TẠP CHÍ

Y DƯỢC HỌC QUÂN SỰ

Journal of Military Pharmaco-medicine

ISSN 1859-0748

Vol 49, N°4 - 2024
Số tiếng Anh

HỌC VIỆN QUÂN Y

MILITARY MEDICAL UNIVERSITY

TẠP CHÍ Y DƯỢC HỌC QUÂN SỰ

HỌC VIỆN QUÂN Y XUẤT BẢN

TRỤ SỞ BAN BIÊN TẬP

Tạp chí Y Dược học Quân sự - Học viện Quân y, 160 Phùng Hưng, Hà Đông, Hà Nội

Điện thoại: 069. 566. 520

Email: tcydhqs@vmmu.edu.vn

Giấy phép xuất bản số 594/GP-BTTTT do Bộ Thông tin và Truyền thông cấp ngày 16 - 12 - 2022

In tại Xưởng in Học viện Quân y

JOURNAL OF MILITARY PHARMACO-MEDICINE N°4 - 2024

TABLE OF CONTENTS

INITIAL EVALUATION OF THE EFFICIENCY OF CRYOPROTECTANT-FREE VITRIFICATION IN PCR TUBES ON A LOW NUMBER OF HUMAN SPERMATOZOA

Nguyen Thanh Tung[1], Tran Van Tuan[1], Do Ngoc Lan[1]
Nguyen Thi Thuc Anh[1], Ho Sy Hung[2], Trinh The Son[1]*

Abstract

Objectives: To inititally evaluate the efficiency of cryoprotectant-free vitrification in PCR tubes on a low number of human spermatozoa. ***Methods:*** A laboratory experimental study was conducted on 30 severe oligospermia treated at the Military Institute of Clinical Embryology and Histology, Vietnam Military Medical University. The semen samples were vitrified and thawed at the following times, then sperm concentration, morphology, viability, and motility were evaluated after thawing. ***Results:*** The viable CSF, motile CSF when vitrifing without using CPAs were 50.45 ± 4.63; 43.35 ± 4.81 (1-week storage), 45.24 ± 4.33; 37.24 ± 4.39 (4-week storage) and 40.69 ± 3.96; 33.96 ± 4.14 (8-week storage), respectively. ***Conclusion:*** Vitrification of human sperm can be achieved without cryoprotectants and could be recommended for routine assisted reproductive technology.

Keywords: Sperm vitrification; Oligospermia; Free-cryoprotectants.

INTRODUCTION

Sperm cryopreservation was first introduced by Lazaro Spallanzani in 1976 by cryopreserving semen in snow. After that, the first baby born from cryopreserved sperm was reported in 1953 by Bunge and Sherman [1]. The principle of this kind of technique is to transform both the extracellular and intracellular fluid into a solid state; therefore, pausing the molecular movement and biological processes in the cell. An ideal cryopreservation technique should ensure that the cells

[1]Military Institute of Clinical Embryology and Histology, Vietnam Military Medical University
[2]Hanoi Medical University
[*]Corresponding author: Trinh The Son (trinhtheson@vmmu.edu.vn)
Date received: 14/12/2023
Date accepted: 12/3/2024
http://doi.org/10.56535/jmpm.v49i4.588

are structurally unaffected and functionally post-thawing. Recently, fertility centers often use two main sperm cryopreservation techniques: Vitrification and slow freezing. The slow freezing technique is more popular and has been used for a long time in laboratories, despite the fact that the rate of sperm recovery after thawing with this technique is usually 50%, varying greatly depending on the sample. In addition, numerous studies around the world have proven that this technique causes major changes in both sperm structure and function [2, 3]. Applying slow cryopreservation techniques for semen samples with a low number of spermatozoa is still a big challenge. Sperm vitrification can overcome the disadvantages of the slow sperm freezing technique for the above sample types because it is quick and simple to perform. Moreover, sperm quantity and quality recover well after thawing, but the temperature reduction rate of up to several tens of thousands of degrees per second can also create ice crystals in sperm cells. Besides, the use of cryoprotective agents (CPAs) during sperm cryopreservation is still controversial among studies. According to Mochida (2014), the use of high-concentration cryopreservation CPA with a small quantity of sperm samples is necessary for sperm cryopreservation [4]. However, human sperm is very sensitive to CPA, so some authors have proposed a sperm cryopreservation method that does not use CPA [5, 8]. Therefore, we conducted this study: *To evaluate the efficiency of cryoprotectant-free vitrification in PCR tubes on a low number of human spermatozoa*.

MATERIALS AND METHODS

1. Materials

* *Research subjects*: 30 oligospermia semen samples at the Military Institute of Clinical Histology and Embryology, Vietnam Military Medical University

* *Inclusion criteria*: Oligospermia semen samples (< 1 million sperm/mL); patients agreed to participate in the study.

