship between health literacy and health perception. BAUN Health Sci J, 12(2): 336-346. https://doi.org/10.53424/balikesirsbd.1177899

Lee CM. 2019. The influence of perceptions of the campus environment and health perception on stress of nursing college students. J Digital Converg, 17(2): 329-338.

Lee RLT, Loke AJTY. 2005. Health-promoting behaviors and psychosocial well-being of university students in Hong Kong. Pub Health Nurs, 22(3): 209-220.

Nacar M, Baykan Z, Cetinkaya F, Arslantas D, Ozer A, Coskun O,

Bati H, Karaoglu N, Elmali F, Yilmaze G. 2014. Health promoting lifestyle behaviour in medical students: a multicentre study from Turkey. Asian Pac J Cancer Prev, 15(20): 8969-8974. https://doi.org/10.7314/apjcp.2014.15.20.8969

Özbaşaran F, Çetinkaya A, Güngör N. 2004. Celal Bayar Üniversitesi Sağlık Yüksekokulu öğrencilerinin sağlık davranışları. Atatürk Üniv Hemş Yüksekokulu Derg, 7(3): 43-55.

Ozdelikara A, Agacdiken-Alkan S, Mumcu N. 2018. Determination of health perception, health anxiety and effecting factors among nursing students. Bakırköy Tıp Derg, 14: 275-282. https://doi.org/10.5350/BTDMJB.20170310015347

Özsoy H, Şentürk S. 2021. Sağlık Hizmetleri Meslek Yüksekokulu öğrencilerinin sağlık algısı ve sağlıklı yaşam biçimi davranışlarının belirlenmesi. İnönü Üniv Sağlık Hiz Meslek Yüksekokulu Derg, 9(3): 896-913. https://doi.org/10.33715/inonusaglik.818550

Sentell T, Zhang W, Davis J, Kromer Baker K, Braun KL. 2013. The influence of community and individual health literacy on self-reported health status. J Gen Intern Med, 29(2): 298-304. https://doi.org/10.1007/s11606- 013-2638-3

Shaw SJ, Armin J, Torres CH, Orzech KM, Vivian J. 2012. Chronic disease selfmanagement and health literacy in four ethnic groups. J Health Commun, 3(03): 67-81. https://doi.org/10.1080/10810730.2012.712623

Şimşek H, Öztoprak D, İkizoğlu E, Safalı F, Yavuz Ö, Onur Ö, Tekel Ş, Çiftçi Ş. 2012. Tıp Fakültesi öğrencilerinde sağlıklı yaşam biçimi davranışları ve ilişkili etmenler. J DEU Med, 26(3): 151-157.

Solak, B. 2022. Necmettin Erbakan Üniversitesi İlahiyat Fakültesi ile Meram Tıp Fakültesi öğrencilerinin sağlık algısı, ölüme karşı tutum ve ölüm anksiyetesi düzeyleri. Uzmanlık Tezi, Necmettin Erbakan Üniversitesi, Meram Tıp Fakültesi, Aile Hekimliği Anabilim Dalı, Konya, Türkiye, pp: 120.

Tuğut N, Bekar M. 2008. Üniversite öğrencilerinin sağlığı algılama durumları ile sağlıklı yaşam biçimi davranışları arasındaki ilişki. Atatürk Üniv Hemş Yüksekokulu Derg, 11: 17-26.

Ünalan D, Şenol V, Öztürk A, Erkorkmaz Ü. 2007. Meslek Yüksekokullarının sağlık ve sosyal programlarında öğrenim gören öğrencilerin sağlıklı yaşam biçimi davranışları ve öz-bakım gücü düzeyleri arasındaki ilişkinin incelenmesi, İnönü Üniv Tıp Fak Derg, 14: 101-109.

Whitehead D. 2005. Health promoting hospitals: The role and function of nursing. J Clin Nurs, 14(1): 20-27.

Zaybak A, Fadıloğlu Ç. 2004. Üniversite öğrencilerinin sağlığı geliştirme davranışı ve bu davranışı etkileyen etmenlerin belirlenmesi. Ege Üniv Hemş Yüksek Okulu Derg, 20: 77-95.

Black Sea Journal of Health Science

doi: 10.19127/bshealthscience.1533161

Open Access Journal
e-ISSN: 2619 – 9041

Araştırma Makalesi (Research Article)
Cilt 7 - Sayı 6: 240-247 / Kasım 2024
(Volume 7 - Issue 6: 240-247 / November 2024)

PRON POZİSYONDA OMURGA CERRAHİSİ UYGULANAN HASTALARDA POZİSYON DEĞİŞİMİ SONRASI GELİŞEN HİPOTANSİYON İÇİN ÖNGÖRÜLEN FAKTÖRLERİN ARAŞTIRILMASI

Selim Can YIRTIMCI[1], Şeyda Efsun ÖZGÜNAY[1]*, Mehmet GAMLI[1]

[1]University of Health Sciences, Yüksek İhtisas Training and Research Hospital, Department of Anesthesiology and Reanimation, Bursa, Türkiye

Özet: Omurga cerrahisi geçiren hastalarda, supin pozisyondan pron pozisyona döndükten sonra hipotansiyon gelişebilmektedir. İntraoperatif hipotansiyonun kısa süreli olsa bile postoperatif ciddi komplikasyonlarla ilişkili olabilir. Amacımız bu hasta grubunda pozisyon değişikliği ile ilişkili hipotansiyon gelişimindeki risk faktörlerini ortaya koymaktır. Prospektif, gözlemsel çalışmamıza 18 yaş üstü, genel anestezi altında pron pozisyonda omurga cerrahisi geçirecek, 103 hasta dahil edildi. Hastaların perioperatif rutin monitörizasyon ve arteriyel kanülasyonundan sonra PPV monitörizasyonu uygulandı. Pron pozisyona döndükten sonra OAB 55 mmHg'nin altında olan veya preoperatif ölçülen OAB'ye göre yüzde 20'den fazla düşen hastalar hipotansif grup (Grup H, 50 hasta), geri kalan hastalar normotansif grup (Grup N, 53 hasta) olmak üzere iki gruba ayrıldı. Grupların demografik verileri, komorbidite sıklıkları, kullandığı antihipertansif ilaçlar, perioperatif PPV değerleri, ejeksiyon fraksiyon oranları, akciğer kompliyansları ve hava yolu basınç değerleri karşılaştırıldı. Grup H'de komorbidite varlığı, hipertansiyon olması, beta-blokör kullanılması, indüksiyon öncesi PPV değerinin yüksek olması istatistiksel anlamlı olarak daha yüksek bulundu. Ayrıca Grup H'de yaş ortalaması daha yüksek, sigara kullanım oranı daha düşüktü. Ejeksiyon fraksiyon oranı Grup H'de anlamlı olarak daha düşük saptandı. Akciğer kompliyansı, tepe inspirasyon basıncı, plato basıncı, akciğer sürücü basıncı arasında iki grup arasında fark tespit edilmedi. Hemoglobin değerleri, laktat seviyeleri, bazal GFR düzeyleri bakımından anlamlı farklılık saptanmadı. Genel anestezi indüksiyonuna bağlı gelişen hipotansiyondan bağımsız olarak, pron pozisyona dönecek olan vertebral cerrahi geçiren hastalarda PPV değerinin yüksek olması, hipertansiyon tanısının olması, beta-blokör kullanımı pozisyon değişikliği sonrası hipotansiyon gelişmesinin sebepleri arasında sayılabilir.

Anahtar kelimeler: Hipotansiyon, Pron pozisyon, Vertebral cerrahi, PPV

Investigation of the Factors Predicted for Hypotension Developing After Position Change in Patients Which Was Performed in the Prone Position

Abstract: Hypotension may develop after returning from the supine position to the prone position in patients undergoing spine surgery. Intraoperative hypotension has been shown to be associated with serious complications. Our aim is to reveal the risk factors in the development of hypotension associated with position change in this patient group. 103 patients over the age of 18 who will undergo spinal surgery in the prone position under general anesthesia were included in our prospective, observational study. The detailed medical history of the patients and the drugs they used were recorded. PPV monitoring was applied to the patients who were taken to the operating room. After returning to the prone position, patients with MAP below 55 mmHg on arterial monitoring or with a blood pressure reduction of more than 20 percent according to preoperatively measured MAP were in the hypotensive group (Group H, 50 patients), the remaining patients were in the normotensive group (Group N, 53 patients) were divided into two groups. Demographic data, comorbidity frequencies, antihypertensive used, perioperative PPV values, ejection fraction rates, lung compliance and airway pressure values were compared between the two groups. The rate of comorbidity, diagnosis of hypertension, beta-blocker drug class, and high pre-induction PPV value were found to be statistically significantly higher in Group H. In addition, the mean age was higher and the rate of smoking was lower in Group H. No significant difference was detected in other demographic data. Ejection-fraction ratio was found to be significantly lower in Group H. There was no difference between the two groups in terms of lung compliance, peak inspiratory pressure, plateau pressure, and lung driving pressure. High PPV value, diagnosis of hypertension, use of beta-blocker can be counted among the reasons for the development of hypotension after repositioning in patients undergoing vertebral surgery that will return to the prone position.

Keywords: Hypotension, Prone position, Vertebral surgery, PPV

***Sorumlu yazar (Corresponding author):** University of Health Sciences, Yüksek İhtisas Training and Research Hospital, Department of Anesthesiology and Reanimation, Bursa, Türkiye
E mail: seyda-efsun@hotmail.com (Ş. E. ÖZGÜNAY)

Selim Can Yırtımcı https://orcid.org/0000-0001-8417-0178
Şeyda Efsun ÖZGÜNAY https://orcid.org/0000-0003-1501-9292
Mehmet GAMLI https://orcid.org/0000-0002-5618-2734

Gönderi: 14 Ağustos 2024 **Received:** August 14, 2024
Kabul: 17 Ekim 20234 **Accepted:** October 17, 2024
Yayınlanma: 15 Kasım 2024 **Published:** November 15, 2024

Cite as: Yırtımcı SC, Özgünay ŞE, Gamlı M. 2024. Investigation of the factors predicted for hypotension developing after position change in patients which was performed in the prone position. BSJ Health Sci, 7(6): 240-247.

1. Giriş

Ameliyat sırasında pozisyonlar kardiyovasküler ve pulmoner değişikliklere neden olabilir. Nöroaksiyel anestezi, kardiyovasküler stabiliteyi koruyan normal kompansatuar mekanizmaları etkiler ve hipoksemi ile sonuçlanabilecek değişikliklere neden olabilir. Hipotansiyon intraoperatif tedavi gerektiren en yaygın hemodinamik bozukluktur (Abbott ve ark., 2018).

Omurga ve omurilik üzerindeki cerrahi prosedürler minimal invaziv, tek seviyeli dekompresyondan; birden çok seviyeli, kapsamlı rekonstrüksiyona kadar komplike vakalar olabilir. 60 yaş altı hastalar en sık dejeneratif omurga hastalığı ve lomber disk hernisi nedeniyle operasyona alınırken, 60 yaşın üzerindeki hastalar spinal dar kanal amacıyla opere edilir (Deyo ve ark., 2010). Anestezi uygulanmış hastalarda pozisyon değişikliğinin neden olduğu hipotansiyon, baroreseptör refleks ve sempatik aktivasyon mekanizmaları bloke olabilir. Omurga cerrahisinde supin pozisyondan pron pozisyona dönen hastalarda kardiyovasküler fizyolojiyi etkileyebilir, intratorasik ve intraabdominal basınç artışı sonrası venöz dönüş azalarak sistemik arteriyel hipotansiyon gelişebilmektedir (Abcejo ve ark., 2017), kalbe venöz dönüş azalır, sol ventrikül kompliyansı azalır ve sonuç olarak kardiyak indeks azalır (Sudheer ve ark., 2006). Son çalışmalar, intraoperatif hipotansiyonun postoperatif istenmeyen klinik sonuçlarla ilişkili olduğunu göstermiştir (Monk ve ark., 2015; Salmasi ve ark., 2017). Özellikle omurga cerrahisi sırasında yüzüstü pozisyonda, intraoperatif hipotansiyon, omurilik iskemisi ve ameliyat sonrası görme kaybı gibi ciddi komplikasyonlara neden olabilir (Kalb ve ark., 2014). Günümüzde 5 dakika süreli intraoperatif hipotansiyonun bile kardiyovasküler ve serebrovasküler istenmeyen etkileri arttırdığı bilinmektedir (Gregory ve ark., 2021).

Dinamik parametreler, beklenen yüksek kan kaybı olan prosedürler için majör invaziv cerrahi geçirecek hastalarda sıvı yanıtını değerlendirmek ve hedefe yönelik sıvı tedavisini yönlendirmek için kullanılan yöntemlerdir (Miller ve Myles, 2019). Bu yöntemlerden biri olan nabız basıncı değişimi (PPV), sistolik kan basıncı (SKB), diastolik kan basıncı (DKB) arasındaki fark olarak tanımlanabilir. PPV ön-yük rezervinin dinamik bir belirtecidir. Genel anestezide mekanik ventilasyonun gibi durumlarda atım hacminde (SV) ve sağ ventrikül dolumunda %20-70 oranında bir azalmaya yol açabilir (Malbouisson ve ark., 2017). Yapılan pek çok çalışma nabız basınç değişimine dayalı dinamik bir parametre olan PPV'nin intraoperatif sıvı yanıtının öngörülmesinde kullanımının son derece değerli olduğunu ortaya koymuştur (Doherty ve Buggy, 2012; Thiele ve ark., 2015).

Klinik uygulamada, anestezi uygulanmış hastalarda supin pozisyondan prone pozisyona geçişte oluşan hipotansiyon ile ilişkili öngörücü faktörlerin belirlenmesi, prone pozisyon gerektiren hastalarda hemodinamik stabilitenin korunmasına yardımcı olabilir. Bu çalışmanın amacı, omurga cerrahisi geçiren hastalarda sırtüstü pozisyondan yüzüstü pozisyona geçiş değişikliği ile ilişkili hipotansiyon gelişme insidansını araştırmak ve risk faktörlerini ortaya koymaktır.

2. Materyal ve Yöntem

Yerel etik kurul onayı (2011-KAEK-25 2020/10-06) ve bilgilendirilmiş onam alınarak, Üçüncü Basamak Eğitim ve Araştırma Hastanesi Anesteziyoloji ve Reanimasyon Kliniği'nde prospektif, kesitsel, gözlemsel olarak 01.11.2020 – 01.07.2021 tarihleri arasında yapıldı. Pron pozisyonda vertebral cerrahi yapılacak, 18 yaşından büyük hastalar çalışmaya dahil edildi. Genel anestezi uygulanmayan, rejyonel anestezi veya sedasyon yöntemi ile opere edilen hastalar, operasyon öncesinde vazopresör, inotrop ajan infüzyonu alan hastalar çalışmaya dahil edilmedi.

2.1. Tasarım

Çalışmaya dahil edilen tüm hastalarda, anestezi poliklinik başvurularında komorbiditeleri, kullanılan ilaçlar, sigara kullanımı öyküsü sorgulanarak kayıt altına alındı. Preoperatif kardiyoloji konsültasyonu istenen hastaların ejeksiyon fraksiyonu (EF) değerleri kayıt altına alındı. Ameliyathaneye alınan hastalara izotonik mayi başlandı. Hastalara rutin olarak elektrokardiyografi (EKG), Periferal Oksijen Satürasyonu (SpO_2), noninvaziv kan basıncı (NİKB), Surgical Pleth Indeks (SPI) monitörizasyonu uygulandı ve kayıt altına alındı. 3 dk % 100 oksijen ile preoksijenizasyon sonrası, hastalara sırasıyla 1 mg/kg lidokain (Lidon® %2, Onfarma ilaç, İstanbul, Türkiye), 1-2 mcg/kg fentanil (Talinat®, Vem, İstanbul, Türkiye) ve 2-3 mg/kg propofol (Propofol 2% Fresenius®, Fresenius Kabi, Bad Hamburg, Almanya), 0,6 mg/kg roküronyum bromür (Curon®, Mustafa Nevzat, İstanbul, Türkiye) İV yoldan uygulandıktan sonra endotrakeal entübasyon (EE) uygulandı. Ardından 20 G İV kateter uygulanarak arteriyel monitörizasyon ve PPV monitörizasyonu uygulandı. Tidal volüm hastanın ideal ağırlığına göre 6-8 ml/kg, solunum sayısı 12/dk, PEEP (Positive End Expiratory Pressure) 5 cmH_2O olacak şekilde hacim garantili basınç kontrollü modda (PCV-VG) ventilasyon GE Avance CS^2 (GE Healthcare P.O, Helsinki, Finland) marka cihaz ile uygulandı. Devamında %50 hava %50 O_2 karırımı ile minimum alveolar konsantrasyon 1 olacak şekilde Sevofluran (Sevorane Likit %100, AbbVie, Queenborough Kent, (İngiltere), 2 lt/dk idame anestezi uygulandı.

Entübasyon sonrası endotrakeal tüp anestezi cihazından ayrılmadan hasta pron pozisyona alındı. Pron pozisyona döndükten sonra arteriyel monitörizasyonda ortalama kan basıncı (OKB) 55 mmHg'nin altında olan ve/veya preoperatif ölçülen OKB'ye göre kan basıncı yüzde 20'den fazla düşen hastalar hipotansif grup (Grup H, 50 hasta), diğer hastalar normotansif grup (Grup N, 53 hasta) olmak üzere iki gruba ayrıldı. Hastaların yaş, boy, kilo, ideal vücut ağırlığı (İVA), beden kitle indeksi (BKİ), ASA (American Society of Anesthesiologists) sınıfı, İV verilen sıvı ve anestezi süreleri kaydedildi. Hastaların ameliyat öncesi ve ameliyat esnasında belirlenen zaman

aralıklarında (T0: Ameliyathane odasına alındığında, indüksiyon öncesi, T1: İndüksiyon sonrası 5. dk, T2: Pron pozisyona alındıktan sonra, T3: İndüksiyon sonrası 30. dk, T4: İndüksiyon sonrası 60. Dk, T5: İndüksiyon sonrası 120. dk, T6: Ekstübasyon sonrası) KAH, SKB, DKB, OKB, SpO_2, $EtCO_2$, PEEP, hava yolu tepe basıncı (PEAK), sürücü basınç (Driving Pressure), Minimum alveoler konsantrasyon (MAC), FiO_2, PPV değerleri kaydedildi.

2.2. Veri Analizi

İstatistiksel analizler JASP 0.16.3.0 yazılımında yapılmıştır. Çalışmada yer alan nicel değişkenlere ait tanımlayıcı istatistikler ortalama, standart sapma (SS), medyan, minimum ve maksimum değerleriyle; nitel değişkenler frekans ve yüzde ile gösterilmiştir. Nicel değişkenlerin normal dağılıma uygunluğu Shapiro Wilk testi ile incelenmiştir. Normal dağılım gösteren nicel değişkenlerin bağımsız iki grup karşılaştırmalarında bağımsız örneklem t testi, normal dağılım göstermeyen nicel değişkenlerin bağımsız grup karşılaştırmalarında Mann Whitney U testi kullanılmıştır. Nitel değişkenlerin gruplar arası karşılaştırmalarında Pearson ki-kare, Yates ki-kare ve Fisher ki-kare testleri kullanılmıştır. İstatistiksel analizlerde önem düzeyi (P) değeri 0,05'in altındaki sonuçlar istatistiksel olarak anlamlı kabul edilmiştir (Önder, 2018).

3. Bulgular

Pron pozisyonda vertebral cerrahi geçiren 120 hasta çalışmaya dahil edildi, PPV kalitesini bozacak aritmi gelişen 2 hasta, vazopresör ajan infüzyon gereken 3 hasta, pron pozisyona döndükten sonra arteriyel monitörizasyon kalitesi bozulan, manşon ile tansiyon takibi yapılması zorunda kalınan 12 hasta olmak üzere toplam 17 hasta çalışmadan çıkarıldı. Toplam 103 hasta istatistiksel analize alındı.

Hastaların demografik verileri Tablo 1'de belirtilmiştir. Yaş ortalaması Grup H'de istatistiksel anlamlı olarak daha yüksekti (P=0,001). Gruplar arasında sigara kullanımı oranı Grup N'de %45,3 iken bu oran Grup H'de %24,0 istatistiksel olarak anlamlı yüksek bulundu (P=0,040). Grup H'de (% 80,0) komorbidite oranı (% 41,5) Grup N'ye göre anlamlı olarak daha yüksekti (P<0,001). Gruplar arası İVA, BMI, ASA sınıflaması, açlık süresi, vertebral cerrahi alanları ve endikasyonlar incelendiğinde gruplar arasında istatistiksel olarak anlamlı fark yoktu (Tablo 1). Preoperatif hemoglobin, EF oranı, intraoperatif verilen toplam sıvı miktarı, idrar çıkışı, hastaların vaka boyunca kanama miktarı Tablo 1'de gösterilmiştir. Gruplar arasında vakada verilen toplam İV sıvı miktarı Grup H'de Grup N'ye göre istatistiksel olarak anlamlı yüksek bulundu (P<0,001). Ayrıca Grup H'de EF istatistiksel anlamlı olarak daha düşük idi (P=0,025) (Tablo 1).

Tablo 1. Demografik veriler

	Grup N	Grup H	P
Yaş (yıl), [Median (Min-Maks)]	46 (13 - 77)	60,5(18-81)	0,001**
Cinsiyet, [n (%)] Erkek	25 (47,2)	26 (52,0)	0,624
Kadın	28 (52,8)	24 (48,0)	
Sigara içen, [n (%)]	24 (45,3)	12 (24,0)	0,040*
Komorbidite varlığı, [n (%)]	22 (41,5)	40 (80,0)	<0,001*
İVA (kg), [Median (Min-Maks)]	60 (40 - 85)	60 (43-80)	0,743
BMI (kg/m^2), Median (Min-Maks)	27,78 (17,7–50,7)	28,4(17,6–40,4)	0,621
ASA Sınıflandırması, [n(%)]			
I	12 (22,6)	5 (10,2)	0,189
II	35 (66)	35 (71,4)	
II	6 (11,3)	9 (18,4)	
Açlık Süresi (saat), [Median(Min-Maks)]	10,00 (8 - 20)	10,50 (8 - 20)	0,786
Operasyon Alanı, [n(%)]			
Servikal	4 (7,5)	0 (0)	0,118
Torakal	4 (7,5)	9 (18)	0,194
Lomber	45 (84,9)	41 (82)	0,895
Tanılar, [n(%)]			
Tümöral	5 (9,4)	5 (10)	1,000
Travmatik	6 (11,3)	5 (10)	1,000
Dejeneratif	34 (64,2)	27 (54)	0,397
Revizyon	8 (15,1)	12 (24)	0,372
Preop Hgb (g/dL) [Median (Min-Maks)]	11,6 (7,5–14,6)	11,6 (9,1–16,4)	0,807
EF % [Median (Min-Maks)]	60 (55-60)	50 (40-60)	0,025**
Vakada verilen toplanan sıvı (mL) [Median (Min-Maks)]	2000 (1000-5500)	2550 (1000-7000)	<0,001**

İVA= ideal vücut ağırlığı, BMI= beden kitle indeksi, ASA= American society of anaesthesiologists, Hgb= hemoglobin, GFR= glomerüler filtrasyon hızı; EF= ejeksiyon fraksiyonu; *Yates Ki-Kare testi; **Mann Whitney U testi.

Tablo 2. Komorbiditelerin gruplara göre dağılımı [n (%)]

	Grup N	Grup H	P
Hipertansiyon	12 (%22,6)	36 (%72)	<0,001*
Kardiyak	8 (%15,1)	13 (%26)	0,259
DM	14 (%13,2)	16 (%16,0)	0,711
Hiperkolesterolemi	2 (%3,8)	3 (%6)	0,672
Nörolojik	1 (%1,9)	1 (%0)	1,000
Renal	0 (%0)	1 (%0)	0,485
Respiratuar	0 (%0)	4 (%0)	0,052
Hepatik	1 (%1,9)	0 (%0)	1,000
Hipotiroidi	0 (%0)	4 (%8)	0,052
Malignensi	0 (%0)	1 (%2)	0,485
Diğer	2 (%3,8)	2 (%4)	1,000

DM= diyabetes mellitus, *Yates Ki-Kare testi.

Tablo 3. Antihipertansif ve antidiyabetik ilaç kullanımının gruplara göre dağılımı [n (%)]

	Grup N	Grup H	P
AHT ilaç kullanımı	13 (%24,5)	33 (%66)	<0,001*
Beta Blokör	3 (%5,7)	20 (%40)	<0,001*
ACEi+ARB	8 (%7,5)	10 (%10,0)	0,707
Ca Kanal Blokörü	4 (%7,5)	7 (%14)	0,459
Diüretik	8 (%15,1)	5 (%10)	0,630
Alfa Blokör	0 (%0)	1 (%2)	0,485
Antidiyabetik ajan	12(%22,6)	16 (%32)	0,398

ACEi= Anjiyotensin dönüştürücü enzim inhibitörleri, ARB= anjiyotensin II reseptör blokörleri, *Yates ki-kare testi (Hastalar birden fazla ilaç kullanabilmektedir).

Gruplar arasında komorbidite varlığı HT dışında istatistiksel anlamlı fark yoktu. Gruplar arasında hipertansiyon tanısı Grup H'de (%72) Grup N'ye (%22,6) göre istatistiksel anlamlı olarak daha yüksek idi (P<0,001) (Tablo 2).

Gruplar arasında antihipertansif (AHT) ilaç kullanımı oranı ve hangi ilaçların ne oranda kullanıldığı Tablo 3'de görülmektedir. Antihipertansif ilaç kullanımı Grup H'de Grup N'ye göre istatistiksel anlamlı olarak daha yüksek idi (P<0,001). Yine Gruplar arasında beta blokör kullanımı bakımından Grup H'de, Grup N'ye göre istatistiksel anlamlı olarak yükseklik vardı (P<0,001). Diğer AHT ilaçların kullanım oranları ve antidiyabetik ajan kullanımı gruplar arasında istatistiksel olarak anlamlı farklılık bulunmadı (P=0,398) (Tablo 3).

Gruplar arasında açlık süresi bakımından istatistiksel olarak anlamlı farklılık saptanmadı (P=0,786). Gruplar arasında preoperatif sistolik kan basıncı bakımından istatistiksel olarak anlamlı farklılık bulundu (P=0,004). Grup H'de preoperatif SKB değerleri daha yüksekti. Gruplar arasında preoperatif DKB bakımından istatistiksel olarak anlamlı farklılık vardı (P=0,031). Grup H'de preoperatif diastolik tansiyon değerleri daha yüksekti. Gruplar arasında preoperatif OKB bakımından istatistiksel olarak anlamlı farklılık vardı (P=0,006). Grup H'de preoperatif OKB değerleri daha yüksekti (Tablo 4).

Pron pozisyona döndükten hemen sonra SKB, DKB, OKB kan basıncı ölçümleri Grup H'de Grup N'ye göre istatistiksel anlamlı olarak daha düşük tespit edildi (P=0,001). Diğer SKB, DKB, OKB ölçümlerinde gruplar arasında istatistiksel olarak anlamlı farklılık yoktu (P>0.005) (Tablo 4).

Gruplar arası 60. dk, 120. dk ve ayılma ünitesi KAH değerleri, Grup H'de Grup N'ye göre istatistiksel olarak anlamlı daha düşük idi (sırasıyla, P=0,015, P=0,027 P=0,024) (Tablo 4).

İki gruptaki tidal hacim, komplians, tepe inspirasyon basınç ölçümleri, Tepe inspirasyon basınç değeri, PEEP değerleri, plato basınç ölçümleri değerleri, sürücü basınç ölçümleri, etCO_2 ölçümleri, her iki grup arasında istatistiksel olarak bezerdi (P>0.005).

Gruplar arasında perioperatif ölçülen PPV değerleri indüksiyon sonrası, pron, 30, 60 ve 120. Dk ölçümleri Grup H'de Grup N'ye göre istatistiksel olarak anlamlı daha yüksek tespit edildi (sırasıyla, P<0,001, P=0.006, P=0.012, P<0.001 ve P=0.002) (Tablo 5).

4. Tartışma

Çalışmamızda genel anestezi altında vertebral cerrahi uygulanan hastaların yarısına yakınında supin pozisyondan pron pozisyona döndüğünde hipotansiyon gelişti. Grup H'de komorbidite varlığı daha fazla idi. Hipertansiyon tanısı olan, antihipertansif ilaç ve/veya betabloker kullanan hastalarda daha fazla hipotansiyon gözlendi. Grup H'de yaşın daha yüksek olduğunu ve sigara kullanımının daha düşük olduğunu gördük. Pron pozisyona dönene kadar verilen kristalloid Grup H'de daha fazla idi.

Tablo 4. Perioperatif SKB, DKB, OKB ve KAH değerlerinin gruplara göre dağılımı [Median (Min- Maks)]

	Grup N	Grup H	P
SKB			
Preop	131,00 (97 - 184)	155,50 (92 - 199)	0,004*
T0	138 (100-182)	135,5 (99 - 252)	0,278
T1	120 (79-237)	118 (81 - 195)	0,378
T2	113 (75 - 198)	79 (61-96)	0,001*
T3	110 (77-164)	104 (76-185)	0,656
T4	101,5 (75-136)	103 (70-140)	0,594
T 5	98,5 (85-139)	99,5 (85-131)	0,579
T 6	120 (82-169)	116 (73-187)	0,299
T 7	135 (95-160)	121 (103-133)	0,165
DKB			
Preop	79 (56 - 101)	83 (53 - 158)	0,031*
T0	80 (59 - 95)	77,50 (51 - 126)	0,131
T1	73 (36 - 127)	68 (45 - 101)	0,138
T2	69 (34 - 108)	41,5 (30 - 67)	0,001*
T3	66 (42 - 99)	65 (38 - 99)	0,989
T4	65,5 (42 - 98)	63,5 (44 - 94)	0,560
T5	59,5 (45- 82)	63 (38 - 82)	0,436
T6	73 (47 - 112)	71 (50 - 106)	0,192
T7	77 (62 - 96)	73 (52 - 88)	0,953
OKB			
Preop	99 (62 - 132)	109 (71 - 167)	0,006×
T0	103 (64-128)	99 (73-167)	0,155
T1	92 (60-160)	89 (61-140)	0,423
T2	86 (60 -140)	55 (40-71)	<0,001*
T3	84 (60-112)	80,5 (49-130)	0,992
T4	79,5 (55-110)	76,5 (53-108)	0,676
T5	74,5 (61-109)	75 (62-102)	0,587
T6	90 (61-132)	89 (58-145)	0,259
T7	99,5 (78-113)	93 (82-109)	0,768
KAH			
T0	84 (52 - 118)	83 (54 - 129)	0,840
T1	87 (59 - 115)	82 (46 - 136)	0,122
T2	83 (57 - 121)	79,5 (45 - 130)	0,088
T3	74 (56 - 113)	71 (44 - 122)	0,255
T4	77,5 (52 - 118)	69 (44 - 110)	0,015*
T5	78 (54 - 111)	70,5 (53 - 90)	0,027*
T6	80 (60 - 110)	79 (58 - 105)	0,248
T7	81 (64 - 106)	71 (63 - 74)	0,024*

SKB= sistolik kan basıncı mmHg, DKB= diastolik kan basıncı mmHg, OKB= ortalama kan basıncı mmHg, KAH= kalp atım hızı, T0= ameliyathane odasına alındığında (indüksiyon öncesi), T1= indüksiyon sonrası (5. Dk), T2= pron pozisyona alındıktan sonra, T3= indüksiyon sonrası (30. dk), T4= indüksiyon sonrası (60. Dk), T5= indüksiyon sonrası (120. dk), T6= ekstübasyon sonrası, T7= ayılma ünitesi, *Mann Whitney U testi.

Tablo 5. Perioperatif PPV değerlerinin gruplara göre dağılımı [Median (Min-Maks)]

	Grup N	Grup H	P
İndüksiyon sonrası PPV (%)	12 (8 - 20)	16 (6 - 36)	<0,001*
Pron PPV (%)	11 (7 - 18)	12,5 (3 - 29)	0,006*
30. dk PPV (%)	10 (5 - 15)	11 (4 - 19)	0,012*
60. dk PPV (%)	9 (6 - 15)	11 (4 - 19)	<0,001*
120. dk PPV (%)	9 (4 - 14)	11 (4 - 16)	0,002*

PPV= pulse pressure variation, *Mann Whitney U testi.

Grup H'de indüksiyon sonrası ve pron pozisyon sonrası PPV değerleri daha yüksekti. Ejeksiyon fraksiyonu ise Grup H'de daha düşük ölçüldü.

Pozisyon değişikliğine bağlı hipotansiyon insidansı, genel anestezi, sedasyon ve rejyonel anestezi altındaki hastalar arasında farklılık gösterebilir (Tabara ve ark., 2005). Venöz dönüşün azalması, kompansatuar mekanizmaların anestezik ilaçlarla indüklenen blokajı, pozitif basınçlı ventilasyon ile artan intratorasik basınç ile kardiyak ön yükün azalması bunun nedenleri arasındadır. İntraoperatif hipotansiyon artmış mortalite ve miyokard enfarktüsü ve postoperatif morbidite ve mortalite riskini artırabilir (Walsh ve ark., 2013; Sessler ve ark., 2018).

Komorbidite varlığı da hipotansiyon nedeni olablir. Hipertansiyon tanısı olup baroreseptör desensitizasyonu gelişmiş, vasküler elastikiyet kaybı olmuş veya intravasküler hacmi yeterli olmayan hastalarda intraoperatif hipotansiyon gelişme riski bulunmaktadır (Intengan ve Schiffrin, 2001). Yüksek tansiyonun pozisyon değişikliği ile baroreseptör refleksini aktive ederek periferik vazodilatasyon ve bradikardiye yol açması beklenebilir (Biais ve ark., 2010). Çalışmamızda da hipotansiyonu olan hastalarda hipertansiyon daha fazla görülmektdir. Spesifik komorbid durumlar, özellikle pulmoner hipertansiyon ve konjestif kalp yetmezliği, omurga cerrahisi sonrası gelişebilecek komplikasyonlarla yüksek oranda ilişkilidir (Memtsoudis ve ark., 2011). Pron pozisyonda, PPV'nin sıvı tepkisini tahmin etme yeteneği değişmemektedir. Ancak, varyasyonun başlangıçta arttığı gösterilmiştir; bu nedenle sıvı tepkisi, supin duruma göre biraz daha fazla gözlenir (Biais ve ark., 2010). Prone pozisyonda abdominal kompresyon diyaframın sefale yer değiştirmesine, pulmoner kompliyansın azalmasına ve tepe hava yolu basıncının artmasına neden olabilir (Palmon ve ark., 1998).

Antihipertansif ilaçlar hipertansiyon yanısıra miyokard enfarktüsü sonrası kardiyoprotektif etki, kalp yetmezliği nedenli akciğer yüklenme bulgularını azaltmak, migren profilaksisi gibi durumlarda da kullanılır. Oral antihipertansif ilaçlara ameliyat zamanına kadar devam edilmeli ve ameliyat tamamlandıktan sonra mümkün olan en kısa sürede yeniden başlanmalıdır (Whelton ve ark., 2017). Literatürde ameliyat öncesi anjiyotensin dönüştürücü enzim inhibitörleri (ACEi) veya anjiyotensin II reseptör blokörleri (ARB) alan hastalarda intraoperatif hipotansiyon riskinin yükseldiğini gösteren çalışmalar vardır (Bradic ve Povsic-Cevra, 2018). Çalışmamızda ise gruplar arasında ACEi+ARB kullanımı açısından anlamlı farklılık saptanmadı. Bunun sebebi söz konusu çalışmaların genel anestezi değil nöroaksiyel anestezi altındaki hastalarda yapılması ve dolayısıyla Renin anjiotensin sisteminin (RAS) blokajının daha yaygın olarak gelişmesi olabilir.

Beta-blokörlerin preoperatif kullanımının potansiyel bir kardiyoprotektif etkiye sahip olduğu bilinse de, baroreseptör refleksini köreltir, intraoperatif hipotansiyon ve bradikardi riskini arttırabilir (Devereaux ve ark., 2008). Kertai ve ark. (2018) tarafından yapılan çalışmada kardiyak olmayan cerrahide beta-blokör kullanımının kesilmesi intraoperatif hipotansiyon insidansını azaltsa da 48 saatlik mortaliteyi arttırdığı gösterilmiştir. Biz de bu çalışmaya benzer olarak beta-blokörlerin preoperatif kullanımının, Grup H'de daha fazla olduğunu saptadık.

Pulse Pressure Variation değerinin supin pozisyonda %11 ila %15'ten, pron pozisyonda ise %14 ila %15'ten yüksek bulunması, hastalarda intravasküler sıvı ihtiyacının olduğunu düşündürür (Biais ve ark., 2010). Shi ve ark. (2022) yaptığı bir çalışmada ise pron pozisyonda düşük tidal hacim ventilasyonu altında olan ARDS'li hastalarda, PPV'deki değişim ile kardiyak debi ölçümlerine gerek kalmadan ön-yük yanıtını güvenilir bir şekilde değerlendirebileceği tespit edilmiştir. Yoon ve ark. (2020) yaptığı bir çalışmada pron pozisyondaki PPV değeri hipotansif grupta normotansiflere göre daha yüksek bulunmuş. Çalışmamızda da gruplar arasında indüksiyon sonrası, pron pozisyon öncesi Grup H'de PPV değeri yüksek idi.

Kalp yetmezliği tanılı hastalar cerrahi sırasında akut dekompanse kalp yetmezliği, hipotansiyon, hipertansiyon ve aritmiler açısından yüksek risk altındadır. Önceki çalışmalarda azalmış ejeksiyon fraksiyonunun <%55 olması, perioperatif hipotansiyon ve bradikardi gibi istenmeyen kardiyovasküler olayları arttırdığı gösterilmiştir (Mantha ve ark., 1994). Çalışmamızda da Grup H'de ejeksiyon fraksiyon ölçümünü daha düşük saptadık.

Sigara kullanımında akut etki olarak; kan basıncında, kalp hızında, miyokardiyal kontraktilitede ve miyokardiyal oksijen tüketiminde artışa yol açan sempatik sinir sistemi aşırı aktivasyonu vardır (Virdis ve ark., 2010). Ancak sigara kullanımının kan basıncı ve hipertansiyon gelişimi üzerindeki kronik etkileri belirsizdir. Bazı çalışmalarda sigara içme alışkanlığı olanlarda basıncı, içmeyenlere göre daha düşük bulunmuştur (Primatesta ve ark., 2001). Bizim çalışmamızda da Grup N'de sigara içme oranı daha yüksek tespit edilmiştir.

5. Sonuç

Sonuç olarak, genel anestezi altında pron pozisyona dönen vertebral cerrahi uygulanan hastalarda, hipotansiyon görülme olasılığı; PPV değeri yüksek, komorbiditeleri arasında hipertansiyonu olan, beta-blokör kullananlarda ve EF<%55 olan hastalarda daha yüksek olması sayılabilir. Dinamik bir parametre olan PPV değerinin hipotansiyonu öngörmede belirleyici bir unsur olduğunu da düşünüyoruz. Daha çok sayıda hasta ile yapılan çok merkezli, prospektif, çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Limitasyonlar

Çalışmamızda intravasküler hacim durumu için dinamik bir parametre olan PPV kullanmamıza rağmen, vasküler direnci, kardiyak debiyi veya ön yükü doğrudan ölçememiz limitasyonlarımızdan biridir. Ayrıca

intraabdominal veya intratorasik basıncı direkt ölçemediğimiz için bunların etkilerini de kesin olarak belirleyemedik. Çalışmamıza dahil olan hastaların detaylı öyküsü alınmasına rağmen kullandığı ilaçların daha da detaylandırılması ileri çalışmalarda faydalı olabilir. Çalışmaya dahil olan hasta sayısının az olması da limitasyonlarımız arasındadır.

Katkı Oranı Beyanı

Yazarların katkı yüzdesi aşağıda verilmiştir. Tüm yazarlar makaleyi incelemiş ve onaylamıştır.

	S.C.Y.	Ş.E.Ö.	M.G.
K	34	33	33
T	34	33	33
Y	34	33	33
VTI	34	33	33
VAY	34	33	33
KT	34	33	33
YZ	34	33	33
KI	34	33	33
GR	34	33	33
PY	34	33	33
FA	34	33	33

K= kavram, T= tasarım, Y= yönetim, VTI= veri toplama ve/veya işleme, VAY= veri analizi ve/veya yorumlama, KT= kaynak tarama, YZ= Yazım, KI= kritik inceleme, GR= gönderim ve revizyon, PY= proje yönetimi, FA= fon alımı.

Çatışma Beyanı

Yazarlar bu çalışmada hiçbir çıkar ilişkisi olmadığını beyan etmektedirler.

Etik Onay/Hasta Onamı

Bu çalışma Sağlık Bilimleri Üniversitesi Etik Kurulu tarafından onaylandı (onay tarihi: 06 Ekim 2020, onay numarası: 2011-KAEK-25). Araştırma Helsinki Deklarasyonu Prensipleri'ne uygun şekilde yapılmıştır.

Kaynaklar

Abbott TEF, Pearse RM, Archbold RA, Ahmad T, Niebrzegowska E, Wragg A. A2018. Prospective ınternational multicentre cohort study of ıntraoperative heart rate and systolic blood pressure and myocardial ınjury after noncardiac surgery: Results of the VISION study. Anesth Analg. 126(6): 1936-1945.

Abcejo AS, Diaz Soto J, Castoro C, Armour S, Long TR. 2017. Profound obstructive hypotension from prone positioning documented by transesophageal echocardiography in a patient with scoliosis: A case report. Case Rep, 9(3): 87-89.

Biais M, Bernard O, Ha JC, Degryse C, Sztark F. 2010. Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. Br J Anaesth, 104(4): 407-413.

Bradic N, Povsic-Cevra Z. 2018. Surgery and discontinuation of angiotensin converting enzyme inhibitors: Current perspectives. Curr Opin Anaesthesiol, 31(1): 50-54.

Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K. 2008. POISE Study Group, Effects of extended-release metoprolol succinate in patients undergoing non- cardiac surgery (POISE trial): a randomised controlled trial. Lancet Lond Engl, 371(9627): 1839-1847.

Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG. 2010. Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. JAMA, 303(13): 1259-1265.

Doherty M, Buggy DJ. 2012. Intraoperative fluids: how much is too much? Br J Anaesth, 109(1): 69-79.

Gregory A, Stapelfeldt WH, Khanna AK, Smischney NJ, Boero IJ, Chen Q. 2021. Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. Anesth Analg, 132(6): 1654-1665.

Intengan HD, Schiffrin EL. 2001. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. Hypertens Dallas Tex, 38(3 Pt 2): 581-587.

Kalb S, Fakhran S, Dean B, Ross J, Porter RW, Kakarla UK. 2014. Cervical spinal cord infarction after cervical spine decompressive surgery. World Neurosurg, 81(5–6): 810-817.

Kertai MD, Cooter M, Pollard RJ, Buhrman W, Aronson S, Mathew JP. 2018. Is compliance with surgical care ımprovement project cardiac (SCIP-Card-2) measures for perioperative β-blockers associated with reduced ıncidence of mortality and cardiovascular-related critical quality ındicators after noncardiac surgery?. Anesth Analg, 126(6): 1829-1838.

Malbouisson LMS, Silva JM, Carmona MJC, Lopes MR, Assunção MS, Valiatti JLDS. 2017. A pragmatic multi-center trial of goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery. BMC Anesthesiol, 17(1): 70.

Mantha S, Roizen MF, Barnard J, Thisted RA, Ellis JE, Foss J. 1994. Relative effectiveness of four preoperative tests for predicting adverse cardiac outcomes after vascular surgery: A meta-analysis. Anesth Analg, 79(3): 422-433.

Memtsoudis SG, Vougioukas VI, Ma Y, Gaber-Baylis LK, Girardi FP. 2011. Perioperative morbidity and mortality after anterior, posterior, and anterior/posterior spine fusion surgery. Spine, 36(22): 1867-1877.

Miller TE, Myles PS. 2019. Perioperative fluid therapy for major surgery. Anesthesiology, 130(5): 825-832.

Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR. 2015. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiology, 123(2): 307-319.

Önder H. 2018. Nonparametric statistical methods used in biological experiments. BSJ Eng Sci, 1(1): 1-6.

Palmon SC, Kirsch JR, Depper JA, Toung TJ. 1998. The effect of the prone position on pulmonary mechanics is frame-dependent. Anesth Analg, 87(5): 1175-1180.

Primatesta P, Falaschetti E, Gupta S, Marmot MG, Poulter NR. 2001. Association between smoking and blood pressure: evidence from the health survey for England. Hypertens Dallas Tex, 37(2): 187-193.

Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI. 2017. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology, 126(1): 47-65.

Sessler DI, Meyhoff CS, Zimmerman NM, Mao G, Leslie K, Vásquez SM. 2018. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: A substudy of the POISE-2 trial. Anesthesiology, 128(2): 317-327.

Shi R, Ayed S, Moretto F, Azzolina D, De Vita N, Gavelli F. 2022. Tidal volume challenge to predict preload responsiveness in

patients with acute respiratory distress syndrome under prone position. Crit Care Lond Engl, 26(1): 219.

Sudheer PS, Logan SW, Ateleanu B, Hall JE. 2006. Haemodynamic effects of the prone position: a comparison of propofol total intravenous and inhalation anaesthesia. Anaesthesia, 61(2): 138-141.

Tabara Y, Tachibana-Iimori R, Yamamoto M, Abe M, Kondo I, Miki T. 2005. Hypotension associated with prone body position: a possible overlooked postural hypotension. Hypertens Res Off J Jpn Soc Hypertens, 28(9): 741-746.

Thiele RH, Bartels K, Gan T-J. 2015. Inter-device differences in monitoring for goal- directed fluid therapy. Can J Anaesth J Can Anesth, 62(2): 169-181.

Virdis A, Giannarelli C, Neves MF, Taddei S, Ghiadoni L. 2010. Cigarette smoking and hypertension. Curr Pharm Des, 16(23): 2518-2525.

Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN. 2013. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology, 119(3): 507-515.

Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C. 2017. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. J Am Coll Cardiol, 71(19): e127-e248.

Yoon H-K, Lee H-C, Chung J, Park H-P. 2020. Predictive factors for hypotension associated with supine-to-prone positional change in patients undergoing spine surgery. J Neurosurg Anesthesiol, 32(2): 140-146.

Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1553323

Open Access Journal
e-ISSN: 2619 – 9041

Research Article
Volume 7 - Issue 6: 248-252 / November 2024

MORPHOLOGICAL CHANGES IN THE LUMBAR AND ABDOMINAL MUSCLES IN INDIVIDUALS WITH SACRALIZATION

Fatih ÇANKAL[1], İlyas UÇAR[2]*, Caner KARARTI[3], Selim ÇINAROĞLU[4]

[1]*Ankara Medipol University, Faculty of Medicine, Department of Radiology, 06000, Ankara, Türkiye*
[2]*Erciyes University, Faculty of Medicine, Department of Anatomy, 38100, Kayseri, Türkiye*
[3]*Kırşehir Ahi Evran University, School of Physical Therapy and Rehabilitation, Department of Physiotherapy and Rehabilitation, 40100, Kırşehir, Türkiye*
[4]*Niğde Ömer Halis Demir University, Faculty of Medicine, Department of Anatomy, 51000, Niğde, Türkiye*

Abstract: Although sacralization is one of the most common congenital anomalies of the spine, its effect on surrounding muscles is still not well known. This study was conducted to determine the size of the lumbar and abdominal muscles of the individuals with sacralization and to compare with the control group. Eighty-five participants with sacralization phenomena and fifty-six asymptomatic participants were included in this study. Sacralization was classified according to the Castellvi classification. The cross-sectional area of the multifidus lumborum, erector spinae and rectus abdominis muscles, and the section thicknesses of external abdominal oblique, internal abdominal oblique and transversus abdominis muscles were measured bilaterally on axial computed tomography images at the L1-2 and L4-5 levels. ANCOVA revealed that there is no any significant group*side interaction effect regarding muscles sizes in terms of two groups in L1-L2 and L4-L5. In addition, ANCOVA revealed a both side effect [(P=0.020; η2p=0.038)] and group*side interaction effect [(P=0.010; η2p=0.049)] regarding length of the L5 transverse process (P>0.05). Regardless of low back pain, muscle sizes are not associated with the sacralization phenomenon.

Keywords: Sacralization, Computed tomography, Paraspinal muscles, Abdominal muscles

***Corresponding author:** Erciyes University, Faculty of Medicine, Department of Anatomy, 38100, Kayseri, Türkiye
E mail: ilyas.ucar@erciyes.edu.tr (İ. UÇAR)
Fatih ÇANKAL https://orcid.org/0000-0003-1066-353X
İlyas UÇAR https://orcid.org/0000-0003-3646-5320
Caner KARARTI https://orcid.org/0000-0002-4655-0986
Selim ÇINAROĞLU https://orcid.org/0000-0002-4495-6106

Received: September 20, 2024
Accepted: October 25, 2024
Published: November 15, 2024

Cite as: Çankal F, Uçar İ, Karartı C, Çınaroğlu S. 2024. Morphological changes in the lumbar and abdominal muscles in individuals with sacralization. BSJ Health Sci, 7(6): 248-252.

1. Introduction

Lumbosacral transitional vertebra (LSTV) is a congenital anomaly seen in approximately one out of every four people in the population, and it includes a spectrum from complete/incomplete L5 sacralization to complete/incomplete S1 lumbarization according to morphological changes (Dar and Peled, 2014). Sacralization, which is one of these anomalies, is the fusion of the fifth lumbar vertebra with the first sacral vertebra in different ways and gaining the characteristic of the sacrum (Carrino et al., 2011). Several authors have reported the incidence of sacralization, which is mostly found incidentally as 4.6-35.9% in the general population (Castellvi, 1984; Hughes and Saifuddin, 2006; Hinterdorfer et al., 2010). In clinical studies, it has been shown that with sacralization, mobility in the lumbar region decreases and it is asymmetrical, and may also cause early degenerative changes (Paik et al., 2013). When mobility is reduced or asymmetrical, changes in muscle structure and size are inevitable. However, studies examining the morphology of both lumbar and abdominal muscles in LSTV anomaly are limited (Becker et al., 2021). However, previous studies have shown that morphological changes can occur in the spine and abdominal muscles in different disorders involving the lumbar region, and that examining the anatomical structures of the musculoskeletal system can provide information about the limits of stability (Uçar et al., 2021). In this context, it was aimed to determine the dimensions of the multifidus, erector spinae and abdominal muscles of the individuals with sacralization in the lower and upper lumbar regions and to compare them with the control group in our study. In addition, by revealing the muscle dimensions of individuals with sacralization, we aim to guide the determination of the treatment protocol for the waist problems encountered in these individuals.

2. Materials and Methods

2.1. Patient Population

In our study, the images of patients aged 18-65 years, who applied to our imaging center with preliminary diagnoses such as urinary system stones, intestinal and visceral organ pathologies, and whose imaging method were computed tomography (CT), between January 2020 and December 2021, scanned retrospectively from the

PACS imaging system. Images of patients with a history of surgery involving the spine, ribs or pelvis, fractures of these bones, a history of spinal cord injury, tumor or infection, and pathology such as arthrosis, spondylolisthesis, and scoliosis were excluded from the study. The images were examined by a specialist radiologist for sacralization, and they were divided into sacralization and control groups, and the body mass index (BMI weight/height^2) was calculated by recording the age, gender, and weight and height information of the patients.

2.2. Computed Tomography Images and Classification

Images of Abdominopelvic examinations taken in the supine position with a multi-slice computed tomography device (MSCT) (General Electric IQ™ 32-Detector Spiral MSCT) without contrast were used. The acquisition parameters are 200-320 mAS, 120 kV, average 350 mm FOV and 1.25 mm section thickness. Images were evaluated both axial and coronal on the workstation, both in the bone window and in the soft tissue window.

LSTV's were recorded as unilateral or bilateral as well as incomplete or complete classification according to Castellvi classification (Castellvi 1984). Type 1 shows unilateral (1a) or bilateral (1b) elongated dysplastic transverse processes, while type 2 includes incomplete unilateral (2a) or bilateral (2b) pseudo-articulation with diarthrodial joint. Type 3 exhibits unilateral (3a) or bilateral (3b) bone fusion of the transverse process. Type 4 includes a unilateral type II with a type III on the contralateral side.

2.3. Evaluation of the Multifidus Lumborum, Erector Spinae and Abdominal Muscles

As the first step in image processing, CT images were opened in RadiAnt, a free DICOM imaging program. CT imagings were recorded in JPEG (Joint Photographic Experts Group) format to calculate the cross-sectional area of the multifidus lumborum muscle (MM), erector spinae muscle (ES) and rectus abdominis muscle (RA) and the section thicknesses of abdominal muscles (external abdominal oblique muscle 'EO', internal abdominal oblique muscle 'IO' and transversus abdominis muscle 'TA'). Then, all these images were displayed simultaneously in the "ImageJ" program, which can be downloaded from https://imagej.nih.gov/ij/download.html. An image series was created by selecting "stack→image to stack" icon under the "image" tab of the ImageJ program. Using the options in the "measurement and tools" tab on the RadiAnt program, the length of any specific spot on the image was measured. In the ImageJ program, the same spot was marked in the same section using the "straight" button. The images were calibrated using "Set Calibrate" option under the "analyze" tab of the ImageJ program (Uçar et al., 2022). In the next step, the boundaries of the MM, ES and RA muscles were determined manually by using the "Free Hand" button of the ImageJ program bilaterally in the axial images at the L1-L2 and L4-L5 levels, and the cross-sectional area was recorded in square centimeters (Figure 1). The section thicknesses of the EO, IO and TA were recorded in millimeters on the transverse line connecting the farthest points of the abdominal wall on the right and left (Figure 1). All these processes were performed on the CT image of each individual separately on the right and left.

2.4. Statistical Analysis

The data were evaluated using the Statistical Package for the Social Sciences 22.0 program for Windows. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to check normality. We used descriptive statistics and reported counts and proportions for categorical data and measures of distribution for continuous data. An independent t test or χ^2 test was performed to compare the baseline characteristics. To evaluate the cross-sectional areas of muscles by using CT, a 2*2 [group (participants with- and without sacralization) * side (right or left)] repeated measures ANCOVA was performed with group as a between-groups factor and side as a within-subjects factor, and with demographical measures set as the covariates. When the F-ratio was significant, Bonferroni's post hoc test was employed to identify the mean differences. Effect sizes were determined as partial eta squared (η^2_p). The level of significance was set at $P<0.05$. ANCOVA (Analysis of Covariance) is a method used in statistical analysis to control the effect of covariates and reduce intergroup variation (Önder, 2018).

Table 1. Descriptive statistics of the participants (Independent samples t test or χ2 test)

Variable	Participants with sacralization (n=85)	Asymptomatic participants (n=56)	P
Age	55.85±12.41	46.53±14.66	<0.001
Body mass index (kg/m^2)	26.14±2.13	25.17±4.34	0.078
Female (%)	35 (41.17)	29 (51.78)	0.231
Castelvi type (%)			
1a	13 (15.29)	-	-
1b	10 (11.76)	-	-
2a	15 (17.64)	-	-
2b	36 (42.35)	-	-
3a	3 (3.52)	-	-
3b	8 (9.41)	-	-

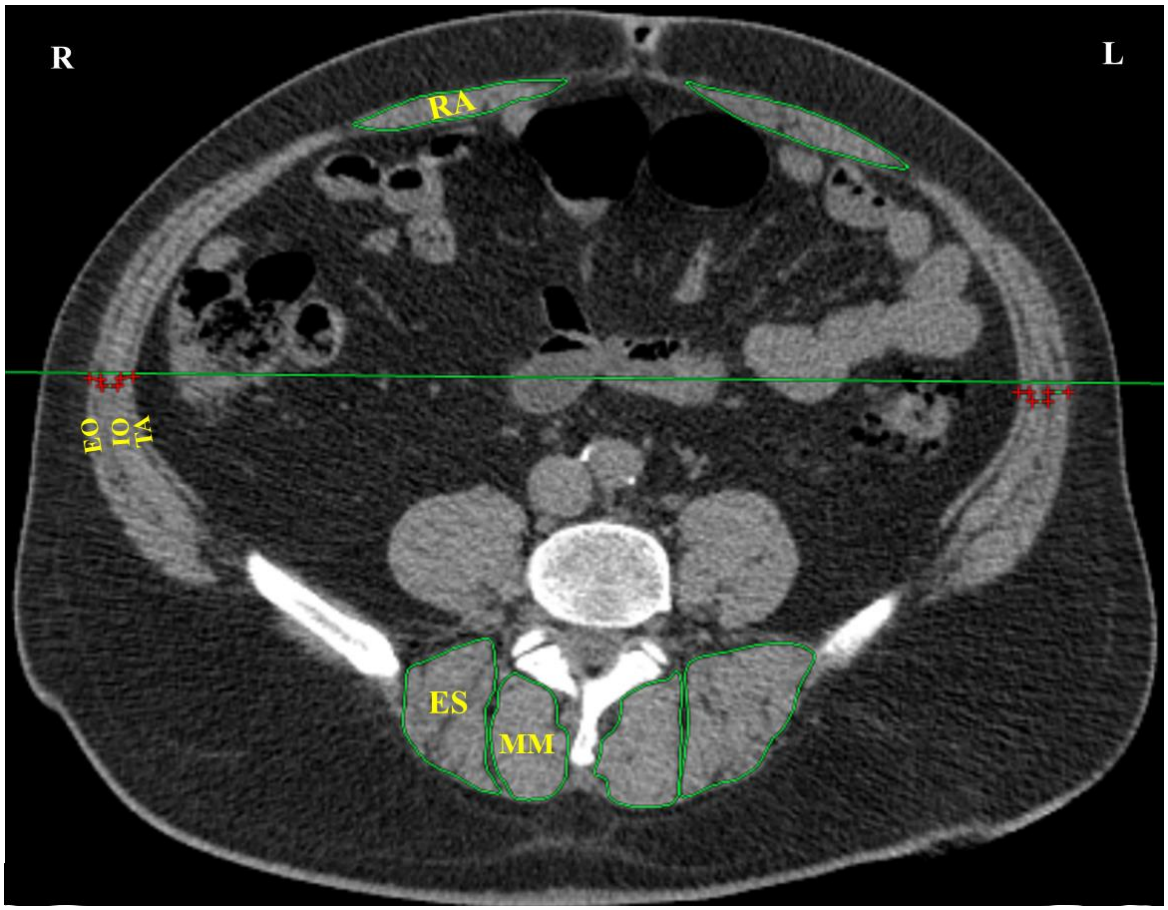

Figure 1. Measurements of muscles sizes (An axial CT image at L4-L5 level. EO= external abdominal oblique muscle, IO= internal abdominal oblique muscle, TA= transversus abdominis muscle, RA= rectus abdominis muscle, MM= multifidus lumborum muscle, ES= erector spina muscle).

3. Results

A total of 141 participants with (n=85) and without (n=56) sacralization were included in the study. Descriptive characteristics of the participants are presented in Table 1. There was no any significant difference between the two groups in terms of baseline characteristics except for age (P>0.05). The mean of age were higher in the sacralization group (P<0.001).

ANCOVA revealed a side effect regarding cross-sectional areas of rectus abdominis muscle [(P=<0.001; η^2_p=0.085)] and erector spinae muscle [(P=0.005; η^2_p=0.055)] in terms of L1-2 measurements. But, there is no any significant group*side interaction effect regarding cross-sectional areas of muscles in terms of two groups in L1-L2 (Table 2).

ANCOVA revealed a side effect regarding cross-sectional areas of rectus abdominis muscle [(P=<0.001; η^2_p=0.107)], internal oblique muscle [(P=0.026; η^2_p=0.035)], and erector spinae muscle [(P=0.003; η^2_p=0.062)] in terms of L4-L5 measurements. But, there is no any significant group*side interaction effect regarding cross-sectional areas of muscles in terms of two groups in L4-L5 (Table 2).

Lastly, ANCOVA revealed a both side effect [(P=0.020; η^2_p=0.038)] and group*side interaction effect [(P=0.010; η^2_p=0.049)] regarding length of the L5 transverse process. This was higher in the sacralization group (Table 2).

4. Discussion

In this study, based on cross-sectional CT imaging from adults with (n=85) and without (n=56) sacralization, the dimensions of the multifidus (MM), erector spina (ES) and abdominal muscles at the L1–2 and L4–5 intervertebral discus levels were evaluated. The data we obtained revealed that the muscle sizes of the individuals with sacralization were similar to the muscle sizes of the individuals in the control group. In addition, according to Castellvi classification, Type 2b was the most common type of sacralization in our study at 42.35%.