* *Exclusion criteria*: Patients tested positive with HIV, HBsAg, and HCV.

* *Location and time*: Conducted at the Military Institute of Clinical Histology and Embryology, Vietnam Military Medical University from September 2022 to September 2023.

2. Methods

* *Research design*: A laboratory experimental study.

* *Data collection*:

- Sample size: 30 severe oligospermia semen samples after analysing according to the WHO-Laboratory manual for the examination and processing of human semen 6th 2021.

- Sampling: Convenience sampling from September 2022 to September 2023.

* *Research process:*

After collecting, the samples were vitrified and thawed at the following times, and sperm concentration, morphology, viability, and motility were evaluated after thawing:

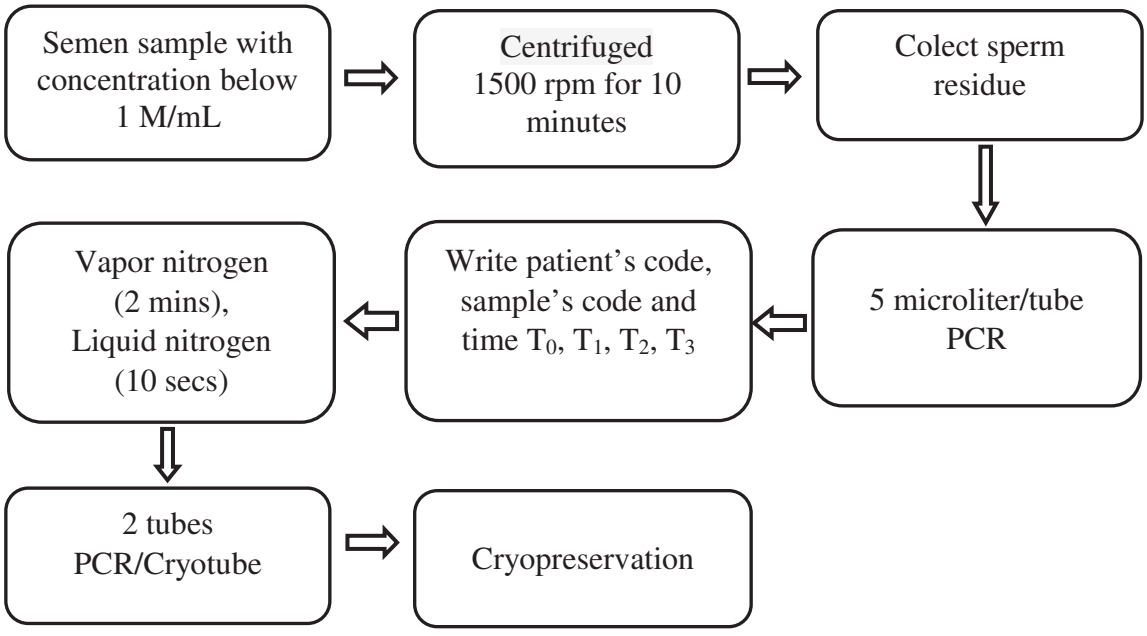
- T_0: After centrifuging the sample, cryopreserved the sperm sample by vitrifying a low number of spermatozoa without using cryoprotective agents (CPAs) in a PCR tube.

- T_1: After 1 week, the stored samples were thawed and compared with T_0.

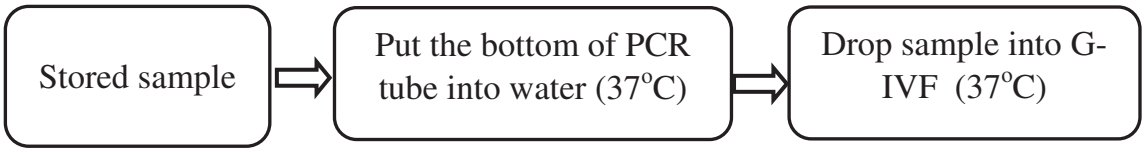
- T_2: After 4 weeks, the stored samples were thawed and compared with T_0 and T_1.

- T_3: After 8 weeks, the stored samples were thawed and compared with T_0, T_1, and T_2.

Sperm sample vitrification process:



Thawing stored sample process:



** Evaluating parameters:*

- Sperm concentration (million/mL).
- Sperm viability (percentage).
- Total motility (PR + NP) and progressive motility (PR) (percentage).
- Sperm morphology (percentage of normal sperm).
- CSF (Cryo-survival Fator):

$$\text{Motile CSF} = \frac{\%\ \text{Motile sperm after cryoperservation}}{\%\ \text{Motile sperm before cryoperservation}} \times 100\%$$

$$\text{Viable CSF} = \frac{\%\ \text{Viable sperm after cryoperservation}}{\%\ \text{Viable sperm before cryoperservation}} \times 100$$

** Data processing methods:* Research data were processed with the Stata 14.0 using a paired t-student test. The difference is statistically significant when the value is < 0.05.