Sacralization, a congenital vertebral anomaly, is a frequently encountered condition in the general population (Jancuska et al., 2015). The relationship between LSTV and low back pain (LBP) is well known and studies on paraspinal muscle dimensions are quite extensive (Peterson et al., 2005; Apaydin et al., 2019; Ulger and Illeez, 2020). However, it is a known fact that the reduced muscle mass in the lumbar region not only affects the global sagittal alignment of the spine but also plays a role in the development of LBP (Ambegaonkar et al., 2014; Uçar et al., 2021).

Table 2. Comparison of cross-sectional areas of muscles and length of the L5 transverse process between two groups

	Participants with sacralization			Asymptomatic participants			2 x 2 ANCOVA	
	Right	Left	p[1]	Right	Left	p[1]	Side p[2] (η^2p)	Group*Side p[2] (η^2p)
L1-L2 measurements								
Rectus abdominis muscle	5.25±1.99	5.37±1.91	0.745	4.90±1.40	5.11±1.36	0.322	<.001 (.085)*	0.336 (0.007)
External oblique muscle	5.39±1.18	5.42±1.18	0.893	6.26±1.20	6.25±1.18	0.956	.551 (.003)	0.573 (0.002)
Internal oblique muscle	6.27±1.36	6.26±1.34	0.968	7.08±1.23	7.05±1.27	0.875	.677 (.001)	0.688 (0.001)
Transversus abdominis muscle	3.66±0.83	3.63±0.87	0.852	4.31±0.84	4.32±0.79	0.936	.711 (.001)	0.513 (0.003)
Lumbar multifidus muscle	9.88±2.23	9.93±2.23	0.905	10.88±3.08	11.17±2.85	0.524	.203 (.012)	0.367 (0.006)
Erector spinae muscle	10.02±2.24	9.86±2.32	0.711	11.29±2.55	11.15±2.50	0.718	.005 (.055)*	0.888 (<0.001)
L4-L5 measurements								
Rectus abdominis muscle	5.71±2.23	5.85±2.16	0.736	5.28±1.50	5.46±1.51	0.436	<.001 (.107)*	0.657 (0.001)
External oblique muscle	5.28±1.32	5.32±1.31	0.872	6.55±1.40	6.57±1.36	0.924	.379 (.006)	0.737 (0.001)
Internal oblique muscle	6.34±1.56	6.29±1.52	0.863	7.92±1.62	7.85±1.53	0.772	.026 (.035)*	0.700 (0.001)
Transversus abdominis muscle	3.20±0.94	3.19±0.91	0.954	4.32±0.79	4.35±0.74	0.798	.554 (.003)	0.533 (0.003)
Lumbar multifidus muscle	8.89±2.15	8.94±2.21	0.903	10.43±2.21	10.30±2.21	0.701	.488 (.003)	0.148 (0.015)
Erector spinae muscle	9.49±1.92	9.34±1.93	0.680	11.04±1.92	10.95±1.82	0.754	.003 (.062)*	0.431 (0.004)
Length of the L5 transverse process	20.62±4.08	22.63±4.11	0.001	15.00±1.91	15.17±2.11	0.582	.020 (.038)*	0.010 (0.049)*

p[1]: Independent samples t test results for within-group side comparisons; p[2]: two-way repeated measures analysis of covariance with a mixed model. Figures in parentheses are effect sizes partial eta squared (η^2p).

In addition, the muscles of the anterior-lateral abdominal wall play an important role in the spine stability (Hodges and Richardson, 1997). Studies investigating the relationship between LSTV and both paraspinal and abdominal muscle sizes are limited, regardless of LBP (Becker et al., 2021). Therefore, in our study, images of patients who applied with pre-diagnoses such as urinary system stones, intestinal and visceral organ pathologies other than LBP, were examined for sacralization, and paraspinal and abdominal muscle sizes of individuals with sacralization and those in the control group were analyzed and compared.

The presented study differs from previous studies that showed individuals with LSVT to have atrophic musculature. Our data showed that there were statistically similarity in the paraspinal and abdominal muscles between the both groups. There could be two reasons for this. First, hypomobility at the sacralization level is compensated by hypermobility of segments above this level. This hypermobility may have caused individuals with sacralization to have similar muscle sizes to the control group, contrary to expectations, as it required more muscular workload. Second, most of the studies on this subject were conducted by examining the images of patients with LBP (Peterson et al., 2005; Apaydin et al., 2019; Ulger and Illeez, 2020). Today, the importance of paraspinal muscle quality in patients with low back pain is widely accepted. Muscle atrophy itself may play an important role in the pathogenesis of LBP. Therefore, studies on images taken for LBP may not only reflect the characteristics of individuals with sacralization. However, a recent study of 46 patients with LSTV reported a reduction in muscle sizes (Becker et al. 2021).

Our study revealed a side effect regarding cross-sectional areas of RA and ES in terms of L1-2 measurements. Also revealed a side effect regarding cross-sectional areas of RA, IO and ES in terms of L4-L5 measurements. This corroborates the studies of Becker et al. showing that individuals with LSTV have a different muscle load than the control group.

Our study has some limitations. First, because it was a retrospective study, we could not analyze clinical findings such as pain, activity limitation, and spasm. This prevented us from separating symptomatic and asymptomatic individuals. Second, morphological and degenerative changes in the facet or disc and fat changes in the muscles were not analyzed. Finally, we would like to point out that the sample size of our study is low. This may affect the statistical significance level of the results.

5. Conclusion

In conclusion, in our analyzes of CTs taken for different reasons, independent of LBP, we determined that sacralization did not have a significant effect on the paravertebral and abdominal muscles sizes of the individual. In order to shed light on the subject, studies with wider participation, including patient symptoms, are required.

Author Contributions

The percentage of the authors contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	İ.U.	F.Ç.	C.K.	S.Ç.
C	40	40	10	10
D	40	40	10	10
S	30	30	30	10
DCP	35	35	20	10
DAI	30	30	30	10
L	50	30	10	10
W	70	10	10	10
CR	20	50	10	20
SR	80	10	5	5
PM	30	50	10	10
FA	30	50	10	10

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Approval/Informed Consent

This study was approved by Ethics Committee of Niğde Ömer Halis Demir University (approval date: December 14, 2021, protocol code: 2021/108) and conducted in accordance with the principles of the Declaration of Helsinki.

References

Ambegaonkar JP, Mettinger LM, Caswell SV, Burtt A, Cortes N. 2014 Relationships between core endurance, hip strength, and balance in collegiate female athletes. Int J Sports Physical Ther, 9(5): 604.

Apaydin M, Uluc M, Sezgin G. 2019. Lumbosacral transitional vertebra in the young men population with low back pain: anatomical considerations and degenerations (transitional vertebra types in the young men population with low back pain). La Radiol Medica, 124(5): 375-381.

Becker L, Ziegeler K, Diekhoff T, Palmowski Y, Pumberger M, Schömig F. 2021. Musculature adaption in patients with lumbosacral transitional vertebrae: a matched-pair analysis of 46 patients. Skeletal Radiol, 50(8): 1697-1704.

Carrino JA, Campbell PD, Lin DC, Morrison WB, Schweitzer ME, Flanders AE, Vaccaro AR. 2011. Effect of spinal segment variants on numbering vertebral levels at lumbar MR imaging. Radiology, 259(1): 196-202.

Castellvi AE, Goldstein LA, Chan DP. 1984. Lumbosacral transitional vertebrae and their relationship with lumbar extradural defects. Spine, 9(5): 493-495.

Dar G, Peled N. 2014. The association between sacralization and spondylolisthesis. Anatomical Sci Int, 89(3): 156-160.

Hinterdorfer P, Parsaei B, Stieglbauer K, Sonnberger M, Fischer J, Wur G. 2010. Segmental innervation in lumbosacral transitional vertebrae (LSTV): a comparative clinical and intraoperative EMG study. J Neurol Neurosurg Psychiatry, 81(7): 734-741.

Hodges PW, Richardson CA. 1997. Contraction of the abdominal muscles associated with movement of the lower limb. Physical Ther, 77(2): 132-142.

Hughes RJ, Saifuddin A. 2006. Numbering of lumbosacral transitional vertebrae on MRI: role of the iliolumbar ligaments. AJR Am J Roentgenol, 187(1): 59-65.

Jancuska JM, Spivak JM, Bendo JA. 2015. A review of symptomatic lumbosacral transitional vertebrae: Bertolotti's syndrome. Int J Spine Surg, 9: 42.

Önder H. 2018. Nonparametric statistical methods used in biological experiments. BSJ Eng Sci, 1(1): 1-6.

Paik NC, Lim CS, Jang HS. 2013. Numeric and morphological verification of lumbosacral segments in 8280 consecutive patients. Spine, 38(10): 573-578.

Peterson CK, Bolton J, Hsu W, Wood A. 2005. A cross-sectional study comparing pain and disability levels in patients with low back pain with and without transitional lumbosacral vertebrae. J Manipulative Physiol Ther, 28(8): 570-574.

Uçar İ, Batın S, Arık M, Payas A, Kurtoğlu E, Karartı C, Unur E. 2022. Is scoliosis related to mastication muscle asymmetry and temporomandibular disorders? A cross-sectional study. Musculoskeletal Sci Pract, 58: 102533.

Uçar İ, Karartı C, Cüce İ, Veziroğlu E, Özüdoğru A, Koçak FA, Dadalı Y. 2021. The relationship between muscle size, obesity, body fat ratio, pain and disability in individuals with and without nonspecific low back pain. Clin Anatomy, 34(8): 1201-1207.

Ulger FEB, Illeez OG. 2020. The effect of lumbosacral transitional vertebrae (LSTV) on paraspinal muscle volume in patients with low back pain. Acad Radiol, 27(7): 944-950.

Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1560769

Open Access Journal
e-ISSN: 2619 – 9041

Research Article
Volume 7 - Issue 6: 253-261 / November 2024

NUTRITIONAL RISK, NUTRITIONAL STATUS AND SOME BIOCHEMICAL PARAMETERS IN ADULT BURN PATIENTS IN BURN INTENSIVE CARE UNIT: A PROSPECTIVE STUDY

Çiler ÖZENİR[1]*, Gül KIZILTAN[2]

[1]*Kırıkkale University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 71100, Kırıkkale, Türkiye*
[2]*Başkent University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 06790, Ankara, Türkiye*

Abstract: Nutritional therapy is very important in burn patients and plays a role in the prevention and treatment of malnutrition. Therefore, it is necessary to assess nutritional status, prevent or minimize nutritional problems, and monitor nutritional therapy. This study was conducted to determine the nutritional risk, nutritional status and biochemical parameters of adult burn patients in the burn intensive care unit. The 59 patients (women: 16, men: 43) between the ages of 19-64 were included in the study. Parameters such as NRS-2002 (admission and discharge), dietary intake, nutritional support status, serum albumin, and total protein (admission and discharge) were evaluated to determine the nutritional risk and nutritional status of the patients. In addition, body weight, mid-upper arm circumference, and triceps skinfold thickness were measured and body mass index was calculated (admission and discharge). The duration of hospitalization and burn percentage of men patients were higher than women ($P<0.05$). A significant decreases were determined in the mean body weight, body mass index, and triceps skinfold thickness of men patients at discharge compared to admission ($P<0.05$). In men patients, a statistically significant difference was found in serum albumin, hemoglobin, and hematocrit values between admission and discharge ($P<0.05$). A statistically significant difference was found in NRS-2002 scores at admission and discharge in both genders, and the scores increased ($P<0.05$). While a significant relationship was found between immunonutrition support and gender ($P<0.05$), no relationship was found between genders in terms of the diet given and the consumption status of the diet intake ($P>0.05$). No statistically significant difference was found between genders in terms of feeding duration with nutritional support products, energy intake with nutritional support products and diet, macronutrients, and total energy expenditure values ($P>0.05$). Since burn injuries can cause serious metabolic disorders, impaired nutritional status was encountered during hospitalization. While the treatment process was positively affected by the increase in the NRS-2002 score during hospitalization, a decrease in parameters such as albumin, total protein, and anthropometric measurement values brought about by the catabolic process was encountered. Therefore, to prevent or treat malnutrition, the nutritional status of patients should be evaluated at the time of hospitalization and they should be able to receive the necessary nutritional support.

Keywords: Burn, Nutritional risk, NRS-2002, Nutritional status, Albumin, Total protein

***Corresponding author:** Kırıkkale University, Faculty of Health Sciences, Department of Nutrition and Dietetics, 71100, Kırıkkale, Türkiye
E mail: cileraslanalp@gmail.com (Ç. ÖZENİR)
Çiler ÖZENİR https://orcid.org/0000-0002-9249-3935
Gül KIZILTAN https://orcid.org/0000-0001-5012-5838

Received: October 03, 2024
Accepted: October 31, 2024
Published: November 15, 2024

Cite as: Özenir Ç, Kızıltan G. 2024. Nutritional risk, nutritional status and some biochemical parameters in adult burn patients in burn intensive care unit: A prospective study. BSJ Health Sci, 7(6): 253-261.

1. Introduction

Burn injuries can cause serious metabolic disorders. Among critically ill patients, the group with the highest metabolic rate is burn patients (Ostadrahimi et al., 2016). Major burns increase this rate almost 2-fold (Shields et al., 2013). Therefore, it is recommended that energy and protein load be replaced well to limit metabolic deficit (Czapran et al., 2015).

Comprehensive nutritional therapy is of great importance in managing burn patients (Suri et al., 2006). If this goal is not achieved, malnutrition may develop (Rodriguez, 2004). Moreover, strong associations have been established between nutritional deficiencies in critically ill patients, prolonging the duration of intensive care or hospital stay, and increasing morbidity and mortality (Sungurtekin et al., 2008). Therefore, timely assessment of nutritional status in critically ill patients is important to prevent or minimize nutritional problems and monitor nutritional therapy (Hejazi et al., 2016).

Clinicians should determine the nutritional status of patients with appropriate assessment tools and reveal their need for nutritional support (Maday, 2017). Anthropometric measurements (such as body weight, height, body mass index, mid-upper arm circumference, triceps skinfold thickness), biochemical findings (such as total protein, albumin, and pre-albumin), immune markers (such as lymphocyte count), and nutritional screening tools can be used to determine the nutritional status of critically ill patients (Hejazi et al., 2016). However, certain limitations are encountered regarding anthropometric measurements and biochemical findings in burn patients (Machado et al., 2011). The frequently

used Nutritional Risk Screening 2002 (NRS-2002) is the tool recommended by The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines primarily for determining indications for nutritional support (Kondrup et al., 2003; Poulia et al., 2017).

This study was conducted to determine the nutritional risk, nutritional status and biochemical findings of adult burn patients in burn intensive care unit.

2. Materials and Methods

2.1. Participants

The study was carried out at the Burns Treatment Center of Ankara Numune Education and Research Hospital between November 1st, 2012 and March 1st, 2013 and among the hospitalized patients, 59 patients composed of 43 men and 16 women at the age range of 19 to 64 was included. All adult patients hospitalized between the dates of the study were included in the study.

2.2. Data Collection

An information form was applied within the scope of the study. The information form was prepared by the researchers as a result of the literature review and consists of six sections (sociodemographic and burn-related information, anthropometric measurements, biochemical parameters, NRS-2002 form, total energy requirements, dietary intake, and nutritional support status).

2.2.1. Anthropometric measurements

Height, body weight, body mass index (BMI), mid-upper arm circumference (MUAC), and triceps skinfold thickness (TSFT) were used as anthropometric measurements of the patients. Height was obtained from the patient file at admission. Body weight, MUAC, and TSFT were measured twice, at the time of admission and discharge. Body mass index (kg/m^2) values were calculated twice from the body weight (kg) and height (cm) measurements at the time of admission and discharge. Body mass index was calculated by dividing body weight by height in m^2 (WHO, 2010).

The body weight of patients who could stand up was determined using an electronic scale with ±0.1 kg sensitivity in the hospital, and the body weight of patients who could not stand up was determined using beds that could measure weight. It was measured by the MUAC and TSFT techniques (McDowell et al., 2008). Measurements of patients with arm burns could not be taken. TSFT was performed using a Holtain brand skinfold caliper. BMI was evaluated according to the World Health Organization (WHO) classification (WHO, 2010).

2.2.2. Biochemical assessment

It includes the standard parameters determined by the hospital for burn treatment. The patient's serum total protein, albumin, hemoglobin, and hematocrit values at admission and discharge were recorded in the information form.

2.2.3. Nutritional risk screening 2002 (NRS-2002) form

To determine the nutritional status of the patients, the NRS-2002 form was filled in twice, at admission and discharge. NRS-2002 was developed by Kondrup et al. in 2002 (Kondrup et al., 2003). Its validity and reliability in Turkish were performed by Bolayır in 2014. It has been shown that NRS-2002 is a valid and reliable method that can be used in hospitalized patients (Bolayır, 2014). This form aims to detect inadequate nutrition and malnutrition risk and to identify patients who may benefit from nutritional support. It is recommended by ESPEN to reveal possible conditions or changes that improve or worsen after illness or surgery (Lochs et al., 2006). The scoring system consists of two sections, 'nutritional status' and 'disease severity', and provides scoring as "no problem", "mild", "moderate" and "severe". Scoring is between 0-3 for each section. In patients over the age of 70, an additional 1 point is added to the score due to age, and patients with a total score of ≥3 are considered to be at nutritional risk (Kreymann et al., 2006; Nişancı Kılınç et al., 2023).

2.2.4. Total energy requirement

The total energy requirements of patients at admission were calculated using the Curreri formula (equation 1) (Chan et al., 2018), which incorporates the total body surface area (TBSA) burn.

Curreri formula: (25 kcal × body weight) + (40 kcal × %TBSA), when the TBSA is >50%, it is calculated as 50%. (1)

2.2.5. Dietary intake and nutritional support status

The nutritional intake of the patients was determined according to the percentage of the hospital diet given to them that was consumed. The nutritional intake of the patients was determined by the researcher's follow-up, the patient's declaration, and the waste control results of the nurses and waiters working in the hospital. The patients' menus were obtained from the hospital's responsible dietician. If the patient's hospitalization period was more than 7 days, energy and nutrients were determined according to the average dietary intake of 7 randomly selected days. If the patient's hospitalization period was less than 7 days, all intakes during the hospitalization period were evaluated. The energy and nutrients taken were calculated in the "Computer Assisted Nutrition Program, Nutrition Information System (BEBIS) 6.1" program developed for Turkey. In addition, enteral or parenteral nutrition product usage was determined and evaluated in terms of energy and nutrients.

2.2.6. Statistical analysis

Statistical analyses of the data were performed using IBM SPSS for Windows Version 21.0 package program. Numerical variables are shown as mean±standard deviation ($\bar{X}$±SD), categorical variables are shown as number (n) and percentage (%), and Median (min-max). Before comparing the groups in terms of numerical

variables, parametric test assumptions (normality and homogeneity of variances) were checked. Whether the numerical variables showed normal distribution was evaluated with the Shapiro-Wilks test. The homogeneity of the variances of the compared groups was examined using the Levene test. If the parametric test assumptions were met, a one-way analysis of variance was used to investigate whether there was a difference between two independent groups in terms of numerical variables. If the parametric test assumptions were not met, Mann Whitney U test was used in comparisons between groups, and the Wilcoxon signed rank test was used in dependent sample comparisons within groups. Whether there was a difference between groups in terms of categorical variables was examined with chi-square goodness of fit and Chi-square independence test or Fisher's exact test. The significance level was determined as P<0.05 (Önder, 2018).

3. Results

The mean age of the patients was 41±14.87 years (45.50±16.74 years in women, 39.49±13.98 years in men) (P=0.170). The hospitalization period of women patients were 14.68±10.53 days, while it was 24.97±17.51 days for male patients (P=0.026). The mean burn percentage of women patients was 4.68±4.04, and men patients were 17.00±22.85 (P=0.010). A statistically significant dependence was found between burn type and gender (P=0.001). The observed dependence was because hot liquid burns were higher in women (68.8%), flame burns were higher in men (58.1%), and electrical burns were higher in men (14.0%). It was determined that lower arm, upper arm, hand, face, and trunk burns were more common in men than in women (P<0.05). First and fourth degree burns were more common in men but not in women (P<0.05) and second degree deep burns were more common in women than in men (P=0.008) (Table 1).

There was no statistically significant difference among genders regarding body weight, BMI, MUAC, and TSFT at admission and discharge (P>0.05). A decrease was determined in body weight, BMI, and TSFT values of men patients at discharge compared to admission (P<0.05).

Table 1. Age of patients, duration of hospitalization and burn status

	Women (n=16)		Men (n=43)		Total (n=59)		
	n	%	n	%	n	%	P
Age, year (Mean±SD)	45.50±16.74		39.49±13.98		41.00±14.87		0.170[a]
Hospitalization day (Mean±SD)	14.68±10.53		24.97±17.51		22.18±16.49		0.026[a]
TBSA burn, % (Mean±SD)	4.68±4.04		17.00±22.85		13.66±20.32		0.010[a]
Burn cause							
Hot liquid	11	68.8	6	14.0	17	28.8	
Flame	4	25.0	25	58.1	29	49.2	
Contact	1	6.3	4	9.3	5	8.5	0.001[b]
Electric	-	-	6	14.0	6	10.2	
Chemical	-	-	2	4.7	2	3.4	
Burn area*							
Lower leg	8	50.0	18	41.9	26	44.1	0.404[c]
Upper leg	4	25.0	16	37.2	20	33.9	0.128[c]
Lower arm	1	6.3	11	25.6	12	20.3	0.001[c]
Upper arm	3	18.8	15	34.9	18	30.5	0.029[c]
Hand	3	18.8	20	46.5	23	39.0	0.001[c]
Face	3	18.8	20	46.5	23	39.0	0.001[c]
Head	1	6.3	3	7.0	4	6.8	0.782[c]
Neck	-	-	6	14.0	6	10.2	0.058[c]
Foot	6	37.5	11	25.6	17	28.8	0.134[c]
Trunk	3	18.8	15	34.9	18	30.5	0.029[c]
Burn depth*							
First degree	-	-	4	9.3	4	6.8	0.011[c]
Superficial second degree	5	31.3	16	37.2	21	35.6	0.467[c]
Deep second degree	14	87.5	24	55.8	38	64.4	0.008[c]
Third degree	4	25.0	17	39.5	21	35.6	0.063[c]
Forth degree	-	-	3	7.0	3	5.1	0.034[c]

TBSA= total body surface area, * More than one option is marked, [a] Mann-Whitney U test, [b] Chi square independence test, [c] Chi square goodness of fit test..

Table 2. Anthropometric measurements, biochemical findings and NRS-2002 scores of the patients at admission and discharge

	Women (n=16)	Men (n=43)	Total (n=59)	P
	Mean±SD	Mean±SD	Mean±SD	
Height (m)	1.61±0.06	1.70±0.07	1.68±0.07	<0.001[y]
Body weight (kg) (A)	72.43±12.00¶	75.70±12.58¶	74.84±12.41¶	0.386[y]
Body weight (kg) (D)	72.33±12.00¶	74.56±13.05§¶	73.93±12.69§¶	0.569[y]
P	0.823[a]	0.006[a]	0.008[a]	
BMI (kg/m^2) (A)	27.73±5.44¶	25.92±4.31¶	26.40±4.65¶	0.198[y]
BMI (kg/m^2) (D)	27.67±5.29¶	25.64±4.63§¶	26.21±4.86§¶	0.172[y]
P	0.725[a]	0.007[a]	0.009[a]	
MUAC (cm) (A)	31.75±2.89¥	30.55±4.17¥	30.82±3.89¥	0.520[y]
MUAC (cm) (D)	31.83±7.14¥	30.32±3.77§¥	30.67±3.56§¥	0.375[y]
P	0.771[a]	0.342[a]	0.420[a]	
TSFT (mm) (A)	17.83±11.09¥	10.75±2.89¥	12.38±6.34¥	0.196[z]
TSFT (mm) (D)	17.83±10.72¥	10.45±2.94§¥	12.15±6.29§¥	0.139[z]
P	1.000[b]	0.047[b]	0.057[b]	
Total protein, mg/dl (A)	67.8±6.51	63.3±11.14	64.3±10.40	0.264[y]
Total protein, mg/dl (D)	63.7±6.65	58.8±12.61§	59.4±12.06§	0.525[y]
P	0.344[a]	0.987[a]	0.921[a]	
Albumin, g/dl (A)	40.5±5.18	39.1±8.08	39.4±7.47	0.576[y]
Albumin, g/dl (D)	33.3±9.86	37.5±13.93§	37.0±13.38§	0.546[y]
P	0.823[a]	0.008[a]	0.008[a]	
Hemoglobin, g/dl (A)	12.4±2.67	14.6±2.54	14.1±2.7	0.005[y]
Hemoglobin, g/dl (D)	10.7±2.35	11.3±2.49§	11.2±2.44§	0.600[y]
P	0.270[a]	<0.001[a]	<0.001[a]	
Hematocrit, % (A)	38.2±6.81	43.6±7.10	42.2±7.36	0.014[y]
Hematocrit, % (D)	34.5±6.61	34.8±7.24§	34.7±7.03§	0.973[y]
P	0.370[a]	<0.001[a]	<0.001[a]	
NRS-2002 score (A)	0.50±0.89	0.86±1.20	0.76±1.13	0.282[y]
NRS-2002 score (D)	1.62±1.02	2.37±1.21§	2.16±1.20§	0.033[y]
P	0.002[a]	<0.001[a]	<0.001[a]	

A= admission, D= discharge, BMI= body mass index, MUAC= mid-upper arm circumference, TSFT= triceps skinfold thickness, NRS-2022= nutritional risk screening 2002, ¶The body weights of one women and one men patient could not be measured during hospitalization due to the severity of the illness, § Four men patients died during the study, ¥ Measurements could not be taken in 3 women and 15 men patients due to upper arm burns, [a] t-test in dependent samples, [b] Wilcoxon signed rank test in dependent samples, [y] ANOVA, [z] Mann-Whitney U test.

No statistically significant difference was determined within genders for MUAC values at admission and discharge (P>0.05). No statistically significant difference was determined between genders regarding total protein value and within genders at admission and discharge (P>0.05). A statistically significant difference was determined in serum albumin, hemoglobin, and hematocrit values between admission and discharge in men patients (P<0.05). Serum albumin, hemoglobin and hematocrit values of men patients decreased. A statistically significant difference was determined between genders in terms of the NRS-2002 score at discharge (P<0.05), and it was found that the NRS-2002 score was lower in women than in men. A statistically significant difference was determined in NRS-2002 scores at admission and discharge in both genders (P<0.05). The NRS-2002 scores of the patients increased (Table 2).

In BMI classification, it was determined that BMI scores at admission and discharge were not dependent on gender (P>0.05). There was no statistically significant difference between BMI values at admission and discharge in women patients (P>0.05), but there was a significant difference in men patients (P<0.05), and the BMI value of men patients decreased (Table 3).

No significant differences were determined between food consumption and gender (P>0.05). It was determined that there was a significant relationship between immunonutrition support and gender (P<0.05); it was determined that there was no need for immunonutrition support in women patients. It was determined that there was a significant relationship between trace element support and gender (P<0.05), and that trace element support was used more in men patients than in women patients. No relationship was determined with gender in terms of the diet given and the consumption status of the given diet (P>0.05) (Table 4).

Table 3. Distribution of patients' BMI values at admission and discharge according to the World Health Organization classification

BMI classification	Women (n=16)		Men (n=43)		Total (n=59)		
	n	%	n	%	n	%	P
BMI, kg/m² (A)¶							
18.5-24.9 normal	6	40.0	17	40.5	23	40.4	
25.0-29.9 overweight	4	26.7	20	47.6	24	42.1	
30.0-34.9 obesity class I	4	26.7	3	7.1	7	12.3	
35.0-39.9 obesity class II	-	-	2	4.8	2	3.5	0.088[a]
≥40.0 obesity class III	1	6.6	-	-	1	1.7	
BMI, kg/m² (D) ¶§							
<18.5 underweight	-	-	1	2.6	1	1.9	
18.5-24.9 normal	6	40.0	17	44.7	23	43.4	
25.0-29.9 overweight	4	26.7	15	39.5	19	35.8	
30.0-34.9 obesity class I	4	26.7	4	10.5	8	15.1	0.504[a]
35.0-39.9 obesity class II	1	6.7	1	2.6	2	3.8	
BMI (A) [Median (Min-Max)]	3 (2:6)		3 (2:5)		3 (2:6)		0.389[c]
BMI (D) [Median (Min-Max)]	3 (2:5)		3 (1:5)		3 (1:5)		0.274[c]
P	0.317[b]		0.046[b]		0.025[b]		

BMI= body mass index, A= admission, D= discharge, ¶ The body weights of one women and one men patient could not be measured during hospitalization due to the severity of the illness, § Four men patients died during the study, [a] Chi-square test of independence, [b] Wilcoxon signed rank test, [c] Mann-Whitney U test.

Table 4. Patients' food consumption, immunonutrition and trace element support, and dietary status

	Women (n=16)		Men (n=43)		Total (n=59)		
	n	%	n	%	n	%	P
Food consumption							
Only oral	15	93.8	28	65.1	43	72.9	
Oral+Enteral	1	6.2	12	28.0	13	22.0	0.178
Oral+Parenteral	-	-	1	2.3	1	1.7	
Not fed	-	-	2	4.6	2	3.4	
Immunonutrition support							
Yes	-	-	13	30.2	13	22.0	0.009
No	16	100.0	30	69.8	46	78.0	
Trace element support							
Yes	5	31.3	27	62.8	32	54.2	0.031
No	11	68.8	16	37.2	27	45.8	
Diet type							
Normal diet	12	75.0	36	83.7	48	81.4	
Diabetic diet	1	6.3	1	6.3	2	3.4	
Salt-free diet	1	6.3	2	4.7	3	5.1	
Heart protective diet	-	-	1	2.3	1	1.7	0.272
Diabetic & salt-free diet	2	12.5	-	-	2	3.4	
Heart protective & salt-free diet	-	-	1	2.3	1	1.7	
Not fed	-	-	2	4.7	2	3.4	
Percentage of diet consumption							
%100	9	56.3	24	55.8	33	55.9	
%75	4	25.0	9	20.9	13	22.0	0.842
%50	3	18.8	8	18.6	11	18.6	
%0	-	-	2	4.7	2	3.4	

Chi-square test of independence.

There were no statistically significant difference was found between genders in terms of the duration of feeding with nutritional support products, the energy intake with nutritional support products and diet, macronutrient elements, and total energy expenditure values (P>0.05) (Table 5).

Table 5. The duration of patients' nutritional support, the energy and macronutrient intake with nutritional support and diet, and total energy requirement values

	Women (n=16)	Men (n=43)	Total (n=59)	
	Mean±SD	Mean±SD	Mean±SD	P
Duration of enteral feeding (day)	12.00	18.00±14.41	17.57±13.94	
Duration of parenteral feeding (day)	-	30.00	30.00	
Duration of feeding with immunonutrition product (day)	-	26.07±14.16	26.07±14.16	0.901[a]
Energy intake with enteral product (kcal)	505.00	814.70±334.54	797.50±332.66	
Carbohydrates intake with enteral product (g)	64.00	120.56±52.52	117.42±52.67	0.489[a]
Protein intake with enteral product (g)	20.00	38.65±14.17	117.42±52.67	0.138[a]
Fat intake with enteral product (g)	18.50	19.77±9.02	19.70±8.76	0.196[a]
Energy intake with parenteral product (kcal)	-	108.00	108.00	0.921[a]
Protein intake with parenteral product (g)	-	27.00	27.00	
Dietary energy (kcal)	1834.32±480.04	1900.40±609.21	1861.00±88.20	0.698[b]
Dietary protein (g)	77.13±20.18	79.91±25.61	78.40±17.60	0.698[b]
Dietary protein (%TE)	16.57±4.33	17.17±5.50	17.10±3.43	0.698[b]
Dietary fat (g)	103.59±27.11	107.32±34.40	104.20±7.44	0.698[b]
Dietary fat (%TE)	36.56±9.56	37.87±12.14	37.30±2.81	0.698[b]
Dietary carbohydrates (g)	270.93±70.90	280.69±89.98	274.10±21.60	0.698[b]
Dietary carbohydrates (%TE)	44.23±11.57	45.82±14.69	45.10±3.33	0.698[b]
TER (with the Curreri formula) (kcal)	1912.46±259.71	2428.50±833.39	2292.70±760.21	0.543[b]

TE= Total energy, TER= Total energy requirement, [a] Mann-Whitney U test, [b] ANOVA.

4. Discussion

Non-fatal burn injuries are among the leading causes of morbidity in the world. Depending on the degree and size of burns, they cause a stress response and metabolic changes in the body. In order to create an adequate response to these changes in the burn patient, it is necessary to determine the nutritional status and nutritional risk of the burn patient. Adequate nutrition increases anabolic metabolism, accelerates wound healing and shortens the length of hospital stay of the burn patient (Karahan et al., 2021). Therefore, this study was conducted to determine the nutritional risk, nutritional status and biochemical findings of adult burn patients in burn intensive care unit.

In this study, the average age of the hospitalized burn patients was 41.00±14.87 years. In a study conducted by Sözen et al., the average age was 32.55±21.96 years (Sözen et al., 2015). While the TBSA burn was %22.18±16.49, it was determined as %16.0±18.2 in another study (Gürbüz and Demir, 2022). While the patients were most frequently burned by flames, another study determined that the most common cause of burns was hot liquids (74.2%) (Albayrak et al., 2018). In this study, the most common burns were in the lower leg region of the body and second-degree deep burns were detected. In contrast, in another study, it was found that the upper and lower extremities were the most frequently burned areas compared to other parts of the body and second-degree superficial burns were encountered most frequently (Sözen et al., 2015). Since burns are traumatic events that occur unexpectedly, it is thought that a wide variety of results can be encountered in the literature regarding the descriptive data of patients regarding age and burns.

In this study, anthropometric measurements such as body weight, BMI, MUAC, and TSFT were used. In this study, it was found that burn patients lost 0.9 kg (loss rate 1.2%) of their body weight from admission to discharge. In a study, burn patients lost an average of 5.8 kg (loss rate 8.1%) during hospitalization (Windle, 2004). Although less body weight loss was determined than in the literature, it was thought that the loss could have been greater. The body weight at follow-up may not reflect the truth due to reasons such as the patients being exposed to dressings with wet gauze and experiencing intense edema. From another perspective, it is also possible to regain the weight lost during hospitalization. The complexity of the clinical course of burn patients and the fact that sometimes the desired intervention cannot be made cause difficulties in obtaining anthropometric measurements.

In this study, it was determined that the BMI value of burn patients at admission was mostly in the range of 25.0-29.9 kg/m^2 (%42.1), and at discharge it was mostly in the range of 18.5-24.9 kg/m^2 (%43.4) ($P<0.05$). In a study, it was reported that 13.2% of burn patients had a BMI below 20 kg/m^2 at admission, while 28.9% of patients had a BMI below 20 kg/m^2 at discharge (Windle, 2004). In this study, the mean MUAC of women burn patients at admission was 31.7 cm and 31.8 cm at discharge; and for men, it was determined as 30.5 cm at admission and 30.3 cm at discharge ($P>0.05$). The TSFT measurement mean was similar for women for admission and discharge, while a decrease was found in men ($P<0.05$). As far as is known, there is no study in the literature that determines the changing MUAC and TSFT

values of burn patients from hospital admission to discharge. It is also important to examine the subcutaneous fat tissue and muscle tissue in hospitalized patients. Therefore, information can be obtained about how much the decreased body weight and BMI detected in the study are related to fat and/or muscle loss thanks to MUAC and TSFT.

Some biochemical parameters such as serum total protein, albumin, hemoglobin, and hematocrit are also used to determine nutritional risk (Durmuş et al., 2016). Blood concentration of albumin and total protein decreases in poor nutritional status and inflammation. In clinical practice, albumin is considered a negative acute phase protein (Kuşcu et al., 2021). In this study, it was determined that serum total protein, albumin, hemoglobin, and hematocrit values in the blood decreased in both genders from admission to discharge, by the literature. However, the decrease in serum albumin, hemoglobin, and hematocrit values only in men was found to be statistically significant ($P<0.05$).

Nutritional risk is defined by ESPEN as "the chance of a better or worse outcome from disease or surgery according to actual or potential nutritional and metabolic status" (Lochs et al., 2006). In this study, the total NRS-2002 score was found to be below three in both genders both at admission and discharge. An increase in the total score was found in both men and women during the period from admission to discharge ($P<0.05$). This situation shows that the patients were not at nutritional risk. It is thought that the increase in the total NRS-2002 score at discharge was because no significant weight loss occurred during hospitalization and that the necessary interventions were made for patients who needed nutritional support. In addition, the patients were mostly able to eat orally and had sufficient energy.

Immunonutrition supplementation can also be administered to burn patients who need nutritional support. Guidelines do not provide definitive recommendations on the use of these products. Although it is difficult to recommend a definitive dose, route of administration, or duration of administration for glutamine, it is an amino acid that becomes necessary for burn patients depending on the situation. It can be mentioned that it positively affects infectious complications, hospital stay, and mortality. There is no evidence to recommend arginine supplementation in burn patients (Rousseau et al., 2013). In this study, it was determined that 22% of the patients received both enteral products and immunonutrition support.

In this study, it was determined that burn patients were fed with an average of 1861 kcal diet. While one study determined that patients consumed an average of 2000 kcal per day and were in a positive energy balance, another study found that the average daily energy intake of patients was 1700-2300 kcal (Herndon et al., 2001; Douglas et al., 2007). The balance of macronutrients is as important as the adequacy of energy intake in the nutrition of burn patients. Carbohydrates are well known as the main energy source for burn patients, but high carbohydrate intake can lead to hyperglycemia, increased exogenous insulin requirements, and delayed wound healing. Adequate fat consumption reduces the patient's carbohydrate needs and prevents essential fatty acid deficiencies. However, excessive fat intake may hurt the immune function of burn patients. Protein is essential for burn patients and protein requirements are increased (Ren et al., 2023). ESPEN reports that the proportion of total energy coming from carbohydrates should be limited to 60% and the proportion coming from lipids should be <30% (Rousseau et al., 2013). In contrast to the recommendations in this study, the proportions were determined as 37.30% for fat and 45.10% for carbohydrates. Diets containing 25-40% fat can be widely used in the early stages of the diet of burn patients (Saffle, 2007). This situation allows fat to come to the forefront due to its high energy supply and low CO_2 production. However, it was concluded from this study that the diet pattern to be given to burn patients should be better adjusted. Dietary protein should be increased a little more, and foods containing direct fat should be reduced and replaced with healthy carbohydrate sources.

5. Conclusion

Burn patients may be at nutritional risk depending on the burn percentage and area. This may affect treatment, hospitalization time, and survival. Therefore, the nutritional and nutritional risk status of burn patients receiving inpatient treatment should be monitored. Because a decrease is detected in the anthropometric measurements and biochemical findings of the patients during their hospitalization. Patient-specific anthropometric measurements such as BMI, MUAC, TSFT, NRS-2002 form, biochemical parameters such as serum total protein, albumin, and hemoglobin, and the amount of hospital food consumed can be used. In this way, the necessary nutritional support can be provided to every new patient to prevent or treat malnutrition.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	Ç.Ö.	G.K.
C	60	40
D	60	40
S	70	30
DCP	100	
DAI	70	30
L	100	
W	80	20
CR	40	60
SR	70	30
PM	70	30

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Approval/Informed Consent

This study was approved by Ethics Committee of Başkent University Non-Interventional Clinical Trials (approval date: April 03, 2013, protocol code: 13/45). A signed written consent form was obtained from each participant by face-to-face interview.

Acknowledgement

This article is extracted from Çiler Özenir's Master's thesis entitled "The determination of nutritional status and biochemical findings of burn patients undergoing inpatient treatment", supervised by Prof. Dr. Gül Kızıltan (Master's Thesis, Başkent University, Ankara, Türkiye, 2013). We would like to thank burn intensive care unit chief, Prof. Dr. Ahmet Çınar YASTI, from whom we had the opportunity to benefit from their experiences, and moral support throughout the study.

References

Albayrak Y, Temiz A, Albayrak A, Peksöz R, Albayrak F, Tanrıkulu Y. 2018. A retrospective analysis of 2713 hospitalized burn patients in a burns center in Turkey. Turkish J Trauma Emerg Surg, 24(1): 25-30.

Bolayır B. 2014. A validity and reliability study of nutritional assessment method NRS-2002 (Nutritional Screening Test-2002) in hospitalized patients. Internal Medicine Speciality Thesis, Hacettepe University, Institute of Health Sciences, Ankara, Türkiye, pp: 61.

Chan LC, Lee MS, Ou YN, Cheng HL, Wang CH. 2018. Energy requirements for ICU burn patients in whom the total body surface area affected exceeds 50 percent: a practical equation. Asia Pac J Clin Nutr, 27(6): 1182-1189.

Czapran A, Headdon W, Deane AM, Lange K, Chapman MJ, Heyland DK. 2015. International observational study of nutritional support in mechanically ventilated patients following burn injury. Burns, 41(3): 510-518.

Douglas CC, Lawrence JC, Bush NC, Oster RA, Gower BA, Darnell BE. 2007. Ability of the Harris Benedict formula to predict energy requirements differs with weight history and ethnicity. Nutr Res, 27(4): 194-199.

Durmuş M, Muhsiroğlu Ö, Yapici AK, Bayram Y, Eski M. 2016. Yanıkta tıbbi beslenme tedavisi. Turk J Plast Surg, 24(4): 166-172.

Gürbüz K, Demir M. 2022. Epidemiological and clinical characteristics and outcomes of inpatient burn injuries in older adults. Turkish J Trauma Emerg Surg, 28(2): 162-169.

Hejazi N, Mazloom Z, Zand F, Rezaianzadeh A, Amini A. 2016. Nutritional assessment in critically ill patients. Iran J Med Sci, 41(3): 171-179.

Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. 2001. Reversal of catabolism by beta-blockade after severe burns. N Engl J Med, 345: 1223-1229.

Karahan S, Sezer Ceren RE, Ünsaldı M. 2021. Yanık hastasının beslenme gereksinimi: güncel öneriler. CUSBED, 6(3): 249-258.

Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, An ad hoc ESPEN Working Group. 2003. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr, 22(3): 321-336.

Kreymann KG, Berger MM, Deutz NEP, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, DGEM, Ebner C, Hartl W, Heymann C, Spies C, ESPEN. 2006. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr, 25(2): 210-223.

Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider St, van den Berghe G, Pichard C. 2006. Introductory to the ESPEN guidelines on enteral nutrition: terminology, definitions and general topics. Clin Nutr, 25(2): 180-186.

Machado MN, Gragnani A, Ferreira ML. 2011. Burns, metabolism and nutritional requirements. Nutr Hosp, 26(4): 692-700.

Maday KR. 2017. The importance of nutrition in critically ill patients. JAAPA. 30(1): 32-37.

McDowell MA, Fryar CD, Ogden CL, Flegal KM. 2008. Anthropometric reference data for children and adults: United States, 2003–2006. Natl Health Stat Rep, 22(10): 1-48.

Nişancı Kılınç F, Özenir Ç, Eşer Durmaz S, Bayındır Gümüş A, Çakır B. 2023. Determination of malnutrition and quality of life at the time of hospitalization of patients. BSJ Health Sci, 6(4): 640-649.

Önder H. 2018. Nonparametric statistical methods used in biological experiments. BSJ Eng Sci, 1(1): 1-6.

Ostadrahimi A, Nagili B, Asghari-Jafarabadi M, Beigzali S, Zalouli H, Lak S. 2016. A proper enteral nutrition support improves sequential organ failure score and decreases length of stay in hospital in burned patients. Iran Red Crescent Med J, 18(2): e21775.

Özkan Kuşcu Ö, Aktay M, Destegül D, Kuşcu F, Özcengiz D. 2021. Yoğun bakım hastalarında inflamasyon belirteçlerinin mortalite tahmininde kullanımı. Kırıkkale Üniv Tıp Fak Derg, 23(1): 75-82.

Poulia KA, Klek S, Doundoulakis I, Bouras E, Karayiannis D, Baschali A, Passakiotou M, Chourdakis M. 2017. The two most popular malnutrition screening tools in the light of the new ESPEN consensus definition of the diagnostic criteria for malnutrition. Clin Nutr, 36(4): 1130-1135.

Ren Y, Wang L, Zhan J, Liao W, Hu R, Luo J, Cheng X. 2023. An overview of current research on nutritional support for burn patients: A bibliometric analysis from 1983 to 2022. Nutrition, 111: 112027.

Rodriguez L. 2004. Nutritional status: assessing and

understanding its value in the critical care setting. Crit Care Nurs Clin North Am, 16(4): 509-514.

Rousseau AF, Losser MR, Ichai C, Berger MM. 2013. ESPEN endorsed recommendations: nutritional therapy in major burns. Clin Nutr, 32: 497-502.

Saffle JR. 2007. Nutritional support of the burned patient. In Herndon DN, editor. Total burn care. Elsevier Health Sciences, Amsterdam, the Netherland, pp: 398-419.

Shields BA, Doty KA, Chung KK, Wade CE, Aden JK, Wolf SE. 2013. Determination of resting energy expenditure after severe burn. J Burn Care Res, 34(1): e22-8.

Sözen İ, Guldogan CE, Kismet K, Sabuncuoğlu MZ, Yasti AÇ. 2015. Outpatient burn management and unnecessary referrals. Turkish J Trauma Emerg Surg, 21(1): 27-33.

Sungurtekin H, Sungurtekin U, Oner O, Okke D. 2008. Nutrition assessment in critically ill patients. Nutr Clin Pract, 23(6): 635-641.

Suri MP, Singh Dhingra VJ, Raibagkar SC, Mehta DR. 2006. Nutrition in burns: need for an aggressive dynamic approach. Burns, 32(7): 880-884.

WHO. 2010. World Health Organization: A healthy lifestyle - WHO recommendations. URL= https://www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations (accessed date: August 1, 2024).

Windle EM. 2004. Audit of successful weight maintenance in adult and paediatric survivors of thermal injury at a UK regional burn centre. J Hum Nutr Dietet, 17: 435-441.

Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1538574

Open Access Journal
e-ISSN: 2619 – 90410

Book Review
Volume 7 - Issue 6: 262-266 / November 2024

BOOK REVIEW: NO MORE KIDNEY STONES

Hülya Gözde ÖNAL[1]*

[1]*Samsun Training and Research Hospital, Department of Pediatric Nephrology, 55090 Samsun, Türkiye*

Abstract: The book "No more kidney stones" is a significant work for understanding the complex world of kidney stone disease. It provides comprehensive information from the formation of kidney stones to treatment options, offering essential guidance for both patients and healthcare professionals. The book emphasizes the importance of a multidisciplinary approach by detailing modern medications and surgical interventions, as well as the roles of various medical specialties in the treatment of kidney stones. The authors aim to raise awareness and develop more effective methods in the treatment of kidney stone disease. The sections cover the formation, symptoms, and treatment methods of kidney stones, diet and lifestyle changes, risk factors, modern medical interventions, and multidisciplinary treatment approaches. The book presents a comprehensive overview of the pathophysiology, diagnostic methods, and treatment options for kidney stone disease. It offers scientifically based guidance, emphasizing the complexity of the disease and the need for a multidisciplinary approach to its management. The importance of customized diagnostic and treatment approaches according to patients' individual characteristics is detailed in each section. The book serves as a valuable reference for anyone seeking information on kidney stone disease, providing practical information for clinical practice. This work enhances nephrologists' professional competence by offering extensive and in-depth knowledge, allowing them to develop a deeper and more comprehensive understanding of kidney stone disease.

Keywords: Kidney stone, Kidney disease, Nephrology, Book review

***Corresponding author:** Samsun Training and Research Hospital, Department of Pediatric Nephrology, 55090 Samsun, Türkiye
E mail: drhulyagozde@hotmail.com (H. G. ÖNAL)
Hülya Gözde ÖNAL https://orcid.org/0000-0002-3691-0933

Received: August 26, 2024
Accepted: September 30, 2024
Published: November 15, 2024

Cite as: Önal HG. 2024. Book review: No more kidney stones. BSJ Health Sci, 7(6): 262-266.

1. Book Review

Rodman JS, Sosa RE, Seidman C. 2007. No More Kidney Stones: The Experts Tell You All You Need to Know about Prevention and Treatment. John Wiley & Sons, New York, US, pp: 288.

"No More Kidney Stones" is an essential work for understanding the complex world of kidney stone disease. The book is divided into three main sections, each offering a detailed explanation through subsections and examples. By covering a wide range of topics, from the formation of kidney stones to treatment options, it provides valuable guidance for both patients and healthcare professionals. The book highlights the importance of a multidisciplinary approach, detailing the role of various medical specialties involved in the management of this condition, alongside modern medications and surgical interventions used in kidney stone treatment. The authors aim to raise awareness and promote the development of more effective treatments for kidney stone disease through this work, enriched with both scientific and practical insights.

The first section comprises 13 chapters. It begins with an explanation of what kidney stones are, followed by a description of how they form, their symptoms, and medical interventions. It provides information on the different types of kidney stones and the distinct causes associated with each type. The authors explain that kidney stones vary in chemical composition, with calcium oxalate stones being the most common. They emphasize the role of genetic factors, dietary habits, and lifestyle in the formation of these stones.

The rising incidence of kidney stones is likely attributable to dietary and environmental factors. In most pediatric patients, the etiology of kidney stones can be determined, with metabolic factors such as hypercalciuria and hypocitraturia, urinary tract infections, and urinary stasis being the primary causes. Additionally, the negative impact of excessive sodium intake, the link between inadequate fluid consumption and stone formation, and the role of plant-based diets in reducing urinary crystal formation compared to animal protein intake are discussed.

In approximately half of pediatric patients, the etiology of kidney stones is related to genetic or lifestyle-driven metabolic factors. A quarter of patients have urinary tract infections, and 20% experience urinary obstruction or stasis. Some researchers suggest that the Western diet, characterized by high protein and salt intake and low vegetable consumption, is a major contributing factor to the increasing prevalence of kidney stones, due to its association with environmental and dietary habits such as hypomagnesiuria and low urine volume (Edvardsson et al., 2018).

Pediatric patients with kidney stones present with

different symptoms depending on their age group. While adolescents commonly report flank pain, younger children may exhibit more vague symptoms such as nausea, vomiting, and irritability (Chu et al., 2016). Although hypercalciuria is considered one of the most significant etiological factors, a study suggests that hypocitraturia accounts for 58% of metabolic causes, followed by hypercalciuria at 48.3%, hyperuricosuria at 2.2%, and hyperoxaluria at 4.4% (Kovacevic et al., 2012).

Disruptions in calcium metabolism are among the most common metabolic abnormalities in pediatric and adolescent kidney stone patients, which could potentially be addressed. Although collecting 24-hour urine samples in children can be challenging for metabolic evaluation, the use of solute/creatinine ratios in spot urine samples can be helpful. Most reference ranges for lithogenic substances in urine are age-dependent.

Hereditary metabolic disorders are also associated with nephrolithiasis (NL). In the differential diagnosis of pediatric stone disease, conditions such as phosphoribosyltransferase (APRT) deficiency, cystinuria, Dent disease, hypercalciuria, nephrocalcinosis (FHHNC), familial hypomagnesemia, and primary hyperoxaluria should be considered. It is known that these disorders, except for cystinuria, often lead to chronic kidney disease (CKD). Children with these conditions typically experience kidney stone attacks within the first decade of life, and recurrent stone formation is commonly observed (Edvardsson et al., 2018).

A basic blood panel assessment should be performed in all patients with kidney stones. In addition to routine biochemical tests, measuring serum phosphorus, uric acid, and bicarbonate levels may also be beneficial (Goldfarb and Arowojolu, 2013). Kidney function should be regularly evaluated, both initially and in the following years. If the initial metabolic assessment (spot urine) does not show abnormalities, it is recommended to measure levels of cystine, magnesium, glycolate, glycerate, and glyoxylate in a 24-hour urine analysis (Yang et al., 2017).

In the section addressing kidney stone treatment methods, the authors discuss surgical interventions and lithotripsy. However, they emphasize that the primary focus should be on preventing stone formation, with an emphasis on dietary and lifestyle modifications. In this context, the importance of which foods to consume or avoid, the significance of fluid intake, and the effects of regular physical activity in reducing the risk of kidney stones are thoroughly explored.

In the second section, which comprises 9 subheadings, the authors emphasize the importance of dietary and lifestyle changes in preventing kidney stone formation. Implementing such changes as a strategy for preventing kidney stones is regarded as a crucial prevention method that requires a multidisciplinary approach in modern medicine. Particularly in the field of urology, research has shown that dietary habits are a determining factor in kidney stone formation and that overly restrictive diets are often unsustainable (Linder et al., 2013; Malieckal and Goldfarb, 2020). Although dietary changes are recommended to reduce the risk of kidney stones, instead of strict restrictions, modifying current dietary habits in a reasonable manner is suggested. In this section, the authors provide an in-depth analysis of the effects of dietary and lifestyle changes on kidney stone formation, offering strategies tailored to individual needs.

When making dietary recommendations for kidney stone patients, individual differences should be taken into account. A personalized diet plan should be developed by considering the patient's medical history, stone type, metabolic analyses, and lifestyle (Siener and Hesse, 2002). Generally, it is more effective to make strategic changes while preserving existing eating habits, rather than completely restructuring the diet to address habits that contribute to kidney stone formation. For instance, limiting excessive animal protein consumption and controlling oxalate and sodium intake are changes that allow patients to maintain the diet plan in the long term. Linder et al. (2013) highlighted in their research that excessive protein consumption is one of the factors contributing to kidney stones, and thus, protein intake should be carefully planned (Linder et al., 2013).

Increasing fluid intake plays a critical role in preventing kidney stone formation. Specifically, maintaining a daily urine output of at least 2-2.5 liters minimizes the risk of stone formation by reducing urine concentration (Malieckal and Goldfarb, 2020). Insufficient fluid intake is a factor that increases crystal formation in the urine. The EPIC study by Turney et al. (2014) demonstrated that maintaining adequate fluid intake through diet can significantly prevent the formation of calcium oxalate stones in particular.

Children with kidney stones should be encouraged to increase water intake, reduce sodium intake, and maintain normal calcium levels in their diet without restriction. Additionally, increasing the consumption of potassium and citrate is important. To achieve these goals, children should be especially directed to increase their intake of fruits and vegetables. Such dietary habits can help reduce the formation of kidney stones and have positive effects on overall health.

Limiting oxalate intake is particularly important for kidney stone patients, as calcium oxalate stones are the most common type of stone (Siener and Hesse, 2002). The consumption of foods high in oxalate, such as chocolate, spinach, beets, and nuts, should be carefully controlled. However, oxalate management is not solely about avoiding these foods; portion control, fat intake, and consuming oxalate with calcium in the same meal are also critical strategies. Calcium binds with oxalate in the intestines, reducing oxalate absorption and thereby lowering the likelihood of oxalate crystallization in the urine (Turney et al., 2014).

In addition to dietary oxalate intake, excessive vitamin C consumption can increase oxalate production in the

body, thereby raising the risk of kidney stones. Special care should be taken with vitamin C supplements, as high doses can increase the risk of kidney stones (Siener and Hesse, 2002). Moreover, herbal products, protein powders, and certain vitamin supplements commonly sold in health stores can also pose risks due to their oxalate content. Therefore, individuals in high-risk groups are advised to carefully examine such products before use.

Animal protein, particularly from meat, fish, and poultry, is a significant factor in kidney stone formation. Excessive consumption of animal protein increases calcium, uric acid, and oxalate levels in the urine, raising the risk of stone formation (Turney et al., 2014). In particular, a decrease in urine pH associated with protein consumption can contribute to the formation of uric acid stones. Therefore, it is important to maintain a balanced protein intake to reduce such risk factors.

In addition, sodium intake has a substantial effect on kidney stone formation. High sodium intake increases calcium excretion in the urine, contributing to the formation of calcium oxalate stones (Siener and Hesse, 2002). Therefore, reducing salt intake and avoiding processed foods is recommended. Reducing foods high in sodium helps balance calcium levels in the urine, thereby lowering the risk of stone formation.

In addition to diet, lifestyle factors play a significant role in the formation of kidney stones. Studies have shown that certain occupational groups have a higher risk of kidney stones. For example, professionals such as teachers, who have limited access to restrooms, may have insufficient fluid intake, leading to decreased urine volume and an increased risk of kidney stones (Malieckal and Goldfarb, 2020). Similarly, individuals such as business travelers or healthcare professionals who stand for extended periods may also have inadequate fluid intake. This can increase the risk of crystallization in the urine, paving the way for kidney stone formation (Linder et al., 2013).

In addition, fluid loss is a significant risk factor for individuals who engage in excessive physical activity or work in hot climates. Particularly, soldiers, construction workers, or individuals who perform intense exercise may experience an increase in concentrated minerals in their urine and a higher risk of kidney stone formation if they do not consume sufficient amounts of fluids (Turney et al., 2014). For these occupational groups, increasing fluid intake stands out as a key strategy for reducing the risk of kidney stones.

The third section of the book consists of five subsections and begins by explaining the various medical specialties involved in the treatment of kidney stones and when these specialists intervene. It is noted that urologists, nephrologists, endocrinologists, infectious disease specialists, and primary care physicians play roles in the treatment of kidney stone disease. Primary care physicians typically manage simple and uncomplicated cases of kidney stones, while more complex cases are referred to urologists or other specialists. Urologists perform surgical interventions and procedures such as stone removal. Nephrologists and endocrinologists investigate and treat the underlying metabolic causes of stone formation. Infectious disease specialists, on the other hand, treat urinary tract infections caused by kidney stones.

This section also explains the modern medications used in the treatment of kidney stone disease and how these drugs work. After discussing ineffective methods used in the past, various drugs used today are detailed. Medications such as alkaline potassium salts, thiazides, allopurinol, and pyridoxine are explored, with a focus on how they are used to prevent kidney stone formation and their potential side effects. It is emphasized that these medications should be used under medical supervision and in recommended doses, as misuse could lead to health problems. For example, while alkaline potassium salts raise urine pH to prevent uric acid stones, thiazides reduce the amount of calcium in the urine. Allopurinol decreases uric acid production and is also used for some patients with calcium oxalate stones.

The author explains when and how kidney stone patients should be treated. Depending on factors such as the size and location of the stone and the patient's overall health, some stones may pass spontaneously, while others may require medical intervention. Conditions requiring urgent intervention include complete kidney blockage or infection. In cases of infection, antibiotic treatment may not be sufficient, and emergency drainage of the kidney may be necessary.

Acute treatment is usually administered in emergency departments, and as in adults, urological interventions are frequently required for pediatric patients (Van Batavia and Tasian, 2016). In cases where pediatric patients present with suspected nephrolithiasis (NL), the first imaging modality of choice is ultrasonography. However, in cases where ultrasonography is diagnostically inadequate and suspicion of NL persists, non-contrast computed tomography (CT) is recommended. It should be noted that CT involves a higher radiation dose and thus its use should be carefully considered (Passerotti et al., 2009).

The author also outlines the historical development of kidney stone treatment methods and the various techniques used today. In modern medicine, open surgery is rarely needed. Instead, methods have been developed to break up stones, allowing them to pass in the urine, or to remove them directly from the kidney using various instruments. These techniques include extracorporeal shock wave lithotripsy (ESWL), cystoscopy, ureteroscopy, and percutaneous stone surgery. Each method has its own advantages and disadvantages. Therefore, the most appropriate treatment option should be determined based on the patient's condition and the characteristics of the stone.

Lastly, the chapter discusses what to expect during the kidney stone treatment process. It emphasizes that

knowing what will happen before, during, and after treatment can alleviate patients' concerns and help them manage the process better. For instance, the process of stent placement and removal, what discomforts patients may experience, and how they can cope with these discomforts are explained in detail. Additionally, the author provides information on kidney stone fragmentation procedures (ESWL) and other surgical interventions. The preparation phases, what will happen during the procedure, and the potential side effects after the procedure are discussed in depth. Important points, such as when patients should consult their doctors in cases of pain, infection, or other complications, are also emphasized.

In conclusion, the book provides a comprehensive overview of the pathophysiology, diagnostic methods, and treatment options for kidney stone disease. The author offers a scientifically grounded guide, highlighting the complexity of the disease and the need for a multidisciplinary approach to its management. The importance of personalized diagnostic and treatment approaches based on the individual characteristics of the patients is detailed and supported in each chapter. The book serves as a valuable resource not only for healthcare professionals interested in kidney stone disease but also for patients, providing them with the knowledge and understanding to participate in the treatment process more consciously.

The entire book is a comprehensive work that allows for a multidimensional and in-depth examination of kidney stone disease. By providing a wide range of information, from the pathophysiology of kidney stones to diagnostic and treatment methods, the author equips readers with a solid academic foundation. The book offers both practical insights for clinical practice and theoretical knowledge that facilitates a better understanding of the disease. By offering scientifically-based guidance, the book helps readers develop a comprehensive understanding of kidney stone disease. Overall, this work is an essential reference source for anyone seeking information about kidney stone disease.