3. Ethics

The study was approved by the Ethics Committee for Biomedical Research of the Military Institute of Clinical Histology and Embryology, Vietnam Military Medical University. Information relating to the research is kept strictly confidential and used only for scientific purposes. Semen samples were disposed of immediately after the study.

RESULTS

Compare sperm quality before and after thawing.

Table 1. Comparison of sperm quality without using CPAs before and after thawing.

	T_0 (0)	T_1 (1)	T_2 (2)	T_3 (3)	p
Concentratrion (milion/mL)	2.78 ± 1.68	2.78 ± 1.66	2.78 ± 1.67	2.79 ± 1.67	$p_{0-1} = 0.491$ $p_{1-2} = 0.587$ $p_{2-3} = 0.424$ $p_{1-3} = 0.217$
Sperm viability (%)	40.54 ± 20.90	20.33 ± 10.31	18.28 ± 9.26	16.44 ± 8.42	$p_{0-1} = 0.000$ $p_{1-2} = 0.000$ $p_{2-3} = 0.000$ $p_{1-3} = 0.000$
PR(%)	4.19 ± 4.97	1.38 ± 1.63	1.18 ± 1.39	1.06 ± 1.26	$p_{0-1} = 0.0001$ $p_{1-2} = 0.0002$ $p_{2-3} = 0.0002$ $p_{1-3} = 0.0001$
NP(%)	12.75 ± 11.27	8.96 ± 12.99	7.69 ± 11.18	7.02 ± 10.09	$p_{0-1} = 0.0153$ $p_{1-2} = 0.0007$ $p_{2-3} = 0.0027$ $p_{1-3} = 0.0011$
PR + NP (%)	16.95 ± 13.35	10.33 ± 12.89	8.87 ± 11.09	8.09 ± 10.01	$p_{0-1} = 0.0026$ $p_{1-2} = 0.0001$ $p_{2-3} = 0.0006$ $p_{1-3} = 0.0002$
Sperm morphology (%)	2.70 ± 0.92	2.67 ± 0.96	2.60 ± 0.81	2.53 ± 0.82	$p_{0-1} = 0.573$ $p_{1-2} = 0.326$ $p_{2-3} = 0.326$ $p_{1-3} = 0.103$

In general, the longer the storage period, the lower the sperm quality. Specifically, the average sperm viability, progressive motility rate, non-progressive motility rate, and total motile sperm rate gradually decreased over

time of thawing; the difference was statistically significant, with $p < 0.05$. The average sperm concentration and the percentage of sperm with normal morphology did not change significantly over the stages, the difference was not statistically significant, with $p > 0.05$.

Table 2. Viable CSF after cryopreservation.

Time	Viable CSF (%)
T_1	50.45 ± 4.63
T_2	45.24 ± 4.33
T_3	40.69 ± 3.96

When evaluating post-thaw the stored samples, the viable CSF index decreased overtime after 1 week, 4 weeks, and 8 weeks; the difference was statistically significant with $p < 0.05$.

Table 3. Motile CSF after cryopreservation.

Time	Motile CSF(%)
T_1	43.35 ± 4.81
T_2	37.24 ± 4.39
T_3	33.96 ± 4.14

When evaluating post-thaw the stored samples, the motile CSF index decreased overtime after 1 week, 4 weeks, and 8 weeks; the difference was statistically significant with $p < 0.05$.

DISCUSSION

Dramatic changes during cryopreservation have detrimental effects on the sperm membrane, resulting in a large increase in the percentage of poorly motile sperm or sperm with abnormal morphology. The negative effects related to high-speed temperature decrease, such as intracellular ice crystal formation, osmotic injury, cellular dehydration, and oxidative stress, can also injure the sperm in ways that affect reproductive outcomes. Sperm cells are rich in mitochondria because a constant supply of energy is required for their motility, and mitochondrial damage during cryopreservation processes is

linked with a loss of membrane permeability. This confirms the fact that cryopreservation affects motility because of mitochondrial damage and also because of physical changes to the tail. Also, human spermatozoa contain large quantities of proteins, sugars, and other components that may act as natural cryoprotectants. It is known that the loss of sperm quality is more significant in patients whose sperm parameters are poor. Therefore, there is a significantly lower post-thaw percent motility, motile sperm concentration, and cryo-survival rate, especially in a group of OAT patients, as in our study (concentration < 1 million/mL). Our group's results on motile CSF and viable CSF are similar to the studies of Widyastuti R (2017) [10] and Nguyen Thi Hang (2018) with the crystal freezing method [7]. In Widyastuti R's study (2017), samples were divided into three groups: The control group, samples mixed with a basic solution, and samples mixed with a vitrification solution. The straws (carriers) were vaporized in liquid nitrogen for 5 seconds, then plunged into liquid nitrogen directly and stored for 24 hours. Sperm motility and viability were observed to evaluate sperm quality before and after vitrification. Overall, vitrified products without preservative agents had a proportion of sperm motility and viability rates of 35% and 48%, respectively [10]. However, in that study, the authors evaluated motile CSF and viable CSF right after 24 hours of storage, earlier than the time T_1, T_2, and T_3 in our study. In this research, we have not explored the stability of epigenetics information in human spermatozoa. However, Wang M and et al. (2022) analyzed epigenetic differences between fresh and cryopreserved spermatozoa using high-throughput RNA sequencing in three groups: Fresh spermatozoa (control group), frozen spermatozoa, vitrified spermatozoa, and concluded that cryopreservation of human spermatozoa is an epigenetically safe method for male fertility preservation; cryoprotectant-free vitrification can induce minor biological changes in human spermatozoa, in comparison with conventional freezing. [9].