Reading this book enhances the professional competence of nephrologists by providing them with extensive and in-depth information. Starting from the pathophysiology of kidney stone disease, the book offers a comprehensive examination that extends to modern treatment methods. As a result, nephrologists gain a better understanding of the root causes, risk factors, and development processes of the disease. In particular, acquiring detailed knowledge about the metabolic causes of kidney stones and how to manage them enables nephrologists to offer more effective treatment options to their patients. Additionally, learning about the role of different medical specialties in kidney stone treatment strengthens multidisciplinary collaboration and allows for the adoption of more integrated approaches during the treatment process.

The book also helps nephrologists update their knowledge by providing current information on modern treatment techniques and innovative approaches. Detailed explanations of techniques such as extracorporeal shock wave lithotripsy (ESWL), cystoscopy, ureteroscopy, and percutaneous stone surgery enable nephrologists to gain a better understanding of the advantages and disadvantages of these methods. This knowledge assists them in making more informed and safer treatment decisions in their clinical practice. Furthermore, by offering guidance on the side effects that patients may encounter during treatment and how to manage these side effects, the book allows nephrologists to provide better education and counseling services to their patients. Such detailed information and guidance improve treatment outcomes and encourage patients to take a more active role in the treatment process. Therefore, the comprehensive and up-to-date information presented in the book enriches nephrologists' clinical practices and elevates the quality of patient care.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	H.G.Ö.
C	100
D	100
S	100
DCP	100
DAI	100
L	100
W	100
CR	100
SR	100

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The author declare that there is no conflict of interest.

References

Chu DI, Tasian GE, Copelovitch L. 2016. Pediatric kidney stones—avoidance and treatment. Curr Treat Option Pediat, 2: 104-111.

Edvardsson VO, Ingvarsdottir SE, Palsson R, Indridason OS. 2018. Incidence of kidney stone disease in Icelandic children and adolescents from 1985 to 2013: Results of a nationwide study. Pediat Nephrol, 33: 1375-1384.

Goldfarb DS, Arowojolu O. 2013. Metabolic evaluation of first-time and recurrent stone formers. Urol Clin, 40: 13-20.

Kovacevic L, Wolfe-Christensen C, Edwards L, Sadaps M, Lakshmanan Y. 2012. From hypercalciuria to hypocitraturia—a shifting trend in pediatric urolithiasis?. J Urol, 188: 1623-1627.

Linder BJ, Rangel LJ, Krambeck AE. 2013. The effect of work location on urolithiasis in health care professionals.

Urolithiasis, 41: 327-331.

Malieckal DA, Goldfarb DS. 2020. Occupational kidney stones. Curr Opin Nephrol Hypertension, 29(2): 232-236.

Passerotti C, Chow JS, Silva A, Schoettler CL, Rosoklija I, Perez-Rossello J. 2009. Ultrasound versus computerized tomography for evaluating urolithiasis. J Urol, 182: 1829-1834.

Siener R, Hesse A. 2002. The effect of different diets on urine composition and the risk of calcium oxalate crystallisation in healthy subjects. Eur Urol, 42(3): 289-296.

Turney BW, Appleby PN, Reynard JM, Noble JG, Key TJ, Allen NE. 2014. Diet and risk of kidney stones in the Oxford cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC). Eur J Epidemiol, 29: 363-369.

Van Batavia JP, Tasian GE. 2016. Clinical effectiveness in the diagnosis and acute management of pediatric nephrolithiasis. Int J Surgery, 36: 698-704.

Yang EM, Yoon BA, Kim SW, Kim CJ. 2017. Clinical utility of spot urine protein-to-creatinine ratio modified by estimated daily creatinine excretion in children. Pediat Nephrol, 32: 1045-1051.

Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1507563

Open Access Journal
e-ISSN: 2619 – 90410

Review
Volume 7 - Issue 6: 267-282 / November 2024

RABIES, THE ADMINISTRATION OF VACCINES AND PUBLIC HEALTH CONCERN, NEGLECTED CHALLENGES AND HISTORICAL PERSPECTIVE IN CHINA

Mohamad Hesam SHAHRAJABIAN[1]*, Wenli SUN[1]

[1]*Chinese Academy of Agricultural Sciences, Biotechnology Research Institute, National Key Laboratory of Agricultural Microbiology, Beijing, China*

Abstract: Rabies virus is transmitted via contact of saliva of a rabid animal with a persons' mucosa or a skin lesion. It is a fatal encephalomyelitis caused by members of expanding *Lyssavirus* genus, and the genus included 17 species. The aim of this literature review is to survey on rabies and vaccination in China, threats and challenges to eliminate it, especially in China. The information provided is obtained from randomized control experiments, review articles, and analytical observations and studies which were gathered from various literature sources such as Scopus, Google Scholar, PubMed, and Science Direct. Rabies virus is a bullet shaped enveloped virion, and the classical rabies virus and its field strains are discovered worldwide and induces to rabies in animals and humans. In recent years, China has made wonderful and significant achievements in rabies prevention and control, and currently, the mortality and incidence rate of human infection with rabies have decreased to the minimum level historically, which has caused a notable foundation for the ultimate elimination of human rabies. Generally, five proteins are available in mature rabies virus (RABV) particles, phosphoprotein, nucleoprotein, glycoprotein, matrix protein, and RNA-dependent RNA polymerase. The main carriers of rabies in China are dogs which are accountable for most of the human rabies deaths in China. Most common way of entry of rabies virus into the body is both via infected neural tissue through open cuts in the skin and salvia. Rabies remain a public health problem and continue to present health risks for both animals and human; It is important to improve access to post-exposure prophylaxis (PEP) in endemic countries where human rabies deaths still happen, but the big problem is its costs that should be curtailed and surveillance strengthened for controlling and eliminating it.

Keywords: Dogs, Glycoprotein, Lyssavirus, Post-exposure prophylaxis, Rabies virus

***Corresponding author:** Chinese Academy of Agricultural Sciences, Biotechnology Research Institute, National Key Laboratory of Agricultural Microbiology, Beijing, China
E mail: hesamshahrajabian@gmail.com (M. H. SHAHRAJABIAN)
Mohamad Hesam SHAHRAJABIAN https://orcid.org/0000-0002-8638-1312
Wenli SUN https://orcid.org/0000-0002-3855-3992

Received: June 30, 2024
Accepted: September 18, 2024
Published: November 15, 2024

Cite as: Shahrajabian MH, Sun W. 2024. Rabies, the administration of vaccines and public health concern, neglected challenges and historical perspective in China. BSJ Health Sci, 7(6): 267-282.

1. Introduction

Rabies is a deadly disease present since ancient times induce by rabies virus that is neurotropic *lyssavirus* causing acute lethal encephalitis (Zhang et al., 2015; Khan et al., 2019; Cui et al., 2023; Shahrajabian and Sun, 2023a,b,c). The virus infection causes encephalomyelitis in humans with a roughly 100% case mortality rate (Jochmans and Neyts, 2019). Rabies cause over 95% of the deaths happening in African and Asian countries (Knobel et al., 2005). It is also considered as a neglected tropical disease that principally influences poor and vulnerable individuals from poverty-stricken countries (Wang et al., 2019). Li et al. (2019) reported around 35,000 human deaths from rabies in Asia every year. The most significant symptoms and signs are aerophobia, hydrophobia, and mental disorders (Wang et al., 2013). The dog, red fox, and raccoon dog are known to have a considerable function in the global epidemiology of rabies (Cliquet et al., 2008). Vaccines have shown important functions in rabies prevention both as companion animals, and also as inactivated vaccines to protect humans, and as reduced live vaccines utilized for oral vaccination in feral and wildlife dogs. Improved vaccination strategies, continuing development of diagnostic tools, and better understanding of the virus-host relationships which affect infection results will all can have roles to future progress of rabies control techniques (Nandin-Davis, 2023). Some of the most important rabies cases reported in wildlife from different families are: (1) *Phyllostomidae*: Common vampire bat (*Desmodus rotundus*), and Great fruit-eating bat (*Artibus lituratus*), (2) *Molossidae*: Brazilian free-tailed bat (*Tadarida brasiliensis*), (3) *Vespertilionidae*: Brazilian brown bat (*Eptesicus brasiliensis incognita/unidentified*), (4) *Canidae*: South American gray fox Hoary fox (*Lycalopex griseus*, *Lycalopex vetulus*, *Lycalopex* spp.), and Crab-eating fox (*Cerdocyon thous*), and Red fox (*Vulpes vulpes*), (5) *Procyonidae*: Kikanjou (*Potus flavus*), Coati (*Nasua nasua*), (6) *Cebidae*: Guianan squirrel monkey (*Saimiri sciureus*), (7) *Callitrichidae*, (8) *Camelidae*, (9) *Cervidae*, and (10) *Leporidae*: *Lepus* spp. (Meske et al., 2021). Vaccines suited for post-exposure prophylaxis

(PEP) are adjuvanted rabies vaccines, protein vaccines, genetically modified and inactivated rabies virus (Ertl, 2019). Clinical symptoms of rabies in animals just can be utilized for presumptive diagnosis due to various types of clinical rabies such as paralytic and furious, which have symptoms that are very similar to other diseases and change between individuals (Ward and Brookes, 2021). The aim of this manuscript is survey on rabies and vaccination in China, threats and challenges to eliminate it, especially in China.

2. Rabies Historical View

The word rabies comes from the Sanskrit word rabbahs which means to do violence, it refers to the Vedic period of India 93th century BC, when the God of Death was represented being presented by a dog, his constant companion and the emissary of death (Fu, 1997; Coertse et al., 2023). Rabies in an always deadly viral disease of global significant, and wildlife has an important function as reservoirs and sources of rabies to domestic humans and animals (Shoemaker et al., 2023). Woldehiwet (2002) also reported that the current English name, rabies, is obtained directly from Latin, meaning raging, savage, furious, or madness, whereas the Greek term hydrophobia is not precisely used for rabies in human.

Table 1. Rabies historical overview

Ancient Greek	Galen, Democritus, Celsus, and Aristotle had warned people of the dangers related to the bite of a mad dog.
First Century AD	The famous Roman writer Cardanus surveyed saliva to be the carrier of the infectious factor.
1804 AD	George Gottfried Zinke who experimentally showed the infectivity of rabid dog salvia by inoculating a healthy dog with the suspected salvia.
Few decades after 1840 AD	French scholar, Viktor Galtier showed that rabbits could serve for both study and diagnosis of rabies.
Few decades after 1840 AD	Louis Pasteur indicated they infective parameter resides in the nervous tissue of the rabid animal.
1884 AD	Pasteur and his colleagues proved their first publication entitled new communication on rabies.
At the beginning of the twentieth century	Dr. Paul Ambroise Remlinger, a Pasteurian scientist showed the capability of infective agent to pass through a Berkfeld filter.

The recorded history of rabies goes back to 2300 BC, when a dog owner in ancient Babylon was charged for a death induced by a dog bite; ancient Greek philosophers like Aristotle, Democritus, and Celsus as well as the famous physician Galen, had warned people of the dangers connected with the bite of a mad dog, indicating that the infectivity of the animal was suspected some 2000 years ago (Wiktor, 1985; Cai et al., 2021; Johnson et al., 2021). Rabies historical overview is shown in Table 1.

3. Rabies Reservoirs, Rabies virus and *Lyssavirus* Genus

The most notable global rabies reservoirs are cats, dogs, foxes, skunks, raccoons, coyotes, bats, and mongooses. The main source of exposure along with being the primary vector for rabies in humans are domestic dogs (Sultan and Khan, 2013; Khan et al., 2019). The main global rabies reservoirs are shown in Table 2. *Lyssavirus* is a genus of RNA viruses include the rabies virus traditional related to the disease. The etiologic agents of rabies encephalitis belong to the *Mononegavirales* order, *Rhabdoviridae* family and *Lyssavirus* genus. *Lyssaviruses* have a 12 kg-long non-segmented RNA genome of negative polarity encoding five viral proteins: nucleoprotein N, phosphoprotein P, matrix protein M, glycoprotein G and polymerase L. The *lyssavirus* genus is shown in Table 3.

Table 2. Predominant global rabies reservoirs (Fu, 1997)

Dogs	Major vector of rabies throughout the world, particularly Asia, Africa, and Latin America.
Foxes	Arctic, Europe, and North America
Raccoons	Eastern United States
Skunks	Midwestern United States, Western Canada
Coyotes	Africa, Asia, and North America
Mongooses	Yellow mongoose in Africa, and Asia; Indian mongoose in the Caribbean Islands
Bats	Vampire bat from Northern Mexico to Argentina, insectivorous bats in North American and Europe.

The Ribonucleoprotein (RNP) core in connection with the matrix protein is condensed into the ordinary bullet-shaped particle that is trait of rhabdoviruses. A lipid bilayer envelope in which the surface trimeric glycoprotein spikes are anchored surrounds the RNP-M structure. The membrane tail shows the trailing piece of envelope that is often observed attached to the virus as it buds from the plasma membrane of the infected cell when viewed under the electron microscope (Wunner, 2007). *Desmodus rotundus* is the major bat species, among vampire bats, which is accountable for frequent cases of rabies in different parts of the world (Oliveira et al., 2022).

Table 3. The *lyssavirus* genus (Warrell, 2010)

Genotype	Reservoir species (potential vectors)[a]	Known distribution
Phylogroup I		
1 - Rabies virus	Dog, fox, raccoon, skunk, bats etc.	Widespread; bats in Americas only
4 – Duvenhage	Insectivorous bat (*Nycteris thebaica*)	South Africa, Zimbabwe, Kenya
5 - European bat *lyssavirus*		
Type 1a	Insectivorous bats (Sheep, cats)	Northern and Eastern Europe
Type 1b	Insectivorous bats	Western Europe
6 - European bat *lyssavirus*		
Type 2a	Myotis dasycneme bats	Netherlands, Germany
	Myotis daubentonii bats	UK
Type 2b	Myotis daubentonii bat	Switzerland, Finland
7 - Australian bat *lyssavirus*	Flying foxes (fruit bats) Insectivorous bats	Australia
Phylogroup II		
3 – Mokola	Shrew, rodents (cats, dogs)	South Africa, Nigeria, Cameroon, Ethiopia
2 - Lagos bat virus	Bats (cats, dog, water mongoose) Has NOT been detected in man	Zimbabwe, South Africa, Kenya

a= mammals infected by reservoir species may become vectors.

The nucleoprotein (N), matrix protein (M), phosphoprotein (P), glycoprotein (G), and large RNA-polymerase protein (L) genes (orange) are separated by intergenic nucleotide sequences and the pseudogene (ψ) sequence and flanked by the leader (Le) RNA and trailer (Tr) RNA sequences (green) at the 3′ and 5′ termini, respectively (Wunner, 2007). Virus enters the cell following attachment via coated pits (viropexis) or through cell surface receptors, mediated by the viral glycoprotein (G) fusing with the cellular membrane (endocytosis). After internalization, the viral G mediates low pH-dependent fusion with the endosomal membrane and the virus is uncoated, releasing the helical nucleocapsid (NC) of the ribonucleoprotein (RNP) core. The five structural genes (N, P, M, G, and L) of the genome RNA in the NC are transcribed into five positive (+) strand monocistronic messenger RNAs and a full-length (+) strand (antigenome) replicative intermediate RNA. The antigenome RNA serves as the template for replication of progeny genome (-) strand RNA. The proteins (N, P, M, and L) are synthesized from their respective mRNAs on the free ribosomes in the cytoplasm and G is synthesized from the G-mRNA on membrane-bound ribosomes (rough endoplasmic reticulum). Some of them N-P molecular complexes produce cytoplasmic inclusion bodies (Negri bodies) in vivo and some N-P complexes encapsidate the (+) strand and (-) strand viral RNAs. After progeny genome RNA is encapsidated by the N-P protein complex, and L protein is incorporated from progeny RNP (both shorter defective and full-length standard) structures the M protein binds to the RNP and condenses the RNP into the skeleton structures. The skeleton structures interact with the trimeric G protein structures anchored in the plasma membrane and assemble into virus particles that bud from the plasma membrane of the infected cell into adjacent extracellular or interstitial space (Wunner 2007).

4. Rabies Diagnostic and Vaccination

It is difficult to establish a definitive clinical diagnosis of human rabies, and it may need the availability of cardinal symptoms in the encephalitic form, and sometimes problem and delay of diagnosis in developed countries is possibly connected to the lack of a clear bite history (Hemachudha et al., 2002). Deubelbeiss et al. (2013) also found that it is difficult to recognize human rabies when a history of exposure is not present. Rabies virus (RABV) is a member of *Lyssavirus* family, *Rhabdoviridae*, and has five structural proteins: nucleoprotein (N), matrix protein (M), phosphoprotein (P), glycoprotein (G), and an RNA dependent RNA polymerase (L) (Wunner et al., 1988; Wang et al., 2014). The rabies virus G protein, which is a trimer of about 67 kDa, is the main antigen accountable for inducing the production of virus-neutralizing antibodies (VNAs), and for conferring immunity against lethal rabies virus infection (Cruz et al., 2008). The G gene was the first RABV gene to be cloned and sequenced. From the nucleotide sequence, a poly peptide (524 amino acids long) was gathered, which included a signal sequence of 19 amino acids (Cruz et al., 2008). Understanding of why and where risks exist are needed to reduce zoonotic disease threats (Muller et al., 2015; Abutarbush et al., 2022; Tierradentro-Garcia et al., 2022). Pfaff et al. (2019) also concluded that fatal disease is basically connected to rabies virus (RABV), a neurotropic single-stranded RNA virus of the family *Rhabdoviridae* in the genus *Lyssavirus* within the order *Mononegavirales*. It is the main antigen protein to be utilized as a good candidate to designed modern anti-rabies DNA vaccines (Perrin et al., 2000; Diogo et al., 2001; Gholami et al., 2014). The frequently used rabies vaccine is a type of inactivated viral vaccine is propagated in cell culture, and usually applied for pre-exposure or post-exposure when combined with rabies immunoglobulin (RIG) to avoid or prevent most rabid

dog bite tragedies (McGettigan, 2010). Wang et al. (2019) noted that the development of novel inexpensive, effective, and safe vaccines has become a prime concern for rabies control worldwide, and the chimpanzee adenovirus-vectored rabies vaccine ChAd68-Gp warrants extensive test for clinical application. Anothaisintawee et al. (2019) showed that mass dog vaccination and post-exposure prophylaxis (PEP) is one of the main appropriate control technique, effectual rabies elimination has yet to be understood. The post-exposure prophylaxis should be grouped as an emergency medical service, and it should be part of the hospital medical emergency, and mass dog vaccination against rabies should be increased to decrease the risk of potential bite of pet dogs and roaming dogs in communities (Gongal et al., 2022). The characteristics of various methods to gain monoclonal antibodies are hybridoma technique, antibody library technique, and B cells immortalization technique (Fan et al., 2022). Quiambao et al. (2022) concluded that 1-week pre-exposure prophylaxis with Vero cell rabies vaccines and human diploid cell vaccine can induce effective priming in 2-64-year-olds, and it has achieved more than 99% seroconversion. In Greece, it has been reported that the main goal and current extensive attempts should be to prevent spread particularly in the domestic and wild animal populations (Tsiodras et al., 2014). He et al. (2006) reported that the recombinant maltose binding protein (MBP)-N fusion protein can be isolated and expressed simply, and it can be appropriate and safe source of antigen to analyze seropositivity in vaccinated canines. Disinfection and cleaning are important to prevent cross-contamination of samples in the laboratory environment, and the effectual disinfection protocol should be considered carefully validated to guarantee reliability of results, and staff safety (Aiello et al., 2016). The criteria and use for choosing different assays change on the basis of the sample analyzed and the goal of the diagnosis, which will also change on the basis of the setting in non-endemic and endemic (Rudd et al., 2005; Duong et al., 2016). Liu et al. (2010a) concluded that it was potentially appropriate for the more development of easily handled, highly sensitive and relatively rapid detection tools/kits for rabies surveillance in those regions of China where rabies is endemic. Undurraga et al. (2020) reported that the elimination programs of dog rabies usually depend on parenteral vaccination, capture-vaccine-release and mobile static point significantly boosted free-roaming dog coverage, and oral vaccination, and door-to-door parentral vaccination was the most cost-effective program. Definition of categories of exposure is presented in Table 4.

Servat et al. (2019) believed that the quality of rabies-inactivated (Rabisin, Boehringer-Ingelheim) vaccines for veterinary use is of greatest importance to change the cross-protection of pets against phylogroup I bat *lyssaviruses* occurring in Europe. Nishizono et al. (2012) showed that Rapid Neutralizing Antibody detection test (RAPINA) is a rapid and easy technique for measuring the level of rabies virus-neutralizing antibody (VNA) levels after and before immunization with the rabies vaccine and it does not require a special skill level nor advanced tools. The Enzyme Linked Immunosorbent Assay (ELISA) method which is characterized the immunogenic from the glycoprotein formulated in vaccines seems to be relevant and is a promising candidate to be standardized the quality of vaccine batches before release (Gibert et al., 2013). Parameter which can limit canine rabies vaccination program are diminished community education and outreach, limited laboratory-based surveillance, underestimation of the population at risk, irregular vaccine applications in time and space, exclusion or puppies, cold chain failure, inaccessible naïve free-ranging dogs, translocation of cases, competing priorities, effect of other species such as wildlife and livestock, lack of adequate resources, accessibility to remote hotspots, cultural disparities, impact of poverty on responsible social ownership and common animal health care, less than appropriate cooperation between human health and veterinary services, sisyphean fatigue, staff burn-out and frustration (Rupprecht et al., 2019). Marosi et al. (2019) found that inhibitors of detrimental host reaction to rabies together with antibodies can be considered among the probable therapeutic and post-exposure choices in human rabies cases. Shi et al. (2018) revealed that adjuvants can be applied as an enhancer in rabies vaccination, and non-sized aluminum maybe a candidate adjuvant for the development of more effective rabies vaccines. Laager et al. (2019) indicated that dog rabies vaccination is an efficacious way of preventing rabies in the dog population and to subsequently decline human exposure. Zhang et al. (2016a,b) noted that PIKA which is a new adjuvant, is an effectual and safe vaccine which has the potential to develop next-generation rabies vaccine and encourage the start of more clinical researches.

Table 4. Definition of categories of exposure (Lee, 2004; Linscott, 2012)

Category	Exposure criteria	Biologic recommendation
I	Touching, feeding of animals or licks on intact skin	No exposure, therefore no treatment (if history is reliable)
II	Minor scratches or abrasions without bleeding or licks on broken and nibbling of uncovered skin	use vaccine alone
III	Single or multiple transdermal bites, scratches or contamination of mucous membrane saliva (i.e., licks)	Use immunoglobulin plus vaccine

Table 5. Rabies vaccines and immunoglobulins

Pasteur (Paris) virus strains (PV, for Pasteur virus) of rabbit fixed rabies virus; also adapted to Vero cells
PV-12 strain of Pasteur rabbit fixed rabies virus; also adapted to BHK-21 cells
Pitman-Moore (PM) strain of fixed rabies virus, adapted to human diploid, primary dog kidney and Vero cells
CVS (challenge virus strain)-11 Kissling strain, adapted to BHK-21 cells
LEP (low egg passage) (40-50 passages) Flury chick embryo-adapted rabies virus, also adapted to primary chick embryo cells and to BHK-21 cells
HEP (high egg passage) (227-230 passages) Flury chick embryo-adapted rabies virus; also adapted to primary chick embryo cells
Kelev (100 passages) chick embryo-adapted rabies virus
ERA (Evelyn Rokitniki Abelseth) strain of Street-Alabama-Dufferin (SAD) virus, adapted to porcine kidney cells; also adapted to BHK-21 cells (in Canada)
Different SAD variants are ERA virus adapted to BHK-21 cells (in Europe)

Luo et al. (2019) showed that the artemisinin derivative ART boosted immune response of inactivated rabies vaccine when used as an adjuvant; in the experiment, the artesunate could be used as a new candidate adjuvant for rabies vaccination. Shafiur Rahaman (2017) noted that sustainable application of programs to manage dog population, dog bite management and awareness raising population can bring out fruitful results, but vaccinating dogs is the most effective plan suggested by researchers. Moghadami et al. (2017) also proved that the vaccination of dogs and cats is important by preventing dogs from being exposed to humans. Rabies vaccines and immunoglobulins is presented in Table 5.

5. Post-Exposure Prophylaxis (PEP)

The progress of human rabies vaccine has evolved dramatically from the first crude nerve tissue vaccine produced them conducted in the presence of Louis Pasterur in 1885 (Tarantola et al., 2019; Saffar et al., 2023). Prophylaxis of animal rabies is important for breaking the transmission cycle and preventing the spread of rabies to humans (Costa et al. 2007; Hu et al., 2007). Rabies in humans can be prevented via appropriate and timely post-exposure prophylaxis (PEP) (Li et al., 2019; Rysava et al., 2019). Appropriate and timely administration of PEP is important to prevent rabies, and even though general public with high risk immunosuppression and exposures can develop rabies despite adherence to core practices, this occurrence remains significantly rare (Whitehouse et al., 2023). Zhai et al. (2022) reported that highly protective potency, the broad-spectrum neutralization activities, and rapid onset of action can make ormutivimab an effectual substitute for human rabies PEP. Rabies vaccine is a main component of modern post-exposure prophylaxis, which included wound care and the infiltration of rabies immunoglobulin, when PEP is timely and properly administrated, expected survivorship approaches 100% (Recuenco et al., 2017). PEP is not effectual after beginning of symptoms and attempts to develop a treatment for clinical rabies have been failed (Rogee et al. 2019). The cost of post-exposure prophylaxis (PEP) is both related to the direct cost of rabies biological and tools and also related to indirect costs that patients experience as a result of travel, loss of work time, and accommodation over the period of time that a PEP regimen requires to be completed (Tarantola et al., 2019). Wambura et al. (2019) also claimed that adoption of the dose-saving intradermal route for PEP administration, reduction of PEP costs to patients, and placing rabies vaccines with the standard vaccines supply and logistics system would significantly improve PEP accessibility and availability to those who are at risk, is a condemnatory step to achieving elimination of human deaths from rabies. They have highlighted that sharing information on practices of PEP more widely among countries may help in programs to increase access to life-saving treatment. PEPE induces antibodies against rabies (Wijaya et al., 2017). Rabies PEP consists of wound washing, immediate rabies vaccination following the possible exposure, and in some cases, rabies immunoglobulin (RIG). Lankester et al., (2014) showed that an important assumption of controlling and eradicating rabies at source through mass dog vaccination is that the public health sector through reduced rabies risk and therefore reduced expenditure on PEP. Changalucha et al. (2019) noted that PEP access could be improved and rabies death reduced through ring-fenced procurement, changing to dose-sparing ID regimens and free provision of PEP. But, PEP is costly and costs can be a major barrier to both bite victims and to low- and middle-income countries (Hampson et al. 2008; Sambo et al. 2013). Currently, only cell-culture or embryonated egg-based rabies vaccines (CCEEVs) are recommended by the World Health Organization (WHO); the original nerve-tissue based vaccine (NTBV) has not been suggested since 1980s (Abela-Ridder et al., 2016). Koraka et al. (2014) found that its native trimeric configuration of rabies virus (RABV-tG) applied in combination with Matrix-M™ is a promising vaccine candidate which overcomes the limitations of currently used vaccines; presently accessible vaccines are expensive, cumbersome to produce and also need intensive immunization and booster schemes to induce and keep protective immunity. Koraka et al. (2019) confirmed that some inflammatory responses may be involved in the pathogenesis of serious disease and the

results proved the effectual intervention included inhibition of virus and host response. The indication and procedure for PEP replies on the type of contact with the suspected rabid animal and immunization status of the patient. For category I exposures, no PEP is needed; for group II, immediate vaccination is suggested; for category III, immediate vaccination is recommended, and application of RIG, in indicated. For categories II and III, through flushing and washing with soap or detergent and copious amounts of water of all bite scratches and wounds should be done instantly, depending on the characteristics of the wound, antibiotics, analgesics and a tetanus vaccination maybe indicated. Beyene et al. (2018) recommended increasing awareness about its fatality and not just vaccine importance but also vaccination for rabies decrease followed eradication by vaccine and vaccination for all source or carrier individuals, and also post exposure treatment should be given after quickly exposure to bite or scratch by rabid animals. Fooks et al. (2019) noted that next generation human rabies vaccines are required to lessen cost and number of doses for PrEP and PEP, and it could be important to develop various vaccine platforms with unique requirement for optimally protective immune responses. They have introduced PrEP vaccines that induce long-lived rabies virus neutralizing antibody and sustained memory B cell responses after a single dose would be needed and replication-defective adenoviral vectors may obtain these requirements. Echevarria et al. (2019) highlighted the need for a comprehensive pan-lysaavirus rabies vaccine, which able to prevent human rabies in all situations. Rabies pre-exposure prophylaxis recommendation is shown in Table 6.

6. DNA Residue

Chinese vaccine products not only secure disease control and prevention domestically, but also provide the needs for international public health (Xu et al., 2015; Deidda et al., 2018; Zhao et al., 2018). Quality control plans account for significant portion of a laboratory budget which should be effectual (Shen et al., 2018; Won et al., 2019). There are two kinds of anti-rabies vaccines; the non-nerve tissue vaccine, and the nerve tissue-based vaccine (Mengesha et al., 2014). Mengesha et al. (2014) reported that the presently available non-nerve tissue vaccines are Purified Chick Embryo Cell (PCEC) vaccines, Human Diploid Cell Vaccine (HDCV), Purified Vero Cell Vaccine (PVRV), and Purified Duck Embryo Vaccine (PDEV). In rabies virus (RV), the viral genome (3′/N-P-M-G-L5′/) encodes a nucleoprotein (N0, a phosphoprotein (P), a glycoprotein (G), a matrix protein (M), and a RNA-dependant RNA polymerase (L) (Wunner, 2007; Osinubi et al., 2009; Luo et al., 2013). The G is closely associated with pathogenicity, and is a basic contributor to protective immunity (Cox et al., 1977; Morimoto et al., 2001). Because the G is the best surface-exposed viral coat protein, it is avle of eliciting the production of virus neutralizing antibodies (VNA), and also accountable for host cell receptor recognition and membrane fusion (Osinubi et al., 2009). G protein is a type I membrane glycoprotein including 505 amino acids in the native form, and it is the mediator of both entry into host cells and binding to cellular receptors (Anilionis and Wunner, 1981; Seif et al., 1985; Coll, 1995).

Table 6. Rabies pre-exposure prophylaxis recommendation (Beyene et al., 2018)

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus presents continuously and often in high concentrations. Specific exposures likely to go unrecognized. Anyways of exposure.	Rabies research laboratory workers; rabies biologics production workers.	Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Any rout of exposure.	Rabies diagnostic laboratory workers, cavers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. A person frequently handle bats.	Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized.	Worker with terrestrial animals in where rabies is uncommon to rare. Veterinary students. Visitor areas where rabies is enzootic. A person frequently handle bats.	No serologic testing or booster vaccination.
Rare	Exposure always episodic with source recognized.	Most population in areas where rabies is epizootic.	No vaccination is necessary.