CONCLUSION

Vitrification of human sperm can be achieved without intracellular cryoprotectants and could be recommended for routine assisted reproductive technology. Carriers are PCR tubes in a cryotube, which will refrigerate samples in very small volumes, safely in laboratories, and limit infection.

Acknowledgment: This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors have no conflicts of interest relevant to this article.

REFERENCES

1. R Bunge and JJN Sherman. Fertilizing capacity of frozen human spermatozoa. 1953; 172(4382):767-768.

2. P Desrosiers, C Légaré, P Leclerc et al. Membranous and structural damage that occur during cryopreservation of human sperm may be time-related events. 2006; 85(6):1744-1752.

3. G Vajta and ZPJRBO Nagy. Are programmable freezers still needed in the embryo laboratory? Review on vitrification. 2006; 12(6):779-796.

4. A Hasegawa, K Mochida, T Tomishima et al. Microdroplet in vitro fertilization can reduce the number of spermatozoa necessary for fertilizing oocytes. 2014; 60(3):187-193.

5. Y Chen, L Li, Y Qian et al. Small-volume vitrification for human spermatozoa in the absence of cryoprotectants by using Cryotop. 2015; 47(6):694-699.

6. WHO-Laboratory manual for the examination and processing of human semen 6th 2021.

7. Nguyễn Thị Hằng. Kết quả bảo quản lạnh mẫu tinh dịch bình thường và thiểu tinh nặng khi sử dụng máy Nicool LM10 và phương pháp đông tinh viên. *Luận văn thạc sỹ y học*. Trường đại học Y Hà Nội. 2018.

8. V Isachenko, E Isachenko, R Maettner, et al. Vitrification of human ICSI/IVF spermatozoa without cryoprotectants: New capillary technology. 2007; 33(3):462-468.

9. Wang M, Todorov P, Wang W, Isachenko E, Rahimi G, Mallmann P, et al. Cryoprotectants-free vitrification and conventional freezing of human spermatozoa: A comparative transcript profiling. *Int J Mol Sci*. 2022; 23(6).

10. R Widyastuti, R Lesmana, A Boediono, S Sumarsono. Effect of cryoprotectants on sperm vitrification. *Advances in Biomolecular Medicine: CRC Press.* 2017; 119-122.

CLINICAL FEATURES OF DIGITAL FLEXOR TENDON SHEATH: AN ANATOMIC STUDY

Luu Danh Huy[1,2], Pham Dang Ninh[2], Dang Hoang Anh[2], Vu Nhat Dinh[2]*

Abstract

Objectives: To study clinical features of digital flexor sheath. ***Methods:*** An observational anatomic study on 26 cadaver hands which were dissected and studied to conclude several anatomic features of the digital flexor sheath contributing to the management of the flexor sheath injuries in clinical practice. ***Results:*** The average length of A1, A2, A4 pulleys in the long fingers were 7.11mm, 16.12mm, and 5.94mm, respectively. The average width and thickness of A2, A4 pulleys in the long fingers were 6.25mm x 3.68mm and 4.98mm x 2.90mm, respectively. The distances from the MCP joint to the proximal border of A2, A4 pulleys on the same digitorium were 6.35mm and 7.96mm, respectively. ***Conclusion*:** A2 has the longest length and biggest cast thickness and width.

Keywords: Anatomy of the digital sheaths; A2; A4 pulley.

INTRODUCTION

It is widely known that the anatomy and function of the pulley system in the digital sheath are relatively complex. The pulley system fundamentally facilitates the conversion from reciprocating motion of flexor tendons into angular motions via interphalangeal joints resulting in the flexion of the PIP and DIP joints. Moreover, the pulley system ensures a tight relationship between flexor tendons and phalanges. The axial motion of the joints prevents "bowstringing" of flexor tendons [1]. A thorough understanding of the anatomy and function of the digital flexor sheath helps surgeons treat injuries of the flexor tendons and the pulley system more effectively. The purpose of this study was: *To describe several anatomic features of adult digital sheaths contributing to surgery of flexor tendon injuries in case of early or late admissions.*

[1]Viet Duc University Hospital

[2]Vietnam Military Medical University

[*]Corresponding author: Luu Danh Huy (huygo78@gmail.com)

Date received: 09/01/2024

Date accepted: 12/3/2024

http://doi.org/10.56535/jmpm.v49i4.668

MATERIALS AND METHODS

1. Materials

26 cadaver hands or amputated hands of adults.

This study was undertaken at the Department of Pathology, Viet Duc University Hospital, and the Department of Anatomy, Ho Chi Minh Medical and Pharmacological University.

2. Methods

* *Study design:* An observational anatomic study was conducted.

To measure the pulley length: A Loup magnifier was used to dissect the proximal and distal ends of A1, A2, and A4 pulleys, thumb cruciate pulleys (C pulleys), and a digital caliper with high precision 0.01 was used to measure. The MCP, PIP, and DIP joints were at 0 degree.

To measure the distance from the MCP joints and proximal interphalangeal joints to the proximal border of the pulley: Pin the joint with tiny pins and measure the distance from the pin to the proximal ends of A2, A4 pulleys and the lowest point of the cruciate pulleys.

To measure the pulley thickness and width: Dissect to remove all the flexor digitorum superficialis, profundus tendons of the long finger and flexor pollicis longus tendon of the thumb, make a plaster cast in each digital sheath, determine the cast diameter by measuring the cast thickness and width.

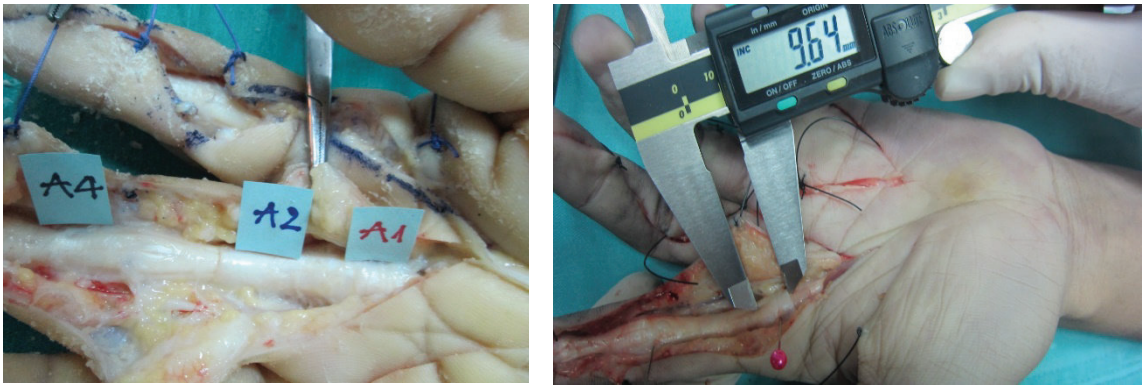


Figure 1. Measure the pulley's length.

* *Data analysis:*

The statistical analysis of the data was done using SPSS Software, version 16.0 (SPSS Inc., Released 2007. SPSS for Windows, version 16.0. Chicago. SPSS Inc.)

RESULTS

1. The pulley length of the thumb and long finger

Table 1. The A1 and C pulley length of the thumb.

Pulley length of the thumb (mm) (n = 26)	A1	C
$\bar{X}$ ± SD	5.45 ± 1.05	14.09 ± 3.00
Min	3.70	8
Max	7.65	21

The average length of the A1 pulley was 5.45mm (3.70 - 7.65mm). The oblique pulley measured from its highest point to its lowest point had an average length of 14.09mm.

Table 2. The A1, A2, and A4 pulley length of the long finger.

Pulley length of the long finger (n = 26)	$\bar{X}$ ± SD (min - max) (mm)		
	A1	A2	A4
The index finger	7.78 ± 1.38 (5.50 - 12.15)	15.72 ± 2.81 (11.60 - 20.98)	6.20 ± 1.23 (5.04 - 10.20)
The middle finger	7.79 ± 1.50 (5.31 - 11.12)	18.95 ± 3.46 (11.10 - 24.53)	6.59 ± 1.22 (5.01 - 11.00)
The ring finger	7.24 ± 1.25 (5.30 - 9.92)	17.28 ± 2.38 (11.40 - 21.25)	6.02 ± 0.91 (5.01 - 8.76)
The little finger	5.66 ± 1.38 (3.40 - 10.36)	12.55 ± 2.56 (6.44 - 16.76)	4.95 ± 0.87 (3.50 - 6.60)
Overall	7.11 ± 1.19 (5.48 - 10.23)	16.12 ± 2.43 (11.53 - 20.7)	5.94 ± 0.86 (4.96 - 8.20)

The longest pulley was A2 (18.95mm in the middle fingers); the shortest pulley recorded was A4 (6.59mm in the middle fingers; 6.2mm in the index fingers). The average A1, A2, and A4 pulley lengths of the long fingers were 7.11mm, 16.12mm, and 5.94mm, respectively.