It contains a transmembrane domain, a cytoplasmatic domain, and an ectodomain exposed domain, a transmembrane domain, and an ectodomain exposed as trimer (3 × 65 kDa) on the virus surface (Gaudin et al., 1992; Rath et al., 2005). Also the G protein induces the production of cell-mediated immunity by cytotoxic T lymphocytes and T helper cells (Macfarlan et al., 1986; Celis et al., 1988). Bassi (2008) found that the glycoprotein (G) of rabies virus (RV) is principal for virus infectivity and induction of the protective immunity. Li et al. (2010) stated that the rabies virus (RV) glycoprotein (G protein) leads to neutralizing antibodies, which are important in protection against rabies. The M protein is the smallest and most abundant protein in the virion, forming a layer between the protein G in the outer membrane and the ribonucleoprotein (RNP) core (Mebatsion et al., 1999), and the M protein is a multi-functional protein vital for virus maturation and budding and of course regulates the expression of both viral and host proteins (Wu et al., 2013). The M protein is active in viral assembly and budding, regulation of the viral genome and mRNA syntheses (Finke et al., 2003). The G and N proteins have been identified as viral antigens (Yang et al., 2013). The N protein is the main antigen that induces T cell immunity (Goto et al., 2000). Protein P has multiple performances at different stages of the viral cycle, forming a complex with the nascent nucleoprotein that prevents the association of the latter with hose-cell RNA and forming a two-subunits viral RNA polymerase complex with protein L (Gerard et al., 2009). Ashraf et al. (2005) claimed that plant-derived G protein induced complete protective immunity in mice against intracerebral lethal challenge with live rabies virus. Zhao et al. (2020) suggested that by replacing the signal peptide, the expression level of the G protein with native conformation could be significantly improved, as G protein from the rabies virus plays an important role in the binding of virus to target cells. Different and various types of vaccine with numerous platforms have been analyzed both clinically and preclinically for rabies PEP or Pre-P, and the most important and promising for PEP are vaccines on the basis of traditional rabies vaccines which have been supplemented with a potential adjuvant, inactivated genetically modified protein vaccines and rabies virus, whereas for Pre-P recombinant vaccines according to replication-defective adenoviruses may provide an affordable substitute to currently utilized vaccines (Ito et al., 2021; Atici and Oguzoglu, 2022; Itakura et al., 2022; Abedi et al., 2023; Challhua et al., 2023; Izumi et al., 2023; Scrima et al., 2023). Both an animal and human health perspective, current rabies vaccines seem able to protect against *lyssaviruses* categorized within phylogroup I. However, no protection is afforded against phylogroup II viruses or other more divergent viruses (Evans et al., 2012). Evan et al. (2012) also recommended that the development of novel vaccines that stimulate a pan-*lyssavirus* neutralizing immune response is of importance to those at occupational risk from infection.

7. Rabies in China and New Studies

The risk of rabies had been significantly decreased to a persistently low level in China, and the constant high-risk regions for rabies in China were Guangxi, Guizhou, Hainan, and Hunan (Li et al., 2023: Sun et al., 2021; Sun et al., 2022). Human rabies was first reported in China in around 556 BC, and has persisted for more than 2500 years (Zhang et al., 2011). In ancient Chinese medicine, rabies was very well described and recognized, and people gained enough awareness and knowledge about it (Miao et al., 2021). Rabies virus has a 12-kb non-segmented negative sense RNA genome encoding five viral proteins (3/ to 5/): phosphoprotein (P), nucleoprotein (N), Glycoprotein (G), matrix protein (M), and RNA-dependent RNA polymerase (L) (Tao et al., 2021). It has a long history in China for more than 2000 years and it was first known in 556BC, and there have been three main epidemics in China since the 1950s, and the third and the current epidemic started in 1997 (Zhang et al., 2009a,b; Huang et al., 2010; Shahrajabian et al., 2020a,b; Shahrajabian et al., 2021). Li et al. (2023) reported that re-emerging high-risk provinces were Anhui and Yunnan in China, and the important point is priority animal vaccination in those identified high-risk provinces. It has been also reported that although, the occurrence of rabies has been decreased significantly in the past decade, it still remains the second most important cause of death from zoonotic infectious diseases in Chinese adolescents and children (Dong et al., 2020; Langguth et al., 2021; Li et al., 2021; Das et al., 2022). On the basis of the data of Chinese Center for Disease Control and Prevention, there were a total of 25,700 rabies deaths from 2004 to 2018 in mainland China, and the cases were basically caused by dog bites (Qian et al., 2019; Qiao et al., 2021). Without extensive education, forced vaccination, and strict administration, dog rabies has spread to ferret badgers (*Melogale moschata*, FBs) in Southeast of China, and the virus presently independently circulates in this animal population (Zhang et al., 2009; Liu et al., 2010b).

The world's top producer and user of rabies vaccine is China which represented around 84% of all rabies vaccine vials needed in 2020 (Li et al., 2023). The cost of rabies control and prevention in China is high, however the result is still not acceptable, and according to the official data, China administers nearly 12-15 million doses of vaccines every year, which is around one billion but has the second highest occurrence after in India (Nadal et al., 2022). China should to boost the animal surveillance and registration system, particularly in regions with high rabies risk, and to do more trials on large-scale dog vaccination (Nadal et al., 2022), to gain the goal of eliminating dog-mediated rabies by 2030 (Yin et al., 2013). Currently, three types of rabies immunoglobulin (RIG) factors are utilized in passive immune treatment: equine rabies immunoglobulin, human rabies immunoglobulin, and high-purity f (ab) 2 fragment created by equine immunoglobulin (Li et al.,

2020). Ormutivimab is the first recombinant human anti-rabies monoclonal antibody which was developed and approved in 2022, and it is an antibody of IgG1 subtype, manufactured by Chinese hamster ovary (CHO) cells, and it can precisely neutralize the linear neutralizing antigen epitope in situ point I of rabies virus glycoprotein (Li et al., 2020). In different parts of China the rabies virus associated with dogs, isolates can be categorized into six genetic lineages (China I-VI), and among these lineages, China I has become the principle epidemic type transmitted and hosted by dogs, and this lineage has replaced the wildlife and dog-associated China II lineage in the past years (Ming et al., 2018). In Inner Mongolia Autonomous Region which is a boundary province located in northern China, human rabies cases boosted from 2005 to 2007, and reduced during 2008-2011, and up until 2014, many rabid animals are reported included raccoon dogs, dogs, cows, red foxes, sheep, cows and camels (Zhu et al., 2015). Zhang et al. (2014) and Xing et al. (2014) reported that high rate of rabies virus carried by domestic dogs possibly was the main reason for current rabies epidemic in China. Zhang et al. (2006a,b,c) reported that phylogenetic analysis showed that all the rabies epidemics of Chinese isolates have a close connection with viruses circulating in Asian canine population in comparison with rabies viruses isolated previously. In Guangdong, which has the third highest human rabies cases among 31 provinces in China, at least 18.2% caused by stray dogs, due to a large number of dogs, both stray and domestic, and vaccination has been found more effective than culling (Hou et al., 2012). On the basis of the results, it has been proved that the rabies viruses in China and Southeast Asia share a common ancestor and form 2 clades with each being further grouped into 3 lineages, and the viruses circulating in Southeast Asia probably derived from China (Gong et al., 2010). It is also important to understand the temporal and spatial patterns of rabies in humans for risk assessment and develop targeted interventions (Guo et al., 2013; Ruan, 2017; Huang et al., 2019), specially for India and China which have the maximum and second highest reported number of rabies, respectively (Ren et al. 2015; Wolelaw et al., 2022). Wang et al. (2022) reported that rabies vaccination after pre-exposure prophylaxis (PEP) could lead to the body to produce enough sufficient RVNA, and rabies vaccination after PEP has indicated comparatively an appropriate immune efficacy and acceptable safety for preventing human rabies. Ding et al. (2020) reported that SYN023, which is a mixture of two anti-rabies humanized monoclonal antibodies (mAbs), namely, CTB012 and CTB011, at 0.3 mg/kg is relatively effectual and safe and can be selected for more clinical researches in Chinese subjects.

The phylogeographic structure showed Chinese rabies viruses have been transmitted extra-provincially and intra-provincially because of human-related characteristics (Meng et al., 2010). Ming et al. (2009) reported that phylogenetic experiment utilizing either partial or complete genomic sequence of HN10 showed that this isolate is most closely connected with viruses previously shown to circulate in Hunan and Guangxi provinces. Taxitiemuer et al. (2017) reported that wild fox bite is a main risk parameter of rabies infection in Xinjiang Province of China. It has been showed that rabies virus isolated from Guangxi have a close genetic connection and topographical distribution (Liu et al., 2007). Liu et al. (2012) proved that botanical polysaccharide preparations from *Echinacea*, *Astragalus*, kelp, and wolfberry could be applied in rabies vaccine formulations for persistent and early prophylaxis. Human rabies virus vaccine strain CTN181 from China was sequenced, and its overall length of the genome was 11,923 nucleotides (nt), including a leader sequence of 58 nt, phosphoprotein (P) gene of 894nt, nucleoprotein (N) gene of 1353nt, glycoprotein (G) gene of 1575nt, matrix protein (M) gene of 609nt, a trailer region of 70nt, and RNA-dependent RNA polymerase (RdRp, L) gene of 6387nt (Du et al., 2008). Li et al. (2013) reported that Sanofi Pasteur has improved a next generation rabies vaccine (PVRV-NG), and it was at least as immunogenic as Verorab and was well tolerates and it presents an appropriate substitute for the prophylaxis of rabies. Liu et al. (2023) reported that vaccine+ormutivimab can protect those who are above 18 years old with category III suspected rabies exposure as a component of postexposure prophylaxis, and ormutivimab has a weaker impact on the immunity response of rabies vaccines. Meng et al. (2011) concluded that although dog rabies viruses comprise six main clades, namely, Africa 2, Africa 3, Arctic-related, Cosmopolitan, Indian and Asian subcontinent clades, the last three clades circulate widely in Asia, with the Arctic-related clade circulating in a large region spreading from central Asia to eastern Asia, and countries such as Nepal, Russia, northeastern Iran, Pakistan, Korea, and the north of India. In some studies, it has been reported that incomplete postexposure prophylaxis and not quick seeking postexposure prophylaxis are usual in rural China and may cause to PEP failure and rabies deaths (Wang et al., 2018; Chen et al., 2019a,b), and people should be well educated on how to treat dog bites and seek quick, and proper PEP, and not use other unapproved methods (Zhao et al., 2019). There are two kinds of oral rabies vaccination which are currently being under commercial licence for the vaccination of different wildlife species, vector-based vaccines (VBVs), and modified live vaccines (MLVs); VBVs are designed by inserting antigenic glycoprotein encoding genetic material from the rabies virus into other vector viruses, and the active component of MLVs is replication-component, live rabies virus which has been modified so that it can induce the body ،s natural immune response (Yale et al., 2022). The main goal of rabies vaccines are providing appropriate amounts of rabies glycoprotein to locations, rich in antigen presenting cell to lead to production of enough rabies virus neutralizing antibodies, as well as memory T and B

cells, for prevention of rabies (Moore, 2021). Different clinical experiments have proved sufficient data to support a decrease in the number of doses, a shorter timeline needed for PEP, and the approval of the intradermal route of application for PEP and pre-exposure prophylaxis (PreP) (Briggs and Moore, 2021). Song et al. (2009) reported that the following suggestions and recommendations should be considered for prevention and treatment of rabies in China, (1) establishing national animal rabies surveillance network is important, (2) strict control of free-ranging dogs and obligatory rabies vaccination should be done, (3) the cost of PEP should be free or reduces, particularly in rural areas, (4) education of the public and health care staff should be increased, and (5) PEP should be decided to withhold or start on the basis of postmortem diagnosis of the biting animal. Chen et al. (2023) concluded that the clinical application of Ormutivimab, boosts post-exposure prophylaxis of rabies in China, and decreases infection rate. Li et al. (2021) observed that after 2011, the rate of negative reaction to rabies vaccine in China has significantly declined, and the rate of negative reaction to rabies vaccine in the midwestern states is higher than the counterpart in the eastern parts.

8. Conclusion

Rabies is the main fatal zoonosis induced by the rabies virus, which infects wild animals, humans, and livestock. Its virus belongs to the *lyssavirus* genus, which also consists of other *lyssavirus* species that cause rabies-like diseases and can be carried by domestic animals, wild carnivores and many bat species. The rabies virus is the only pathogen accountable for the large majority of rabies cases in humans. Rabies virus infects the peripheral nerves and then migrates into the central nervous system of the brain through the spinal cord, causing fatal encephalitis and myelitis and resulting the death of the infected subjects. Basic rabies reservoirs are dogs in major vector of rabies throughout the world, particularly Asia, Latin American and Africa; foxes, in Europe, North American, and Arctic; Raccoons in Eastern United States; skunks in Modwestern United States, Western Canada; coyotes in Africa, Asia, and North America, mongooses in yellow mongoose in Africa, and Asia, Indian mongoose in the Caribbean Islands, and bats in North American Europe, South and Center America. The genomic RNA of the classic rabies virus (RAVB) encodes five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G0), and large protein (L). The G protein is the only protein on the surface of mature virus and acts an essential role in virus infection. Also, the G protein is a major antigenic stimulus of the host immune system during infection and vaccination. There are three categories of exposure, (I) touching, feeding of animals or licks on intact skin, (II) Minor scratches or abrasions without bleeding or licks on broken and nibbling of uncovered skin which needs immediate vaccination and administration of rabies immunoglobulin, (III) single or multiple transdermal bites, scratches or vaccine contamination of mucous membrane saliva which needs local wound treatment. Vaccination against rabies is of primary importance in control of infection in both humans and animals. WHO also recommended only vaccines of high quality and efficacy. Rabies is preventable through prompt administration of post-exposure prophylaxis (PEP) to exposed persons, but PEP access is limited in many rabies-endemic countries. The death toll can be significantly reduced through access to post-exposure prophylaxis (PEP), consisting of wound cleaning, rabies immunoglobulin (RIG) and vaccination. Access to PEP is limited in many developing and under-developed countries with endemic rabies and PEP is often only available from health facilities in mega cities. Patients also need to pay for PEP and the costs are reported as a major obstacle for many victims. Rabies have been reported in all over the China, especially Hunan, Sichuan, Guangdong, Guangxi, Hubei, Guizhou, Jiangxi, Shandong, Anhui, Henan, Jiangsu, Fujian, Hebei, Yunnan, and Liaoning. In China, rabies remains is still a public health issue and the techniques to control and prevent human rabies should be included public education and awareness about rabies, elimination of stray animals, pet vaccination programs, and enhanced post-exposure management. Domestic dogs are the primary vector and reservoir of rabies transmission in China, although RAVB has been isolated and identified in other animal species, such as ferret badger, cat, fox, cattle, pig, and donkey. Unsuccessful control of rabies and inadequate PEP of cases may be the principle factors inducing to the serious human rabies epidemic in China. It is widely approved that rabies elimination requires an integrated approach by human and animal related services. There is an urgent need to have public health management which may improve effectiveness and sustainability of rabies eliminating programs. China needs to focus on prevention, strengthen multi-agency coordination mechanism, boost the quality of public health services in the years to come.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	M.H.S.	W.S.
C	50	50
D	50	50
S	50	50
DCP	50	50
L	50	50
W	50	50
CR	50	50
SR	50	50
PM	50	50
FA	50	50

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding accustion.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgements

This work was supported by the National Key R&D Program of China (Grant No. 2019YFA0904700). This research was also funded by the Natural Science Foundation of Beijing, China (Grant No. M21026).

References

Abedi M, Haftcheshmeh SM, Bashar R. 2023. Rabies vaccine: Recent update and comprehensive review of in vitro and in vivo studies. Process Biochem, 124: 201-220. https://doi.org/10.1016/j.procbio.2022.11.011

Abela-Ridder B, Knopf L, Martin S. 2016. The beginning of the end of rabies? Lancent Glob Health, 4: e780-781.

Abutarbsh SM, Hamdallah A, Hawawsheh M, Alsawalha L, Elizz NA, Dodeen R, Mousa AB, Alhawarat MN, Hailat E, Mahrous H. 2022. Implementation of one health approach in Jordan: Joint risk assessment of rabies and avian influenza utilizing the tripartite operational tool. One Health, 15: 100453. https://doi.org/10.1016/j.onehlt.2022.100453

Aiello R, Zecchin B, Caenazzo ST, Cattoli G, De Benedictis P. 2016. Disinfection protocols for necropsy equipment in rabies laboratories: Safety of personnel and diagnostic outcome. J Virol Meth, 234: 75-79. https://doi.org/10.1016/j.jviromet.2016.03.017

Anilionis WH, Wunner PJ. 1981. Curtis, Structure of the glycoprotein gene in rabies virus. Nature, 294: 275-278.

Anothaisintawee T, Genuino AJ, Thavorncharoensap M. 2019. Cost-effectiveness modeling studies of all preventive measures against rabies: a systematic review. Vaccine, 37: A146-A153.

Ashraf S, Singh PK, Yadav DK, Shahnawaz Md, Mishra S, Sawant SV, Tuli R. 2005. High level expression of surface glycoprotein of rabies virus in tobacco leaves and its immunoprotective activity in mice. J Biotechnol, 119: 1-14.

Atici YT, Oguzoglu TC. 2022. The comparison of full G and N gene sequences from Turkish rabies virus field strains. Virus Res, 315: 198790. https://doi.org/10.1016/j.virusres.2022.198790

Bassi EJ. 2008. Expression, purification and immunodetection of a recombinant fragment (residue 179-281) of the G protein from rabies virus ERA strain. Protein Express Purif, 59: 309-313.

Beyene K, Derese A, Teshome G, Teshome D. 2018. Review on rabies vaccine: as prevention and control option of rabies. Austin J Vet Sci Anim Husb, 5(3): 1049.

Briggs DJ, Moore SM. 2021. The route of administration of rabies vaccines: Comparing the data. Viruses, 13: 1252. https://doi.org/10.3390/v13071252

Cai L, Wang L, Guan X, Wang L, Hu X, Wu Y, Tong Y, Wang P. 2021. Epidemiological analysis of rabies in central China from 2013 to 2018. Infect Drug Resis, 2753-2762. https://doi.org/10.2147/IDR.S314881

Celis E, Ou D, Dietzschold B, Koprowski H. 1988. Recognition of rabies and rabies-related virus by T cells derived from human vaccine recipients. J Virol, 62: 3128-3134.

Challhua R, Akashi L, Zuniga J, de Carvalho Ruthner Batista HB, Moratelli R, Champi A. 2023. Portable reduced graphene oxide biosensor for detection of rabies virus in bats using nasopharyngeal swab samples. Biosens Bioelectron, 232: 115291. https://doi.org/10.1016/j.bios.2023.115291

Changalucha J, Steenson R, Grieve E. 2019. The need to improve access to rabies post-exposure vaccines: lessons from Tanzania. Vaccine, 37: A45-A53.

Chen F, Liu QY, Jiang QQ, Shi J, Luba TR, Hundera AD, Fang P, Cao S, Lu Z. 2019a. Risk of human exposure to animal vites in China: a clinical-based cross-sectional study. Ann N Y Acad Sci, 1452(1): 78-87. https://doi.org/10.1111/nyas.14202

Chen T, Zhou X, Qi Y. 2019b. Feline herpesvirus vectored-rabies vaccine in cats: a dual protection. Vaccine, 37: 2224-2231.

Chen R, Li H, Zhu W, Cheng H, Li Y. 2023. Expert consensus on the clinical application of ormutivimab injection for use against the rabies virus. Expert Opin Drug Saf, 23(6): 755-762. https://doi.org/10.1080/14740338.2023.2233411

Cherian S, Singh R, Singh KP. 2015. Phylogenetic analysis of Indian rabies virus isolates targeting the complete glycoprotein gene. Infect Gene Evol, 36: 333-338.

Cliquet F, Barrat J, Guiot AL. 2008. Efficacy and bait acceptance of vaccinia vectored rabies glycopteotin vaccine in captive foxes (Vulpes vulpes), raccoon dogs (Nyctereutes procyonoides) and dogs (Canis familiaris). Vaccine, 26: 4627-4638.

Coertse J, Viljoen N, Weyer J, Markotter W. 2023. Comparative neutralization activity of commercial rabies immunoglobulin against diverse Lyssaviruses. Vaccines, 11: 1255. https://doi.org/10.3390/vaccines11071255

Coll JM. 1995. The glycoprotein G of rhabdoviruses. Arch Virol 140: 851-987.

Costa WA, Cunha RS, Bolzan VL. 2007. Immunogenicity and safety of a new Vero cell rabies vaccine produced using serum-free medium. Vaccine, 25: 8140-8145.

Cox JH, Dietzschold B, Schneider LG. 1977. Rabies virus glycoprotein II: biological and serological characterization. Infect Immunol, 16: 754-759.

Cruz ET, Romero IAF, Mendoza JGL. 2008. Efficient post-exposure prophylaxis against rabies by applying a four-dose DNA vaccine intranasally. Vaccine, 26: 6936-6944.

Cui H, Shahrajabian MH, Kuang Y, Zhang HY, Sun W. 2023. Heterologous expression and function of cholesterol oxidase: A review. Protein Pept Lett, 30(7): 531-540. https://doi.org/10.2174/0929866530666230525162545

Das LJ, Isloor S, Santosh AK, Bhat A, Sharada R, Rathnamma D, Veeregowda BM, Phanşraj KL, Kumar NA, Vanak AT. 2022. A comparative evaluation of the estimation of rabies virus

antibodies among free-roaming, vaccinated dogs in Bengaluru, India. Viruses, 14: 484. https://doi.org/10.3390/v14030484

Deidda R, Orlandini S, Hubert P, Hubert C. 2018. Risk-based approach for method development in pharmaceutical quality control context: a critical review. J Pharm Biomed Anal, 161: 110-121.

Deubelbeiss AN, Rachsel Ch, Bachli EB, Kuffer A, Budka H, Eniseyskiy P, Zimmermann H, Wallace RM, Farley S, Zanoni RG. 2013. Imported human rabies in Switzerland 2012: A diagnostic conundrum. J Clin Virol, 57(2): 178-181. https://doi.org/10.1016/j.jcv.2013.02.001

Ding Y, Wu M, Zhang H, Zhu X, Hu Y, Li X, Liu J, Tsao E, Liu M, Li C. 2020. Safety, pharmacokinetics and pharmacodynamics of SYN023 alone or in combination with a rabies vaccine: An open, parallel, single dose, phase 1 bridging study in healthy Chinese subjects. Antivir Res, 184: 104956. https://doi.org/10.1016/j.antiviral.2020.104956

Diogo MM, Ribeiro SC, Queiroz JA. 2001. Production, purification and analysis of an experimental DNA vaccine against rabies. J Gene Med, 3: 577-584.

Dong Y, Wang L, Burgner DP, Burgner DP, Miller, JE, Song Y, Ren X, Li Z, Xing Y, Ma J, Sawyer SM, Patton G. 2020. Infectious diseases in children and adolescents in China: analysis of national surveillance data from 2008 to 2017. BMJ, 369: m1043. https://doi.org/10.1136/bmj.m1043

Du J, Zhang Q, Tang Q, Li H, Tao X, Morimoto K, Nadin-Davis SA, Liang G. 2008. Characterization of human rabies virus vaccine strain in China. Virus Res, 135(2): 260-266. https://doi.org/10.1016/j.virusres.2008.04.002

Duong V, Tarantola A, Ong S, Mey C, Choeung R, Ly S, Bourhy H, Dussart P, Buchy P. 2016. Laboratory diagnostics in dog-mediated rabies: an overview of performance and a proposed strategy for various settings. Int J Infect Dis, 46: 107-114. https://doi.org/10.1016/j.ijid.2016.03.016

Echevarria J, Banyard AC, McElhinney LM, Fooks AR. 2019. Current rabies vaccine do not confer protective immunity against divergent lyssaviruses circulating in Europe. Viruses, 11: 892.

Ertl HCJ. 2019. New rabies vaccines for use in humans. Vaccines, 7: 54. https://doi.org/10.3390/vaccines7020054

Evans JS, Horton DL, Easton AJ, Fooks AR, Banyard AC. 2012. Rabies virus vaccines: Is there a need for a pan-lyssavirus vaccine? Vaccine, 30: 7447-7454.

Fan L, Zhang L, Li J, Zhu F. 2022. Advances in the progress of monoclonal antibodies for rabies. Human Vaccin Immunother, 18(1): 2026713. https://doi.org/10.1080/21645515.2022.2026713

Finke S, Conzelmann KK. 2003. Dissociation of rabies virus matrix protein functions in regulation of viral RNA synthesis and virus assembly. J Virol, 77: 12074-12082.

Fooks AR, Banyard AC, Ertl HCJ. 2019. New human rabies vaccines in the pipeline. Vaccine, 37:A140-A145.

Fu ZF. 1997. Rabies and rabies research: past, present and future. Vaccine, 15: S20-S24.

Gaudin Y, Ruigrok R, Tuffereau C, Knossow A. 1992. Flamand, Rabies glycoprotein is a trimer. Virology, 187: 627-632.

Gerard FCA, Ribeiro JrEDA, Leyrat C, Ivanov I, Blondel D, Longhi S, Ruigrok RWH, Jamin M. 2009. Modular organization of rabies virus phosphoprotein. J Mol Biol, 388: 978-996.

Gholami A, Fayaz A, Farahtaj F. 2014. Rabies in Iran: past, present and future. J Med Microbiol Infec Dis, 2(1): 1-10.

Gibert R, Alberti M, Poirier B, Jallet C, Tordo N, Morgeaux S. 2013. A relevant in vitro ELISA test in alternative to the in vivo NIH test for human rabies vaccine batch release. Vaccine, 31: 6022-6029.

Gong W, Jiang Y, Za Y, Zeng Z, Shao M, Fan J, Sun Y, Xiong Z, Yu X, Tu C. 2010. Temporal and spatial dynamics of rabies viruses in China and Southeast Asia. Virus Res, 150(1-2): 111-118. https://doi.org/10.1016/j.virusres.2010.02.019

Gongal G, Sampath G, Kishore J, Bastola A, Punrin S, Gunesekera A. 2022. The impact of Covid-19 pandemic on rabies post-exposure prophylaxis services in Asia. Human Vaccin Immunother, 18(5): 2064174. https://doi.org/10.1080/21645515.2022.2064174

Gongal G, Wright AE. 2011. Human rabies in the WHO Southeast Asia region: forward steps for elimination. Adv Prev Med, 2011: 383870.

Goto H, Minamoto N, Ito H, Sugiyama M, Kinjo T, Kawai A. 2000. Mapping of epitopes and structural analysis of antigenic sites in the nucleoprotein of rabies virus. J General Virol, 81: 119-127.

Guo D, Zhou H, Zou Y, Yin W, Yu H, Si Y, Li J, Zhou Y, Zhou X, Magalhaes RJS. 2013. Geographical analysis of the distribution and spread of human rabies in China from 2005 to 2011. Plos One, 8: e72352. https://doi.org/10.1371/journal.pone.0072352

Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs DJ, Cleaveland S, Costa P, Freuling CM, Hiby E, Knopf L, Leanes F, Meslin F-X, Metlin A, Miranda ME, Muller T, Nel LH, Recuenco S, Rupprecht CE, Schumacher C, Taylor L, Global Alliance for Rabies Control Partners for Rabies Prevention. 2015. Estimating the global burden of endemic canine rabies. PLoS Negl Trop Dis, 9(4). http://doi.org/10.1371/journal.pntd.0003709e0003709.

Hampson K, Dobson A, Kaare M, Dushoff J, Magoto M, Sindoya E, Cleaveland S. 2008. Rabies exposures, post-exposure prophylaxis and deaths in a region of endemic canine rabies. PLoS Negl Trop Dis, 2(11): e 339.

He Y, Gao D, Zhang M. 2006. Expression of the nucleoprotein gene of rabies virus for use as a diagnostic reagent. J Virol Meth, 138(1-2): 147-151. https://doi.org/10.1016/j.jviromet.2006.08.006

Hemachudha T, Laothamatas J, Rupprecht CE. 2002. Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges. Lancet Neurol, 1(2): 101-109. https://doi.org/10.1016/S1474-4422(02)00041-8

Hou Q, Jin Z, Ruan S. 2012. Dynamics of rabies epidemics and the impact of control efforts in Guuangdong province, China. J Theor Biol, 300: 39-47. https://doi.org/10.1016/j.jtbi.2012.01.006

Hu RL, Liu Y, Zhang SF, Zhang F, Fooks AR. 2007. Experimental immunization of cats with a recombinant rabies-canine adenovirus vaccine elicits a long-lasting neutralizing antibody response against rabies. Vaccine, 25: 5301-5307.

Huang J, Ruan S, Shu Y, Wu X. 2019. Modeling the transmission dynamics of rabies for dog, Chinese ferret badger and human interactions in Zhejiang province, China Bull Math Bio, 81: 939-962. https://doi.org/10.1007/s11538-018-00537-1

Huang Y, Tang Q, Nadin-Davis SA, Zhang S, Hooper CD, Ming P, Du J, Tao X, Hu R, Liang G. 2010. Development of a reverse genetic system for a human rabies virus vaccine strain employed in China. Virus Res, 149(1): 28-35. https://doi.org/10.1016/j.virusres.2009.12.009

Itakura Y, Tabata K, Morimoto K, Ito N, Chambaro HM, Eguchi R, Otsuguro K-I, Hall WW, Orba Y, Sawa H, Sasaki M. 2022. Glu333 in rabies virus glycoprotein is involved in virus attenuation through astrocyte infection and interferon responses. iScience, 25(4): 104122. https://doi.org/10.1016/j.isci.2022.104122

Ito N, Okamoto T, Sasaki M, Miyamoto S, Takahashi T, Izumi F, Inukai M, Jarusombuti S, Okada K, Nakagawa K, Fuji Y, Nishiyama S, Masatani T, Sawa H, Sugiyama M. 2021. Safety enhancement of a genetically modified live rabies vaccine strain by introducing an attenuating Leu residue at position 333 in the glycoprotein. Vaccine, 39(38): 3777-3784. https://doi.org/10.1016/j.vaccine.2021.05.002

Izumi F, Miyamoto S, Masatani T, Sasaki M, Kawakami K, Takahashi T, Fujiwara T, Fujii Y, Okajima M, Nishiyama S, Sawa H, Sugiyama M, Ito N . 2023. Generation and characterization of a genetically modified live rabies vaccine strain with attenuating mutations in multiple viral proteins and evaluation of its potency in dogs. Vaccine, 41(33): 4907-4917. https://doi.org/10.1016/j.vaccine.2023.06.076

Jochmans D, Neyts J. 2019. The path towards effective antivirals against rabies. Vaccine, 37: 4660-4662.

Johnson SR, Slate D, Nelson KM, Davis AJ, Mills SA, Forbes JT, VerCauteren KC, Gilbert AT, Chipman RB. 2021. Serological responses of Raccoons and striped skunks to Ontario rabies vaccines bait in West Virginia during 2012-2016. Viruses, 13: 157. https://doi.org/10.3390/v13020157

Kasem S, Hussein R, Al-Doweriej A, Qasim I, Abu-Obeida A, Almulhim I, Alfarhan H, Hodhod AA, Abel-Latif M, Hashim O, Al-Mujalli D, Al-Sahaf A. 2019. Rabies among animals in Saudi Arabia. J Infect Public Health, 12: 445-447.

Khan A, Ayaz R, Mehtab A, Naz K, Haider W, Gondal MA, Umer M, Afzal MI, Shah NA, Afzal MS, Yayi G, Ahmad KS, Ahmed H. 2019. Knowledge, attitude and practices (KAPs) regarding rabies endemicity among the community members, Pakistan. Acta Tropica, 200: 105156.

Knobel DL, Cleaveland S, Coleman PG, Fevre EM, Meltzer MI, Miranda MEG, Shaw A, Zinsstag J, Meslin F-X. 2005. Re-evaluating the burden of rabies in Africa and Asia. Int L Pub Health, 83: 360-368.

Koraka P, Bosch BJ, Cox M, Chubet R, Amerongen GV, Lovgren-Bengtsson K, Martina BEE, Roose J, Rottier PJM, Osterhaus ADME. 2014. A recombinant rabies vaccine expression the trimeric from the glycoprotein confers enhanced immunogenicity and protection in outbred mice. Vaccine, 32: 4644-4650.

Koraka P, Martina BEE, Smreczak M. 2019. Inhibition of caspase-1 prolongs survival of mice infected with rabies virus. Vaccine, 37: 4681-4685.

Laager M, Lechenne M, Naissengar K. 2019. A metapopulation model of dog rabies transmission in N,Djamena, Chad. J Theor Biol, 462: 408-417.

Langguth A, Leelahapongsathon K, Wannapong N, Kasemsuwan S, Ortmann S, Vos A, Boer M. 2021. Comparative study of optical markers to assess bait system efficiency concerning vaccine release efficiency concerning vaccine release in the oral cavity of dogs. Viruses, 13: 1382. https://doi.org/10.3390/v13071382

Lankester F, Hampson K, Lembo T, Palmer G, Taylor L, Cleaveland S. 2014. Implementing Pasteur,s vision for rabies elimination. Science, 345: 1562-1564.

Lee L. 2004. The current state of public health in China. Annu Rev Pub Health, 25: 327-339.

Li AJ, Sreenivasan N, Siddiqi UR, Tahmina S, Penjor K, Sovann L, Gunesekera A, Blanton JD, Knopf, Hyde TB. 2019. Descriptive assessment of rabies post-exposure prophylaxis procurement, distribution, monitoring, and reporting in four Asian countries: Bangladesh, Bhutan, Cambodia, and Sri Lanka, 2017-2018. Vaccine, 37: A14-A19.

Li D, Liu Q, Chen F, Jiang Q, Wang T, Yin X, Lu Z, Cao S. 2021. Knowledge, attitudes, and practices regarding rabies and its prevention and control among bite victims by suspected rabid animals in China. One Health, 13:100264. https://doi.org/10.1016/j.onehlt.2021.100264

Li H, Li Y, Chen Y, Chen B, Su Q, Hu Y, Xiong C. 2023. Mapping rabies distribution in China: a geospatial analysis of national surveillance data. Int J Infect Dis, 131: 140-146. https://doi.org/10.1016/j.ijid.2023.04.002

Li L, Li Y, Bai Y, Li G, Zhang J, Yang L, Zhao W, Zhao W, Luo F, Zhao Q, Zhang Z, Liu Y, Lu Q, Wang H, Zhang J, Zhang Y, Gao J, Shi N. 2022. Neutralizing antibody activity, safety and immunogenicity of human anti-rabies virus monoclonal antibody (Ormutivimab) in Chinese healthy adults: A phase IIb randomized, double-blind, parallel-controlled study. Vaccine, 40: 6153-6162. https://doi.org/10.1016/j.vaccine.2022.09.022

Li R, Huang L, Li J, Mo Z, He B, Wang Y, Wu X, Minutello M, Guinet-Morlot F, Pichon S. 2013. A next-generation, serum-free, highly purified Vero cell rabies vaccine is safe and as immunogenic as the reference vaccine Verorab® when administered according to a post-exposure regimen in healthy children and adults in China. Vaccine, 31(50): 5940-5947. https://doi.org/10.1016/j.vaccine.2013.10.043

Li W, Liu S, Qian S, Zhu J, Selvaraj JN, Zhang X. 2021. Is the rate of adverse reaction to rabies vaccine in China really as the public thinks?-based on a meta analysis. Human Vaccin Immunother, 17(3): 714-722. https://doi.org/10.1080/21645515.2020.1794218

Li X, Luo J, Wang S, Shen Y, Qiu Y, Wang X, Deng X, Liu X, Bao W, Liu P, Zhou J, Ding C, Ma Z. 2010. Engineering, expression, and immune-characterization of recombinant protein comprising multi-neutralization sites of rabies virus glycoprotein. Protein Express Purif, 70: 179-183.

Linscott AJ. 2012. Rabies. Clin Microbiol Newslett, 34(22): 177-180.

Liu Q, Xiong Y, Luo TR, Wei Y-C, Nan S-J, Liu F, Pan Y, Feng L, Zhu W, Liu K, Guo J-G, Li H-M. 2007. Molecular epidemiology of rabies in Guangxi Province, south of China. J Clin Virol, 39(4): 295-303. https://doi.org/10.1016/j.jcv.2007.04.021

Liu X, Feng X, Tang Q, Wang Z, Qiu Z, Li Y, Wang C, Feng Z, Zhu J, Guan X. 2010a. Characterization and potential diagnostic application of monoclonal antibodies specific to rabies virus. J Biomed Res, 24(5): 395-403. https://doi.org/10.1016/S1674-8301(10)60053-X

Liu Y, Zhang SD, Wu XF, Zhao J, Hou Y, Zhang F, Velasco-Villa A, Rupprecht CE, Hu R. 2010b. Ferret badger rabies origin and its revisited importance as potential source of rabies transmission in Southeast China. BMC Infect Dis, 10: 234. https://doi.org/10.1186/1471-2334-10-234

Liu Y, Zhang S, Zhang F, Hu R. 2012. Adjuvant activity of Chinese herbal polysaccharides in inactivated veterinary rabies vaccines. Int J Biol Macromol, 50(3): 598-602. https://doi.org/10.1016/j.ijbiomac.2012.01.035

Liu Y, Chen Q, Zhang F. 2013. Evaluation of rabies biologics against irkut virus isolated in China. J Clin Microbiol, 51(11): 3499-3504.

Liu Y, Zhang S, Zhao J, Zhang F, Hu. 2013. Isolation of Irkut virus from a Murina leucogaster bat in China. PLoS NeglTrop Dis, 7: e2097.

Liu Y, Zhang S, Zhao J, Zhang F, Li N, Lian H, Wuengege, Guo S, Hu R. 2014. Fox- and raccoon-dog-associated rabies ourbreaks in northern China. Virol Sin, 29(5): 308-310.

Liu Y, Zhang HP, Zhang SF, Wang J-X, Zhou H-N, Zhang F, Wang Y-M, Ma L, Li N, Hu R-L. 2016. Rabies outbreaks and vaccination in domestic camels and cattle in northwest China. PLoS Negl Trop Dis, 10: e0004890.

Liu X, Li Y, Li J, Zhou J, Guo J, Pu Y, Jiang Y, Zhou Y, Jiang Z, Shu Q, Wang C, Wang J, Zhao Y, Zhao W, Wang H, Wei J, Yu H, Gao J Li X. 2023. Comparing recombinant human rabies monoclonal antibody (ormutivimab) with human rabies immunoglobulin (HRIG) for postexposure prophylaxis: A phase III, randomized, double-blind, non-inferiority trial. Int J Infect Dis, 134: 53-62. https://doi.org/10.1016/j.ijid.2023.05.017

Luo J, Zhang Y, He H, Liu Q, Huang S, Guo X. 2019. Artesunate enhances the immune response of rabies vaccine as an adjuvant. Vaccine, 37: 7478-7481.

Luo Y, Zhang Y, Liu X, Yang Y, Yang X, Zheng z, Deng X, Wu X, Guo X. 2013. Characterization of a wild rabies virus isolate of porcine origin in China. Infect Gen Evol, 17: 147-152.

Macfarlan RI, Dietzschold B, Koprowski H. 1986. Stimulation of cytotoxic T-lymphocyte responses by rabies virus glycoprotein and identification of an immunodominant domain. Mol Immunol, 23: 733-741.

Marosi A, Dufkova L, Forro B. 2019. Combination therapy of rabies-infected mice with inhibitors of pro-inflammatory host response, antiviral compounds and human rabies immunoglobulin. Vaccine, 37: 4724-4735.

McGettigan JP. 2010. Experimental rabies vaccines for humans. Expert Rev. Vaccines, 9: 1177-1186.

Mebatsion T, Wiland F, Conzelmann KK. 1999. Matrix protein of rabies virus is responsible for the assembly and budding of bullet-shaped particles and interacts with the transmembrane spike glycoprotein G. J Virol, 73: 242-250.

Meng S, Xu G, Wu X. 2010. Transmission dynamics of rabies in China over the last 40 years: 1969-2009. J Clin Virol, 49(1): 47-52. https://doi.org/10.1016/j.jcv.2010.06.014

Meng S, Sun Y, Wu X. 2011. Evolutionary dynamics of rabies viruses highlights the importance of China rabies transmission in Asia. Virology, 410: 403-409. https://doi.org/10.1016/j.virol.2010.12.011

Mengesha A, Hurisa B, Tesfaye T. 2014. Adaptation of local rabies virus isolates to high growth titer and determination of pathogenicity to develop canine vaccine Ethiopia. J Vaccin Vaccin, 5: 245.

Meske M, Fanelli A, Rocha F. 2021. Evolution of rabies in South America and inter-species dynamics (2009-2018). Trop Med Infect Dis, 6: 98. https://doi.org/10.3390/tropicalmed6020098

Miao F, Li N, Yang J, Chen T, Liu Y, Zhang S, Hu R. 2021. Neglected challenges in the control of animal rabies in China. One Health, 12: 100212. https://doi.org/10.1016/j.onehlt.2021.100212

Ming MF, Teng C, Ye L, Feng ZS, Fei Z, Nan L, Liang HR. 2018. Emerging new phylogenetic groups of rabies virus in Chinese ferret badgers. Biomed. Environ. Sci., 31(6): 479-482. https://doi.org/10.3967/bes2018.064

Ming P, Du J, Tang Q, Yan J, Nadin-Davis SA, Li H, Tao X, Huang Y, Hu R, Liang G. 2009. Molecular characterization of the complete genome of a street rabies virus isolated in China. Virus Res, 143(1): 6-14. https://doi.org/10.1016/j.virusres.2009.02.014

Moghadami M, Poormoghaddam A, Kashfi SM. 2017. Epidemiologic study of animal bites and rabies referring to rabies prevention and treatment center of Jahrom university of medical sciences in 2011-2016. J. Human Environ. Health Promot, 2(4): 226-233.

Moore SM. 2021. Challenges of rabies serology: Defining context of interpretation. Viruses, 13: 1516. https://doi.org/10.3390/v13081516

Morimoto K, MsGettigan JP, Foley HD. 2001. Genetic engineering of live rabies vaccines. Vaccine, 19: 3543-3551.

Muller T, Freuling CM, Wysocki P. 2015. Terrestrial rabies control in the European Union: Historical achievements and challenges ahead. Vet J, 203(1): 10-17. https://doi.org/10.1016/j.tvjl.2014.10.026

Nadal D, Beeching S, Cleaveland S, Cronin K, Hampson K, Steenson R, Abela-Ridder B. 2022. Rabies and the pandemic: lessons for one health. Trans R Soc Trop Med Hyg, 116: 197-200. https://doi.org/10.1093/trstmh/trab123

Nandin-Davis SA. 2023. Special issue Advances in Rabies Research. Viruses, 15: 1557. https://doi.org/10.3390/v15071557

Nishizono A, Yamada K, Khawplod P, Shiota S, Perera D, Matsumoto T, Wimalaratne O, Mitui MT, Ahmed K. 2012. Evaluation of an improved rapid neutralizing antibody detection test (RAPINA) for qualitative and semiquantitative detection of rabies neutralizing antibody in humans and dogs. Vaccine, 30: 3891-3896.

Oliveira FAS, Castro RJS, Oliveira JFD, Barreto FM, Farias MPO, Marinho CLDOC, Soares MJDS, Silva-Junior A, Schwarz DGG. 2022. Geographical and temporal spread of equine rabies in Brazil. Acta Trop, 227: 106302. https://doi.org/10.1016/j.actatropica.2022.106302

Osinubi MOV, Wu X, Franka R, Niezgoda M, Nok AJ, Ogunkoya AB, Rupprecht CE. 2009. Enhancing comparative rabies DNA vaccine effectiveness through glycoprotein gene modifications. Vaccine, 27: 7214-7218.

Perrin P, Jacob Y, Tordo N. 2000. DNA-based immunization against Lyssaviruses. Inter-virol, 43: 302-311.

Pfaff F, Muller T, Freuling CM. 2019. In-depth genome analyses of viruses from vaccine-derived rabies cases and corresponding live-attenuated oral rabies vaccines. Vaccine, 37: 4758-4765.

Qian M-B, Chen J, Bergquist R. 2019. Neglected tropical diseases in the People's Republic of China: progress towards elimination. Infect Dis Poverty, 8: 86. https://doi.org/10.1186/s40249-019-0599-4

Qiao Y-C, Wang F, He Y-L, Yang Q, Yang J, Wei Y-S. 2021. Regional and age difference of human rabies prevalence of the past fourteen years in China. Prevent Vet Med, 187: 105161. https://doi.org/10.1016/j.preventmed.2020.105161

Quiambao BP, Lim JG, Castells VB, Augard C, Petit C, Bravo C, Delore V, Houillon G. 2022. One-week intramuscular or intradermal pre-exposure prophylaxis with human diploid cell vaccine or Vero cell rabies vaccine, followed by simulated post-exposure prophylaxis at one year: A phase III, open-label, randomized, controlled trial to assess immunogenicity and safety. Vaccine, 40(36): 5347-5355. https://doi.org/10.1016/j.vaccine.2022.07.037

Rath A, Choudhury S, Batra D, Kapre SV, Rupprecht CE, Gupta SK. 2005. DNA vaccine for rabies: relevance of the trans-membrane domain of the glycoprotein in generating an antibody response. Virus Res, 113: 143-152.

Recuenco S, Warnock E, Osinubi MOV, Rupprecht CE. 2017. A single center, open label study of intradermal administration of an inactivated purified chick embryo cell culture rabies virus vaccine in adults. Vaccine, 35: 4315-4320.

Ren J, Gong Z, Chen E. 2015. Human rabies in Zhejiang province, China. Int J Infect Dis, 38: 77-82. https://doi.org/10.1016/j.ijid.2015.07.013

Rogee S, Larrous F, Jochmans D. 2019. Pyrimethamine inhibits rabies virus replication in vitro. Antivir Res, 161: 1-9.

Ruan S. 2017. Modeling the transmission dynamics and control rabies in China. Math Biosci, 286: 65-93. https://doi.org/10.1016/j.mbs.2017.02.005

Rudd RJ, Smith JS, Yager PA, Orciari LA, Trimarchi CV. 2005. A need for standardized rabies-virus diagnostic procedures: Effect of cover-glass mountant on the reliability of antigen detection by the fluorescent antibody test. Virus Res, 111(1): 83-88. https://doi.org/10.1016/j.virusres.2005.03.014

Rupprecht CE, Kuzmin IV, Yale G, Nagarajan T, Meslin F-X. 2019. Priorities in applied research to ensure programmatic success in the global elimination of canine rabies. Vaccine, 37: A77-A84.

Rysava K, Miranda ME, Zapatos R, Lapiz S, Rances P, Miranda LM, Roces MC, Friar J, Townsend SE, Hampson K. 2019. On the path to rabies elimination; the need for risk assessments to improve administration of post-exposure prophylaxis. Vaccine, 37: A64-A72.

Saffar F, Heinemann M, Heitkamp C, Stelzl DR, Ramharter M, Schnuk M, Rothe C, Buhler S. 2023. Rabies post-exposure prophylaxis of international travellers- Results from two major German travel clinics. Travel Med Infect Dis, 53: 102573. https://doi.org/10.1016/j.tmaid.2023.102573

Sambo M, Cleaveland S, Ferguson H. 2013. The burden of rabies in Tanzania and its impact on local communities. PLoS Negl Trop Dis, 7(11): e2510.

Scrima N, Bars RL, Nevers Q. 2023. Rabies virus P protein binds to TBK1 and interferes with the formation of innate immunity-related liquid condensates. Cell Rep, 42(1): 111949. https://doi.org/10.1016/j.celrep.2022.111949

Seif I, Coulon P, Rollin PE, Flamand A. 1985. Rabies virulence effect on pathogenicity and sequence characterization of rabies virus mutations affecting antigenic site III of the glycoprotein. J Virol, 53: 926-934.

Servat A, Wasniewski M, Cliquet F. 2019. Cross-protection of inactivated rabies vaccines for veterinary use against bat lyssaviruses occurring in Europe. Viruses, 11: 936.

Shafiur Rahaman Kh. 2017. Free roaming dogs: a threat to public health. Int J Epidemiol Res, 4(3): 182-184.

Shahrabian MH, Kuang Y, Cui H et al. 2023. Metabolic changes of active components of important medicinal plants on the basis of traditional Chinese medicine under different environmental stresses. Curr Org Chem, 27(9): 782-806.

Shahrajabian MH, Sun W, Cheng Q. 2020a. Product of natural evolution (SARS, MERS, and SARS-CoV-2); deadly disases, from SARS to SARS-CoV-2. Hum. Vaccines Immunother, 17(1): 62-83. https://doi.org/10.1080/21645515.2020.1797369

Shahrajabian MH, Sun W, Soleymani A, Cheng Q. 2020b. Traditional herbal medicines to overcome stress, anxiety and improve mental health in outbreaks of human coronaviruses. Phytother Res, 2020(1): 1-11. https://doi.org/10.1002/ptr.6888

Shahrajabian MH, Sun W, Cheng Q. 2021. Different methods for molecular and rapid detection of human novel coronavirus. Curr Pharm Des, 27: 1-10. https://doi.org/10.2174/1381612827666210604114411

Shahrajabian MH, Sun W. 2023a. Mechanism of action of collagen and epidermal growth factor: A review on theory and research methods. Mini-Rev Med Chem, 24(4): e160823219749. https://doi.org/10.2174/1389557523666230816090054

Shahrajabian MH, Sun W. 2023b. Study of different types of fermentation in wine-making process and considering aromatic substances and organic acid. Curr Org Synth, 20: e030823219388. https://doi.org/10.2174/1570179420666230803102253

Shahrajabian MH, Sun W. 2023c. Various techniques for molecular and rapid detection of infectious and epidemic diseases. Lett Org Chem, 20(9): 779-801. https://doi.org/10.2174/1570178620666230331095720

Shen Q, Zhang J, Hou YX. 2018. Quality control of the agricultural products supply chain based on "Internet +". Inform Process Agri, 5: 394-400.

Shi W, Kou Y, Xiao J, Zhang L, Gao F, Kong W, Su W, Jiang C, Zhang Y. 2018. Comparison of immunogenicity, efficacy and transcriptome changes of inactivated rabies virus vaccine with different adjuvants. Vaccine, 36: 5020-5029.

Shoemaker SR, Li TX, Wu W, Pak JE, Marqusee S. 2023. Exploring the conformational landscape of the rabies virus glycoprotein using HDX-MS. Biophys J, 122(3): 189. https://doi.org/10.1016/j.bpj.2022.1.1162

Song M, Tang Q, Rayner S. 2014. Human rabies surveillance and control in China, 2005-2012. BMC Infect Dis, 14: 212.

Song M, Tang Q, Wang DM. 2009. Epidemiological investigations of human rabies in China. BMC infect Dis, 9: 210.

Sultan F, Khan A. 2013. Infectious diseases in Pakistan: a clear and present danger. Lancet, 381(9884): 2138-2140.

Sun W, Shahrajabian MH, Cheng Q. 2021. Natural dietary and medicinal plants with anti-obesity therapeutics activities for treatment and prevention of obesity during lock down and in post-covid-19 era. Appl Sci, 11(17): 7889. https://doi.org/10.3390/app11177889

Sun W, Shahrajabian MH, Lin M. 2022. Research progress of fermented functional foods and protein factory-microbial fermentation technology. Fermentation, 8(12): 688. https://doi.org/10.3390/fermentation8120688

Tao X, Liu S, Zhu W, Rayner S. 2021. Rabies surveillance and control in China over the last twenty years. Biosaf Health, 3: 142-147. https://doi.org/10.1016/j.bsheal.2020.11.004

Tarantola A, Tejiokem MC, Briggs DJ. 2019. Evaluating new rabies post-exposure prophylaxis (PEP) regimens or vaccines. Vaccine, 37: A88-A93.

Taxitiemuer A, Tuerdi G, Zhang Y, Wushouer F, Tao XY, Talipu J, Yimamu T, Ma HL. 2017. An investigation of the first case of human rabies caused by a fox in China in May 2016. Biomed Environ Sci, 30(11): 825-828. https://doi.org/10.3967/bes2017.110

Tierradentro-Garcia L, Cortes-Albornoz MC, Talero-Gutierrez C. 2022. Of love and other demons: depicting human rabies in Colombia. Heliyon, 8(6): e09703. https://doi.org/10.1016/j.heliyon.2022.e09703

Tsiodras S, Korou L-M, Tzani M, Tasioudi KE, Kalachanis K, Mangana-Vougiouka O, Rigakos G, Dougas G, Seimenis Am, Kontos V. 2014. Rabies in Greece; historical perspectives in view of the current re-emergence in wild and domestic animals. Travel Med Infect Dis, 12(6): 628-635. https://doi.org/10.1016/j.tmaid.2014.01.013

Undurraga EA, Millien MF, Allel K, Etheart MD, Cleaton J, Ross Y. 2020. Vaccine Evaluation Team; Wallace, R.M. Costs and effectiveness of alternative dog vaccination strategies to improve dog population coverage in rural and urban settings during a rabies outbreak. Vaccine, 38(39): 6162-6173. https://doi.org/10.1016/j.vaccine.2020.06.006

Walker PJ, Kongsuwan K. 1999. Deduced structural model for animal rhabdovirus glycoproteins. J Gen Virol, 80(Pt 5): 1211-1220.

Wambura G, Mwatondo A, Muturi M, Nasimiyu C, Wentworth D, Hampson K, Bichanga P, Tabu C, Juma S, Ngere I, Thumbi SM. 2019. Rabies vaccine and immunoglobulin supply and logistics: challenges and opportunities for rabies elimination in Kenya. Vaccine, 37: A28-A34.

Wang DL, Zhang XF, Jin H, Chen XQ, Duan CX, Wang XC, Bao CJ,

Zhou MH, Ahmad T. 2018. Post-exposure prophylaxis vaccination rate and risk factors of human rabies in mainland China: a meta-analysis. Epidemiol Infect, 147: 1-6. https://doi.org/10.1017/S095026881800.175

Wang L, Tang Q, Liang G. 2014. Rabies and rabies virus in wildlife in mainland China, 1990-2013. Int J Infect Dis, 25: 122-129. https://doi.org/10.1016/j.ijid.2014.04.016

Wang L, Zhang J, Meng S, Ge L, You Y, Xu Q, Wang H, Yang J, Wang S, Wu H. 2022. Safety and immunogenicity of human rabies vaccine for the Chinese population after PEP: A systematic review and meta-analysis. Vaccine, 40(32): 4371-4379. https://doi.org/10.1016/j.vaccine.2022.06.035

Wang W, Ni Y, Gao K, Lu Q, Li X. 2013. Spontaneous pneumomediastinum due to paralytic rabies. Brazil J Infect Dis, 17(1): 94-96.

Wang X, Fang Z, Xiong J, Yang K, Chi Y, Tang X, Ma L, Zhang R, Deng F, Lan K, Zhou D. 2019. A chimpanzee adenoviral vector-based vaccine protects beagle dogs from lethal rabies virus challenge. Virology, 536: 32-38.

Ward MP, Brookes VJ. 2021. Rabies in our neighbourhood: preparedness for an emerging infectious diseases. Pathogens, 10: 375. https://doi.org/10.3390/pathogens10030375

Warrell M. 2010. Rabies and African bat lyssavirus encephalitis and its prevention. Int J Antimicrob Agents, 36: S47-S52.

Whitehouse ER, Mandra A, Bonwitt J, Beasley EA, Taliano J, Rao AK. 2023. Human rabies despite post-exposure prophylaxis: a systematic review of fatal breakthrough infections after zoonotic exposures. Lancet Infect Dis, 23(5): e167-e174. https://doi.org/10.1016/S1473-3099(22)00641-7

Wijaya L, Tham CYL, Chan YFZ, Wong AWL, Wang L-F, Bertoletti A, Low JG. 2017. An accelerated rabies vaccine schedule based on toll-like receptor 3 (TLR3) agonist PIKA adjuvant augments rabies virus specific antibody and T cell response in healthy adult volunteers. Vaccine, 35: 1175-1183.

Wiktor T. 1985. Historical aspects of rabies treatment. Koprowski H, Plotkin SA (editors), World's Debt to Pasteur. Alan R. Liss, New York, US, pp: 141-151.

Woldehiwet Z. 2002. Rabies: recent developments. Res Vet Sci, 73: 17-25.

Wolelaw GA, Yalew WA, Azene AG, Wassie GT. 2022. Rabies prevention practices and associated factors among household heads in Bure Zuria district, North West Ethiopia. Sci Rep, 12: 7361. https://doi.org/10.1038/s41598-022-10863-z

Won YL, Ko KS, Park JO, Choi JO, Lee H, Sung J-M, Lee M-Y. 2019. Achievements, problems, and future direction of the quality control program for special periodic health examination agencies in Republic of Korea. Saf Health Work, 10: 125-129.

Wu H, Wang L, Tao X, Li H, Rayner S, Liang G, Tang Q. 2013. Genetic diversity and molecular evolution of the rabies matrix protein gene in China. Infect Genet Evol, 16: 248-253.

Wu X, Franka R, Svoboda P, Pohl J, Rupprecht CE. 2009. Development of combined vaccines for rabies and immunocontraception. Vaccine, 27: 7202-7209.

Wunner WH, Larson JK, Dietzschold B, Smith CL (1988) The molecular biology of rabies viruses. Rev Infect Dis, 10(4): S771-784.

Wunner WH. 2007. Rabies virus. In: Jackson AC, Wunner WH (eds.) Rabies. Academic Press, San Diego, US, pp: 23-68.

Xing C, Zhang Z, Jiang Q-W. 2014. Analysis on phosphoprotein and matrixprotein gene of rabies virus in Henan Province, China. Int J Infect Dis, 21(1): 187. https://doi.org/10.1016/j.ijid.2014.03.811

Xu M, Liang Z, Xu Y, Wang J. 2015. Chinese vaccine products go global: vaccine development and quality control. Expert Rev Vaccine, 14(5): 763-773.

Yale G, Lopes M, Isloor S, Head JR, Mazeri S, Gamble L, Dukpa K, Gongal G, Gibson. 2022. Review of oral rabies vaccination of dogs and its application in India. Viruses, 14: 155. https://doi.org/10.3390/v14010155

Yang L, Cen J, Xue Q, Li J, Bi Y, Sun L, Liu W. 2013. Identification of rabies virus mimotopes screened from a phage display peptide library with purified dog anti-rabies virus serum IgG. Virus Res, 174: 47-51.

Yang ZW, Dong LG. 2012. Current status of canine rabies in China. Biomed Environ Sci, 25(5): 602-605.

Yin CP, Zhou H, Wu H, Tao X-Y, Rayner S, Wang S-M, Tang Q, Liang G-D. 2012. Analysis on factors related to rabies epidemic in China from 2007-2011. Virol Sinica, 27(2): 132-143.

Yin W, Dong J, Tu C, Edwards J, Guo F, Zhou H, Yu H, Vong S. 2013. Challenges and needs for China to eliminate rabies. Infect Dis Poverty, 2: 23. https://doi.org/10.1186/2049-9957-2-23

Zhai L-L, Wang H, Zhao W, Zhang SF, Miao FM, Cao Y, Chen C, Li YF, Gao J, Lv RY, Zhang SX, Cao JB, Zhang XF, Yang MM, Zhang B, Zhao J, Wei JS, Gao J. 2022. Efficacy of ormutivimab, a novel recombinant human anti-rabies monoclonal antibody, in post-exposure prophylaxis animal models. Travel Med Infect Dis, 46: 102267. https://doi.org/10.1016/j.tmaid.2022.102267

Zhang F, Liu Y, Zhang SF. 2006a. Survey of neutralizing antibody against in dogs in China cities and suburbs. China J Vet Sci, 26(6): 634-636.

Zhang YZ, Xiong CL, Zou Y, Wang DM, Yu C, Zhou JZ, Wang ZX, Zhang YR, Zhen F. 2006b. An epidemiological study of rabies in Anlong County of Guizhou Province. Virol Sinica, 21(4): 394-400.