2. The digital sheath width and thickness

Table 3. The digital sheath width and thickness of the thumb at C pulley.

Digital sheath at C pulley (mm); (n = 26)	Thickness	Width
$\overline{X}$ ± SD	3.57 ± 0.58	5.08 ± 0.69
Min	2.60	3.6
Max	4.73	6.22

Table 4. The digital sheath thickness at A2 and A4 pulleys.

The digital sheath thickness (mm); (n = 26)	A2 $\overline{X}$ ± SD (min - max)	A4 $\overline{X}$ ± SD (min-max)
The index finger	3.55 ± 0.49 (2.50 - 4.47)	2.92 ± 0.42 (2.21 - 4.06)
The middle finger	4.20 ± 0.46 (3.16 - 5.22)	3.18 ± 0.56 (2.18 - 4.56)
The ring finger	3.85 ± 0.41 (3.00 - 4.61)	2.99 ± 0.37 (2.06 - 3.56)
The little finger	3.11 ± 0.41 (2.36 - 4.23)	2.52 ± 0.37 (1.75 - 3.19)
Overall	3.68 ± 0.35 (2.97 - 4.52)	2.90 ± 0.27 (2.37 - 3.39)

Table 5. The digital sheath width at A2 and A4 pulleys.

The annular pulley width (mm)	A2 $\overline{X}$ ± SD (min - max)	A4 $\overline{X}$ ± SD (min - max)
The index finger	6.17 ± 0.74 4.96 - 7.48	5.14 ± 0.58 3.67 - 6.12
The middle finger	6.91 ± 1.18 2.26 - 8.09	5.42 ± 0.63 4.32 - 6.55
The ring finger	6.49 ± 0.66 5 - 7.61	5.12 ± 0.59 4.14 - 6.24
The little finger	5.43 ± 0.79 3.74 - 6.62	4.26 ± 0.55 2.78 - 5.21
Overall	6.25 ± 0.60 (5.15 -7.13)	4.98 ± 0.38 (4.24 - 5.61)

The width and thickness of long fingers: At the A2 pulley was 6.25mm x 3.68 mm; at the A4 pulley was 4.98mm x 2.90mm. The widest and thickest portion was located in the middle finger: At A2 pulley: 6.91mm x 4.20mm; at A4 pulley: 5.42mm x 3.18mm. The most narrow and thinnest portion was in the little finger: At A2: 5.43mm x 3.11mm, at A4: 4.26mm x 2.52mm. The average width and thickness of long fingers were 6.25mm x 3.68mm.

The average distance from the MCP joint to the most proximal part of the C pulley of the thumb was 4.67mm.

The distance from the MCP and PIP joints to the distal ends of A2, and A4 pulleys on the same long fingers were 6.35mm and 7.96mm, respectively. At A2 and A4 pulleys (mm) in the index finger: 7.16mm and 7.89mm; in the middle finger: 6.61mm and 8.85mm; in the ring finger: 6.08mm and 8.0mm; in the little finger 5.56mm and 7.08mm.

DISCUSSION

1. The pulleys of the thumb

In 1977, Doyle and Blythe [2] studied the pulley system of the thumb and showed only one oblique pulley running from the radial side to the ulnar side of the thumb and 2 cruciate pulleys A1 annular pulley whose length is 7 - 9mm overlies the MCP joint; similarly, A2 annular pulley (average length 8 - 10mm) overlies the PIP joint; lastly oblique pulley (average length 9 - 11mm) runs from the extended ulnar side of the adductor pollicis tendon to its radial portion between A1 and A2 pulleys. According to Doyle et al., the oblique pulley has the most important role in the thumb, which ensures appropriate gliding of the flexor pollicis longus tendon against the "bowstringing effect". In 1994. Zissimos et al. [3] affirmed that: If the A1 and C pulleys of the thumb are cut, considerable bowstringing can be observed simultaneously with decreased angular ROM of interphalangeal joints. Besides, the A2 pulley is the least to contribute to the arc motion of the thumb. Therefore, the authors emphasized that C pulley reconstruction could restore normal ROM of the thumb.

Bayat A [4] studied 14 cadaver hands and indicated that A1 pulleys are entirely transverse retinacular pulleys. Its proximal two-thirds were at the level of the volar plate at the MCP joint, with the distal one-third overlying the base of the proximal phalanx. The average length is 6mm (4 - 8mm). The

oblique pulley originating from the ulnar side of the proximal half of the proximal phalanx and connecting to the radial side of the base of the distal phalanx has an average width of 4.1mm (3 - 5mm). The A2 pulley is thinner, its proximal two-thirds covered the head of the proximal phalanx and the volar plate of the interphalangeal joint, while the distal third overlying the base of the distal phalanx of the thumb. Its average length is 8mm (5 - 10mm). The authors showed 4 types of pulleys of the thumb, while we have not studied and dissected them to research further yet.

Dissection of 26 cadaver thumbs, we recognized the appearance of all pulleys. The average length of the A1 pulley is 5.45mm (3.70 - 7.65mm), which is insignificantly shorter than the A1 pulley length from the previous international studies. The oblique pulley measured from its highest point to its lowest point has an average length of 14.09mm. The average distance from the MCP joint pin to the distal end of the oblique pulley is 4.67mm, which serves as an anatomic landmark for surgeons in oblique pulley reconstruction, more importantly, in 2-stage tendon reconstruction.

2. The pulleys of the long fingers

Although pulley construction was described in 1933, until 1975, Doyle et al. informed anatomic as well as physiological knowledge of pulleys. The very first description was about 4 annular pulleys and 3 cruciate pulleys, then Hunter complemented that the 5th annular pulley attaches the volar plate of the DIP joint. The pulleys are fibrous bands in ring-shaped or cruciform configurations. A1, A3, and A5 pulleys attach the volar plates and insert them onto the adjacent bony surface of MCP, PIP, and DIP joints. A2 and A4 pulleys just attach the respective proximal and middle phalanges. The thickest portion of the A2 pulley (0.75mm) localizing at the distal part is described as a long, large pulley and less likely to be restricted during finger flexion compared to other pulleys, which functionally hold the flexor tendons close to the axis of motion of the joints [2]. The pulley length is 7.9mm (A1), 16.8mm (A2), 2.8mm (A3), 6.7mm (A4), and 4.1mm (A5) [5]. Dissection of 26 cadaver hands comprising 104 long fingers, we observed that the longest pulley was A2 (18.95mm in the middle fingers; 17.28mm in the ring fingers), and the second longest pulley was A1 (7.79mm in the middle fingers,

7.78mm in the index fingers). The shortest pulley recorded was A4 (6.59mm in the middle fingers; 6.2mm in the index fingers). The average A1, A2, and A4 pulley lengths of the long fingers are 7.11mm, 16.12mm, and 5.94mm, respectively.

Pulley reconstruction is a vital procedure after the flexor tendon injury which is less common in an intact pulley disruption. Surgery, to be more specific - pulley reconstruction, is indicated in the "bowstringing tendon" to restore the normal kinematics of the flexor tendon system. The biomechanical studies showed that A2 and A4 pulleys play the most decisive role in bowstringing flexor tendon resistance. The whole function of the fingers was ensured. A1 and A5 pulleys are the least likely to affect finger motions during work [5, 6].

Chow JC (2014) [7] and Christopher J Dy (2013) [8] showed the importance of the proximal part of A2 and A4 pulleys in normal kinematics of the fingers, especially the PIP joints serve the most important in normal ROM of the fingers. The changes in the proximal part of A2 and A4 could affect the flexion ROM of the fingers. "Bowstringing tendons" are observed when the pulleys are unavailable or cut, reducing the angles of rotation, which enhances the axial motion at the respective joint. The proximal parts of A2 and A4 are the anatomic structures close to the MCP and PIP joints, which are the most important factors to prevent the "bowstringing tendons" of these joints. The authors support the opinion of cutting the distal parts of A2 and A4 in several specific case scenarios. In our studies, the distance from the most proximal part of the A2 to the MCP joint pin is 6.35mm, and the distance from the PIP joint pin to the distal end of the A4 pulley is 7.96mm. In clinical practice, we need to follow the original anatomic structures to restore normal functions.

The width and thickness of long fingers: At the A2 pulley is 6.25mm x 3.68 mm; at the A4 pulley is 4.98mm x 2.90mm. The widest and thickest portion is located in the middle finger: At A2 pulley: 6.91mm x 4.20mm; at A4 pulley: 5.42mm x 3.18mm. The narrowest and thinnest portion is in the little finger: At A2: 5.43mm x 3.11mm; at A4: 4.26mm x 2.52mm. The average width and thickness of long fingers are 6.25mm x 3.68mm. From these results, the orthopedic surgeons can choose the size of the available equipment for 2-stage tendon gliding tunnel reconstruction from the first stage.