Zhang YZ, Xiong CL, Zou Y, Wang DM, Jiang RJ, Xiao QY, Hao ZY, Zhang LZ, Yu YX, Fu ZF. 2006c. Molecular characterization of rabies virus isolates in China during 2004. Virus Res, 121(2): 179-188. https://doi.org/10.1016/j.virusres.2006.05.010

Zhang S, Tang Q, Wu X, Liu Y, Zhang F, Rupprecht CE, Hu R. 2009a. Rabies in ferret badgers, southeastern China. Emerg Infect Dis, 15(6): 946-949. https://doi.oorg/10.3201/eid1506.081485

Zhang Y-Z, Xiong C-L, Lin X-D, Zhou DJ, Jiang RJ, Xiao QY, Xie XY, Yu XX, Tan YJ, Li MH, Ai QS, Zhang LJ, Zou Y, Huang C, Fu ZF. 2009b Genetic diversity of Chinese rabies viruses: Evidence for the presence of two distinct clades in China. Infect Genet Evol, 9(1): 87-96. https://doi.org/10.1016/j.meegid.2008.10.014

Zhang J, Jin Z, Sun G-Q, Zho T, Ruan S. 2011. Analysis of rabies in China: Transmission dynamics and control. Plos One, 6(7): e20891. https://doi.org/10.1371/journal.pone.0020891

Zhang Z, Xiong C, Jiang Q-W. 2014. Survey on rabies virus carried by domestic dogs in Henan and Shaanxi Province, China. Int J Infect Dis, 21(1): 186. https://doi.org/10.1016/j.ijid.2014.03.809

Zhang J, Han Q, Song Y, Chen Q, Xia X. 2015. Analysis of subcellular prefoldin 1 redistribution during rabies virus infection. Jundishapur J Microbiol, 8(7): e24757.

Zhang W, Zheng X, Cheng N, Gai W, Xue X, Wang Y, Gao Y, Shan J, Yang S, Xia X. 2016a. Isatis indigotica root polysaccharides as adjuvants for an inactivated rabies virus vaccine. Int J Biol Macromol, 87: 7-15.

Zhang Y, Zhang S, Li W, Hu Y, Zhao J, Liu F, Lin H, Liu Y, Wang L, Xu S, Hu R, Shao H, Li L. 2016b. A novel rabies vaccine based on toll like receptor 3 (TLR3) agonist PIKA adjuvant exhibiting excellent safety and efficacy in animal studies. Virology, 489: 165-172.

Zhao H, Zhang J, Cheng C, Zhou YH. 2019. Rabies acquired through mucosal exposure, China, 2013. Emerg Infect Dis, 25(5): 1028-1029. https://doi.org/10.3201/eid2505.181413

Zhao J, Liu Y, Zhang S, Zhang F, Wang Y, Mi L, Wang S, Hu R. 2014. Molecular characterization of three ferret badger (Melogale moschata) rabies virus isolates from Jiangxi province, China. Arch Virol, 159(8): 2059-2067.

Zhao J, Ma SC, Li SP. 2018. Advanced strategies for quality control of Chinese medicines. J Pharm Biomed Anal, 147: 473-478.

Zhao R, Shan Y, Li M et al. 2020. Novel strategy for expression and characterization of rabies virus glycoprotein. Protein Express Purif, 168: 105567.

Zhou H, Li Y, Chen RF, Tao XY, Yu PC, Cao SC, Li L, Chen ZH, Zhu WY, Yin WW, Li YH, Wang CL, Yu HJ, Chinese Center for Disease Control and Prevention. 2016. Technical guideline for human rabies prevention and control. Zhonghua Liu Xing Bing Xue Za Zhi, 37: 139-163.

Zhu H, Chen X, Shao X, Ba H, Wang F, Wang H, Yang Y, Sun N, Ren J, Cheng S, Wen Y. 2015. Characterization of a virulent dog-originated rabies virus affecting more than twenty fallow deer (Dama dama) in Inner Mongolia, China. Infect Genet Evol, 31: 127-134. https://doi.org/10.1016/j.meegid.2014.12.024

Black Sea Journal of Health Science

doi: 10.19127/bshealthscience.1551540

Open Access Journal
e-ISSN: 2619 – 9041

Review
Volume 7 - Issue 6: 283-287 / November 2024

EFFECT OF ENVIRONMENTAL FACTORS ON THE PRODUCTION OF SILVER NANOPARTICLES BY YEAST STRAINS

Mirmusa M. JAFAROV[1,3], Ergin KARİPTAŞ[2]*, Kamala S. ALKISHIYEVA[3]

[1]*Baku State University, Faculty of Biology, Department of Microbiology, 1148, Baku, Azerbaijan*
[2]*Samsun University, Faculty of Medicine, Department of Medical Microbiology, 55080, Samsun, Türkiye*
[3]*Institute of Microbiology, Ministry of Science and Education of the Republic of Azerbaijan, 1004, Baku, Azerbaijan*

Abstract: In the presented work, the literature data on the influence of various environmental factors were analyzed on the formation of silver nanoparticles by yeast strains. According to literature information and our obtained results, it was determined that the optimal conditions for the synthesis of silver nanoparticles by the yeast strain *Saccharomyces ellipsoideus* BSU-XR1 were on the 21st day of incubation, on 4-6 days of incubation in different strains of *Saccharomyces cerevisiae*, and between 2-10 days in *Candida* strains. The optimal amount of wet biomass was between 8 and 10 g for *Candida* strains and 10 g for *Saccharomyces* strains. The temperature limit for *Saccharomyces* was observed at 25-35 °C, and for *Candida* at 25-37 °C. For strains, synthesis of silver nanoparticles was optimal in the pH range of 4-10, and pH range of 7 for *Candida* strains. Depending on the concentration of $AgNO_3$ (silver nitrate), salt, the optimal synthesis of silver nanoparticles occurred at concentrations of 0.5 and 1 mM for *Saccharomyces*, and 1 mM for *Candida*. The optimal incubation conditions for both types of strains were under dark environment.

Keywords: Yeast strains, Silver nanoparticles, Incubation time, Amount of biomass, Medium acidity (pH)

***Corresponding author:** Samsun University, Faculty of Medicine, Department of Medical Microbiology, 55080, Samsun, Türkiye
E mail: ergin.kariptas@samsun.edu.tr (E. KARİPTAŞ)
Mirmusa M. JAFAROV https://orcid.org/0000-0003-1219-2825
Ergin KARİPTAŞ https://orcid.org/0000-0001-6513-9589
Kamala S. ALKISHIYEVA https://orcid.org/0009-0001-1788-2244

Received: September 17, 2024
Accepted: October 25, 2024
Published: November 15, 2024

Cite as: Jafarov MM, Kariptaş E, Alkishiyeva KS. 2024. Effect of environmental factors on the production of silver nanoparticles by yeast strains. BSJ Health Sci, 7(6): 283-287.

1. Introduction

One of the recent advancements in bionanotechnology is the biological production of silver nanoparticles, which have potential applications in medicine, biotechnology, and the food industry. Therefore, the interaction between microorganisms and silver ions has gained significant attention. As a result, extensive research works have been conducted on obtaining silver nanoparticles from molds (Bhainsa and D'Souza, 2006; Prakasham et al., 2010; Abd El-Aziz., 2012; Guangquan et al., 2012; Honary et al., 2013; Ganbarov et al., 2014), bacteria (Gurunathan et al., 2009; Punjabi et al., 2012; Mousavi et al., 2020), and Actinomycetes (Ganbarov et al., 2016; Hasanova et al., 2017). It has been determined that, depending on the type of microorganism, silver nanoparticles can be produced directly by living cells, as well as by the cell-free culture fluid of the microbial culture (Bozkurt et al., 2017). It has been known that the microbiological synthesis of silver nanoparticles varies depending on the physicochemical parameters (for example, the age of the cell and its mass, temperature, environmental acidity (pH), incubation time, concentration of $AgNO_3$ salt) (Azadaliyeva et al., 2018; Ganbarov et al.,2018; Jafarov et al., 2020; Azadaliyeva et al., 2021). The microbiological synthesis of silver nanoparticles varies depending on several physicochemical parameters, such as cell age and biomass, temperature, environmental pH, incubation time and the concentration of $AgNO_3$.

There is enough information in the literature regarding the acquisition of silver nanoparticles by *Saccharomyces* (Kaler et al., 2013; Roy et., al 2014) and Candida yeasts (Revina et al., 2005; Hassan et al., 2013; Chauhan et al., 2014; Varquez et al., 2014; Saminathan, 2015).

The main goal of the presented article was to collect data on the influence of environmental factors on the formation of silver nanoparticles by yeast strains and to compare it with the strain of *Saccharomyces ellipsoideus* BSU-XR1 isolated from sour milk.

From the above literature data and from our experimental results, it is clear that the formation time of silver nanoparticles varies significantly depending on the yeast strain and species. Of course, this process primarily depends on the incubation conditions and the metabolic characteristic features of the fungal organism.

2. Effects on Silver Nanoparticles

2.1. Effect of Incubation Period on the Production of Silver Nanoparticles

The dependency of the incubation period was determined on the synthesis of silver nanoparticles by the yeast strain (Azadaliyeva et al, 2018).

It was found that on the 21st and 30th days of incubation $AgNO_3$ salt with the wet biomass of *Saccharomyces*

ellipsoideus strain BSU-XR1, the dark brown colored reaction mixture gave 420 nm wavelength absorption in the UV-VIS spectrophotometer. Scanning electron microscope analysis revealed that, the silver nanoparticles formed were spherical, with sizes ranging from 17.2 to 22.4 nm. During different incubation periods, each fungal strain exhibits a color change, which serves as an early indicator for the formation of silver nanoparticles, depending on the species and strain. For example, the reaction mixture of the commercial strain of *Saccharomyces cerevisiae* yeast started to darken from light yellow to brown after 4 days of incubation, and in the UV spectrophotometer, silver nanoparticles had an absorption at 450 nm wavelength. The reaction mixture of another strain of *Saccharomyces cerevisiae* yeast began to darken on the 6th day of incubation. At this time formed silver nanoparticles showed absorption at 430 nm wavelength (Baranova et al., 2005).

The formation of nanoparticles with the wet biomass of another strain of *Saccharomyces cerevisiae* (a yeast used in baking) has been studied. In this case, the formation of nanoparticles started after 24 h of incubation. The processed nanoparticles were in cuboidal shape, and had a very small size of 67.2 Å (angstroms**).** As a result of the study of the formation of silver nanoparticles with the culture liquid of another strain of the yeast *Saccharomyces cerevisiae,* it was determined that after 48 hours, nanoparticles with a spherical shape and a size of 25 nm were formed. In the UV spectrum, the absorption of nanoparticles was at a wavelength of 413 nm (Roy et al., 2014).

The production of silver nanoparticles by Candida yeasts was slightly different from that of Saccharomyces. The silver nanoparticles produced by the wet biomass of *Candida albicans NCIM-3100* strain during 48 h of incubation showed absorption at 420 nm wavelength in the UV spectrum. The size of silver nanoparticles varied between 20-60 nm and formed aggregates. The nanoparticles were spherical in shape. Another strain produced silver nanoparticles after 96 h of incubation, which showed absorbtion in the UV spectrum at 370 nm and had a size of 80nm. They were spherical in appearance. Silver nanoparticles produced by *Candida albicans* strain ATCCSC5314 within 72 h were 3-60 nm in size. In the UV spectrophotometer, these particles showed absorption at a wavelength of 415 nm. Another strain of yeast fungus *Candida albicans* darkened the color of the reaction mixture during 24 h of incubation and the formed silver nanoparticles had absorption at 400 nm wavelength in UV spectrophotometer. The size of nanoparticles was in the range of 20-100 nm and formed a conglomerate (Varquez et al., 2014; Mare et al., 2015).

The wet biomass of *Candida utilis NCIM3469* yeast strain started to form silver nanoparticles after 24 h of incubation. Silver nanoparticles had an absorbance at a wavelength of 401 nm in a UV spectrophotometer. Nanoparticles were spherical in shape and 20-80 nm in size. In the experiments conducted with the wet biomass of another strain of *Candida utilis*, silver nanoparticles were formed after 48 h. The size of 55% of processed silver nanoparticles was 2-3 nm, and the size of 45% was 8 nm. Nanoparticles showed absorption at a wavelength of 380 nm in a UV spectrophotometer. Cluster formation of silver nanoparticles was determined in the electron microscope (Baranova et al., 2005; Revina et al., 2005).

The wet biomass of *Candida guilliermondii BSU-217* and *Candida macedoniensis BSU-GA48* and *Candida macedoniensis BSU-MI44* yeast strains and the darkening of the reaction mixture color (from light yellow to dark brown) of $AgNO_3$ salt changed between 3-10 days of incubation. The synthesis of silver nanoparticles by the wet biomass of *Candida macedoniensis BSU-MI44* strain occurred on the 3rd-7th days of incubation, after the 7th day, the formation of nanoparticles weakened and after the 10th day of incubation, the formation of nanoparticles decreased sharply. Intensive formation of silver nanoparticles by *Candida guilliermondii BSU-217* yeast biomass occurred on 3-10 days of incubation, and then the process weakened, while *Candida macedoniensis BSU-MI44* yeast biomass was observed on 3-7 days of incubation. After day 7, the rate of nanoparticle formation slowed, and after day 10 of incubation, nanoparticle formation was dramatically reduced (Dzhafarov et al., 2016; Bozkurt et al., 2017; Ganbarov et al., 2019).

2.2. Effect of Biomass Amount on the Biosynthesis of Silver Nanoparticles

It has been determined that the amount of wet biomass plays a crucial role in the synthesis of silver nanoparticles by yeast fungi (Dzhafarov et al., 2016; Azadaliyeva et al., 2021). Thus, *Saccharomyces ellipsoideus BSU-XR1* strain incubated with different biomasses during analysis in a UV spectrophotometer in the reaction mixture of 5 g of biomass and silver nitrate salt at a wavelength of 400 nm suitable for silver nanoparticles, at a wavelength of 420 nm at 10 g, and at a wavelength of 15 g It had absorption at a wavelength of 415 nm. The scanning electron microscope showed that the silver nanoparticles have a spherical shape and different sizes. The size of nanoparticles formed varied with the amount of biomass: 8.6-16.9 nm with 5g of biomass, 22.4nm with 10g, and 17.2nm with 15g. Therefore, depending on the amount of wet biomass, the size of the silver nanoparticles formed was also different. The optimal biomass of *Saccharomyces ellipsoideus BSU-XR1* strain for the synthesis of silver nanoparticles was 10 g.

It is clear from the literature that the optimal biosynthesis of silver nanoparticles in *Candida albicans NCIM-3100* strain was carried out in 10 grams of wet biomass, in another strain of *Candida albicans* and in yeast fungus *Candida glabrata*, the formation of silver nanoparticles was also carried out with 10 g of wet biomass. Some authors have used 8-10 g of wet biomass in the production of silver nanoparticles by the yeast *Candida albicans* (Varquez et al., 2014; Mare et al., 2015).

The formation of silver nanoparticles was manifested in 8 g of wet biomass of yeast strain *Candida utilis NCIM3469*, and in 8-9 g of another strain of *Candida utilis* species (Revina et al., 2005).

2.3. Effect of Temperature on the Biosynthesis of Silver Nanoparticles

The temperature factor has a great role in microbial cultures synthesizing silver nanoparticles (Dzhafarov et al., 2017; Ganbarov et al., 2018).

The production of silver nanoparticles by *Saccharomyces ellipsoideus BSU-XR1* yeast was studied depending on the temperature, and it was determined that the formation of silver nanoparticles was observed in mixtures incubated at 25 °C and 30 °C due to color change. Spectrophotometric analysis of the taken samples showed that absorption (peak) at 410-413 nm wavelength was observed in the samples incubated at 25 °C and 30 °C. Scanning electron microscopy revealed the presence of spherical silver nanoparticles, with sizes 22.4 nm and 17.2 nm. It was found that the optimal temperature limit for this strain to synthesize silver nanoparticles is in the range of 25-30 °C.

It is known from the literature that the formation of silver nanoparticles in *Candida albicans NCIM-3100* strain occurs at a temperature of 25 °C, in another strain of the yeast *Candida albicans* and in the yeast *Candida glabrata* - at a temperature of 37 °C, in another strain of the yeast *Candida albicans* - at a temperature of 30 °C, in *Candida albicans ATCC SC5314* strain – 37 °C, formation of nanoparticles with *Candida albicans* fungus culture liquid occurred at 30°C temperature, in *Candida glabrata ATCC90030, Candida krusei ATCC6258, Candida albicans ATCC90028* strains - at 35 °C temperature. Formation of nanoparticles in *Candida utilis NCIM 3469* strain at 30 °C, in another strain of this species – at 28 °C, in *Candida diversa JA1* strain – at 28 °C, in *Candida guillermondi* fungus at 30°C, in yeast fungi *Candida utilis 22* and *Kluyveromyces marxianus* – recorded at 30 °C. The optimal temperature for the formation of silver nanoparticles in *Candida guillermondi BDU-217 strain* was 25 °C, and in *Candida macedoniensis BDU-MI44* strain it was 30 °C (Mare et al., 2015; Bozkurt et al., 2017; Ganbarov et al., 2019).

Depending on the species and strain, the formation of nanoparticles in *Saccharomyces* yeast fungi took place under different temperature conditions. For example, the yeast strain *Saccharomyces cerevisiae* used in baking used silver nanoparticles at a temperature of 30°C, but another fungus *S. cerevisiae* used in baking carried out this process optimally at a temperature of 35°C, some strains of the species *Saccharomyces cerevisiae* used silver nanoparticles at 25 °C and 27 °C formed at temperatures. The optimum temperature for the formation of silver nanoparticles for the extrophilic yeast *Saccharomyces cerevisiae* was 22 °C. Optimal synthesis of silver nanoparticles by the yeast *Saccharomyces bourlardii* took place at a temperature of 35 °C. Thus, it is clear from the above literature data that depending on the type and strain of the fungus, the optimal temperature for the formation of silver nanoparticles can change (Baranova et al., 2005; Roy et al., 2014).

2.4. Effect of Initial Environmental Acidity on the Biosynthesis of Silver Nanoparticles

As an environmental factor, initial environmental acidity also has an effect on the production of silver nanoparticles by yeast fungi (Jafarov et al., 2020). The formation of silver nanoparticles by *Saccharomyces ellipsoideus BSU-XR1* strain was determined depending on the acidity of the environment, and the color change in the reaction mixtures was noticeable starting from the 7th day of incubation. During the spectrophotometric analysis, it was determined that the absorption peak between the wavelength of 408-412 nm was observed in the reaction mixtures with pH of 6.0, 7.0, 8.0. The silver nanoparticles produced by this strain at pH 7.0 were characterized by their spherical appearance in the scanning electron microscope. The size of nanoparticles was equal to 22.4 nm.

It is known from the literature that silver nanoparticles can be actively synthesized during the incubation of *Saccharomyces cerevisiae* yeast cells with silver nitrate salt when the pH of the solution is above 8. Metabolism products collected by the yeast played the role of regulator for the formed silver nanoparticles. It is believed that silver nanoparticles are formed as a result of the reduction of silver ions by secretion, and this is one of the possible causes of formation. The research showed that, microbial cultures can synthesize a higher quantity of silver nanoparticles in alkaline environments compared to acidic ones. When the acidity of the environment exceeds pH 10, it causes the death of cells. Microorganisms synthesize more nanoparticles under neutral alkaline conditions than under acidic conditions. *Saccharomyces cerevisiae*, a yeast used in baking, was able to synthesize silver nanoparticles in a wide pH range (pH 4-10). Optimum biosynthesis of silver nanoparticles for extrophilic yeast was pH 2.5. Although the yeast *Saccharomyces boulardii* can synthesize silver nanoparticles in a wide pH range, the optimal pH was 7 (Baranova et al., 2005, 26, Varquez et al., 2014). *Candida guillermondi BSU-217* and *Candida macedoniensis BSU-MI44* yeast fungi were also able to synthesize silver nanoparticles in the pH range of 7 (Mare et al., 2015; Bozkurt et al., 2017).

In general, it can be noted that the optimal biosynthesis of silver nanoparticles in *Saccharomyces* and *Candida* yeasts occurs mainly in a neutral environment (pH 7). The results obtained using the strain *Saccharomyces ellipsoideus BSU-XR1* confirm this again.

2.5. Effect of $AgNO_3$ Salt Concentration on the Biosynthesis of Silver Nanoparticles

According to Azadaliyeva et al., (2021), yeast strains produce silver nanoparticles depending on the concentration of $AgNO_3$ salt. The synthesis of silver nanoparticles by *Saccharomyces ellipsoideus BSU-XR1* yeast cells was observed on the 7th day of incubation in

the reaction mixtures containing 0.5 and 1.0 mM silver nitrate. During the spectrophotometric analysis, absorption peaks at 405 and 408 nm wavelength were observed in the samples of silver nitrate salt incubated at concentrations of 0.5 and 1.0 mM. The scanning electron microscope showed that the silver nanoparticles have a spherical shape and different sizes. The size of nanoparticles was equal to 22.4 nm in 0.5 mM mixture of silver nitrate salt and 35.5 nm in 1.0 mM concentration. These results are similar to those obtained in the yeast *Saccharomyces cerevisiae.* Thus, the size of the silver nanoparticles produced by this fungus at concentrations of 0.5 and 1.0 mM silver nitrate salt was 34.2 nm and 37.5 nm, respectively.

Various strains of the baking fungus *Saccharomyces cerevisiae* and *Saccharomyces boulardii* have produced silver nanoparticles at 1.0 mM concentrations of silver nitrate salt (Baranova et al., 2005; Kaler et al., 2013; Roy et al., 2014). The extromophilic yeast was tolerant to a higher concentration of silver nitrate salt and was able to form silver nanoparticles at a concentration of 0.3 mM of AgNO3 salt (Ganbarov et al., 2014). *Candida yeasts* were able to produce silver nanoparticles at concentrations of 1.0 mM of silver nitrate salt (Hassan et al., 2013; Mare et al., 2015; Bozkurt et al., 2017; Ganbarov et al., 2019).

It is known that silver nitrate salt has a toxic effect on microorganisms. So, yeast fungi studied by various researchers were able to produce silver nanoparticles at a very low concentration (0.1-0.3 mM) of silver nitrate salt.

The effect of dark and light factor on the formation of silver nanoparticles is great (Dzhafarov et al., 2021). Incubation of the reaction mixture of silver nitrate salt with wet biomass of *Saccharomyces ellipsoideus BSU-XR1 strain* was carried out in two environments (dark and light). As a result of the analysis of the reaction mixture of this strain with silver nitrate salt in the UV-spectrophotometer, it was determined that the absorption peak was observed at the wavelength of 414 nm in the sample incubated in the dark environment, and at the wavelength of 409 nm in the sample incubated in the light environment. However, when viewed under a scanning electron microscope, spherical silver nanoparticles with a diameter of 17.2 nm were identified in a sample incubated in a dark environment and silver nanoparticles were not observed in the sample incubated in the light environment.

It should be noted that microbiological synthesis of silver nanoparticles was mainly carried out in dark conditions (in a thermostat) (Khudaverdi et al., 2013; Dzhafarov et al., 2021).

3. Discussion and Conclusion

Thus, the optimal incubation periods were reported as the 21th day for *Saccharomyces ellipsoideus BSU-XR1*, between the 4th and 6th days for various strains of *Saccharomyces cerevisiae,* and between the 2nd and 10th days for *Candida* strains. The optimal amount of wet biomass was 10 g for *Saccharomyces* strains and 8-10 g for *Candida* strains.

The temperature limit for *Saccharomyces* was observed at 25-35 °C, and for *Candida* at 25-37 °C. Synthesis of silver nanoparticles was in the pH range of 4 to 10 for *Saccharomyces* strains, and pH 7 was optimal for *Candida* strains. Depending on the concentration of $AgNO_3$ salt, optimal synthesis of silver nanoparticles occurred at concentrations of 0.5 and 1 mM for *Saccharomyces* and 1 mM for Candida. The most suitable incubation conditions for both yeasts turned out to be a dark environment.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	M.M.J.	E.K.	K.S.A.
C	34	33	33
D	34	33	33
S	34	33	33
DCP	34	33	33
DAI	34	33	33
L	34	33	33
W	34	33	33
CR	34	33	33
SR	34	33	33

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision.

Conflict of Interest

The authors declared that there is no conflict of interest.

References

Abd El- Aziz ARM, Al-Othman MR, Saleh A. Alsohaibani SA, Mahmoud MA, Sayed SRM. 2012. Extracellular biosynthesis and characterization of silver nanoparticles using Aspergillus niger isolated from Saudi Arabia (strain KSU – 12). Digest J Nanomat Biostruct, 7(4): 1491.

Azadaliyeva SF, Jafarov MM, Agamaliyev ZA, Eyvazova QI, Ganbarov XQ. 2018. The effect of incubation period on the formation of silver nanoparticles by Saccharomyces ellipsoideus BSU – XR1 yeast strain. Scient Works Inst Microbiol ANAS, 6(1): 42.

Azadaliyeva SF, Ganbarov KG, Jafarov MM, Huseynova SI. 2021. Influence of biomass quantity on the formation of silver nanoparticles by saccharomyces ellipsoideus BSU-XR1. Современная наука: актуальные проблемы теории и практики. Серия: Естественные и Технические Науки, 5: 7-11.

Baranova EK, Mulyukin AL, Kozlova AN. 2005. Naukoemkie Tekhnologii, 6(5): 33-37.

Bhainsa KC, D'Souza SF. 2006. Extracellular biosynthesis of silver nanoparticles using the fungus Aspergillus fumigatus. Colloids Surfaces B.: Biointerfaces, 48(2): 190.

Bozkurt HC, Jafarov MM, Seyidova KQ. 2017. Formation of silver nanoparticles in the culture liquid of Candida guillermondii BSU-217 yeast strain. Scient Works Inst Microbiol ANAS, 15(1): 214.

Chauhan R, Reddy A, Abraham J. 2014. Biosynthesis and antimicrobial potential of silver and zinc oxide nanoparticles using Candida diversa strain JA1. Der Pahrma Chemica, 6(3): 39.

Ganbarov KHG, Musayev EM, Ahmadov IS, Ramazanov MA, Eyvazova GZ, Agamaliyev A. 2014. The concentration effect of the formation of silver nanoparticles by the mold fungus Aspergillus niger BDU A4. J Biotechnol, 185: 28.

Ganbarov KHG, Agayeva NA, Ramazanov MA, Abdulhamidova SM, Agamaliyev ZA, Eyvazova GM. 2016. Extracellular formation of silver nanoparticles by the cell filtrate of Actinomyces sp. NSX-333. Int J Res Stud Biosci, 4(11): 1.

Ganbarov KHG, Jafarov MM, Azadaliyeva SF, Huseynova SI, Eyvazova GI. 2018. Effect of temperature on the formation of silver nanoparticles by Saccharomyces ellipsoideus BSU – XR1 yeast strain. International Scientific Conference on Current Problems of Modern Natural and Economic Sciences, Ganja, Azerbaijan, pp: 293-299.

Ganbarov KHG, Jafarov MM, Huseynova SÝ. 2019. The impact of temperature on synthesis of silver nanoparticles by Candida macedoniensis BDU-MI44. Sci Educ Soc Bull Scient Conf Tambov, 9-2(49): 2.

Gurunathan S, Kalishwaralal K, Vaidyanathan R, Venkataraman D. 2009. Biosynthesis, purification and characterization of silver nanoparticles using Escherichia coli. Colloids Surface Biol Biointerf, 74: 328.

Guangquan L, He D, Qian Y, Guan B, Gao S, Cui Y, Yokoyama K. 2012. Fungus - mediated green synthesis of silver nanoparticles using Aspergillus terreus. Int J Mol Sci, 13(1): 466.

Hassan A, Mansour M, Mahmoud H. 2013. Biosynthesis of silver nanoparticles by Candida albicans and its antifungal activity on some fungal pathogens. New York Sci J, 6(3): 27.

Hasanova S, Guliyeva SM, Kelbiyeva SA, Suleymanova G, Babayeva RF, Ganbarov K. 2017. The study of morphological and cultural properties of Actinomycetes forming silver nanoparticles. Advances in Biology and Earth Sciences, 2(2): 168.

Honary S, Barabadi H, Gharaei E, Naghibi F. 2013. Green synthesis of silver nanoparticles induced by the fungus Penicillium citrinum. Tropic J. Pharm. Res, 12(1): 7.

Jafarov MM, Azadaliyeva SF. Huseynova SI, Babayeva IT, Eyvazova GI. 2020. Influence of environmental acidity (pH) on the production of silver nanoparticles by the yeast strain Saccharomyces ellipsoideus BSU-XR1. Actual problems of modern natural sciences. International Scientific Conference, May 3-4, Ganja, Azerbaijan, pp: 123-127.

Dzhafarov MM, Azadalieva SF, Guseynova SI, Babaeva IT. 2021. The dependence of the synthesis of silver nanoparticles by saccharomyces Ellipsoideus Bdu - Xr1 yeast fungus on light and dark environment. Nat Technic Sci, 11: 67.

Kaler A, Jain S, Banerjee UC. 2013. Green and rapid synthesis of anticancerous silver nanoparticles by Saccharomyces boulardii and insight into mechanism of nanoparticle synthesis. BioMed Res Int, 2013: 1.

Khudaverdi G, Ganbarov MM, Jafarov S, Huseynova İ, Shoaib M, Alkishiyeva KS. 2013. Extracellular biosynthesis of Ag nanoparticles by commercial Baker's yeast. Adv Mater Res, 785: 370.

Mare AD, Ciurea CN, Man A, Mareş M, Toma F, Berţa L, Tanase C. 2015. Silver colloidal nanoparticles antifungal effect against Candida albicans and Candida glabrata adhered cells and biofilms. Biofouling, 27(7): 71.

Mousavi SMAA, Mirhosseini SA, Panahi MRS, Hosseini HM. 2020. Characterization of biosynthesized silver nanoparticles using Lactobacillus rhamnosus GG and its in vitro assessment against colorectal cancer cells. Probiotics Antimicrob Proteins, 12(2): 740.

Prakasham RS, Buddana SK, Yannam SK, Girija SG. 2010. Extracellular biosynthesis of silver nanoparticles using the filamentous fungus Penicillium sp. Arch Appl Sci Res, 12: 161.

Punjabi K, Yedurkar S, Doshi S, Deshapnde S, Vaidyaeevan S. 2012. Extracellular biosynthesis of silver nanoparticles by culture supernatant of Pseudomonas aeruginosa. Ind J Biotech, (11): 72.

Revina AA, Dzhafarov MM, Guseynova SI, Azadalieva SF. 2005. Some features of the effect of cluster silver on yeast cells Candida utilis. Electron J Res Russia 139: 1403.

Roy K, Sarkar C, Ghosh C. 2014. Photocatalytic activity of biogenic silver nanoparticles synthesized using yeast (Saccharomyces cerevisiae) extract. Appl Nanosci, 10(8): 953.

Saminathan K. 2015. Biosynthesis of silver nanoparticles from dental caries causing fungi Candida albicans. Int J Curr Microbiol Appl Sci, 4(3): 1084.

Varquez R, Avalos M, Castro E. 2014. Ultrastructural analysis of Candida albicans when exposed to silver nanoparticles. PloS One, 9(10): 870.