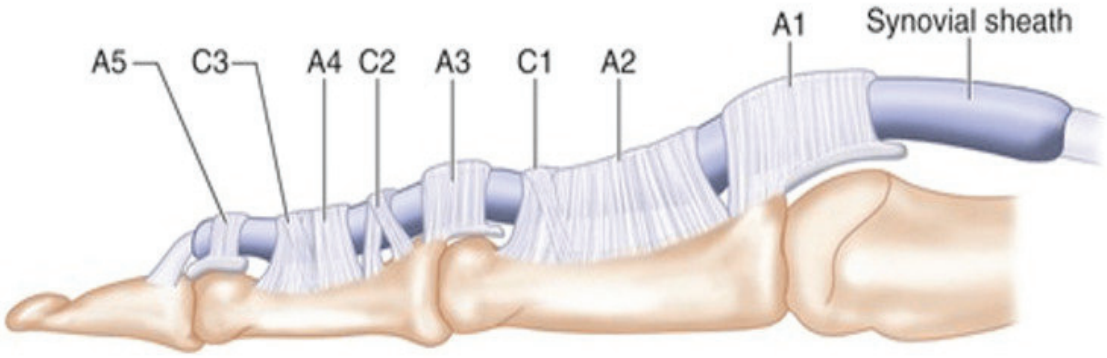


Figure 2. Pulley system of flexor tendons of the hand: The pulley system consist of five annular (A1 through A5) and three curciate (C1 through C3) pulleys that fix the tendons to the phalangeal bones [9].

CONCLUSION

From our anatomic study on clinical features of the digital shealths in 26 adult cadaver hands, we conclude that the A2 pulley has the maximal length at the middle finger (18.95mm); and the minimal length at the ring finger (4.95mm). In terms of the A4 pulley, the maximal and minimal lengths are at the middle finger (6.59mm) and the little finger (4.95mm), respectively. The average pulley lengths of the long fingers at A1, A2, and A4 pulleys are 7.11mm, 16.12mm, and 5.94mm, respectively. About the thumb, the width of the oblique pulley and A1 pulley is 14.09mm and 5.45mm, respectively. The width and thickness of the digital sheaths of long fingers at A2, and A4 pulleys are 6.25mm x 3.68mm and 4.98mm x 2.90mm, respectively. The distance from the MCP and PIP joints to the distal ends of A2, and A4 pulleys on the same long fingers are 6.35mm and 7.96mm, respectively. The average distance from the MCP joint to the most proximal part of the C pulley of the thumb is 4.67mm.

REFERENCES

1. Vishal Mehta, Craig S. Phillips. Flexor tendon pulley reconstructiom. *Hand Clin*. 2005; 21:245-251.

2. Doyle JR, Blythe WF. Anatomy of the finger flexor tendon sheath and pulleys of the thumb. *J Hand Surg*. 1977; 2:149-151.

3. Zissimos AG. Bio-mechanics of the thumb flexor pulley system. *J Hand Surg*. 1994; 19A:475-479.

4. Bayat A, Shaaban H. The pulley system of the thumb: Anatomic and biomechanical study. *The Journal of Hand Surgery*. 2002; 27A(4):628-635.

5. Doyle JR. Anatomy of the finger flexor tendon sheath and pulley system. *The J Hand Surg*. 1988; 13(4):473-484.

6. John G Seiler. Fraser J Leversedge. Digital flexor sheath: Repair and reconstruction of the annular pulley and membranous sheath. *J South Orthop Assoc*. 2000; 9(2):81-90.

7. Chow JC. Importance of proximal A2 and A4 pulleys to maintaining kinematics in the hand: A biomechanical study. *HAND (AAHS)*. 2014; 9:105-111.

8. Christopher J Dy. Flexor pulley reconstruction. *Hand Clin*. 2013; 29:235-242.

9. Ahmed F Alkandari. Isolated flexor digitorum profundus injuries in flexor zone ii of the hand: A report of five cases. *Cureus*. 2023; 15(1):e34360.

DNA-DEPENDENT PROTEIN KINASE INHIBITOR INDUCES APOPTOSIS IN COLON CANCER CELLS

Tran Phuong Linh[1], *Bui Khac Cuong*[1,2*]

Abstract

Objectives: Among all types of DNA damage, DNA double-strand breaks (DSBs) are considered the most deleterious form induced by either endogenous factors (oxi-dative damages, mismatches, altered chromatin structures, and missing, or modified nucleotides) or exogenous factors, i.e., ultraviolet (UV) radiation, ionizing radiation (IR), and chemicals or drugs. DNA-dependent protein kinase (DNA-PK) plays a crucial role in repairing DSBs through non-homologous end joining (NHEJ). Cells lacking DNA-PK exhibit heightened sensitivity to IR and various DNA-damaging agents. The inhibition of DNA-PK further intensifies cellular susceptibility to IR and DNA-damaging agents. Several small molecules that inhibit DNA-PK have been developed. This study aimed to evaluate the effect of DNA-PK inhibitor (DNA-PKi) NU7441 on the HCT116 cell line. ***Methods:*** DNA-PKi NU7441 was used to assess the effect on anti-proliferation and induction of apoptosis on the HCT116 colorectal cancer cell line. Cells were cultured under standard conditions; crystal violet and apoptosis assay were applied to evaluate cell proliferation and apoptosis. Data were analysed using GraphPad Prism 8.4. ***Results:*** DNA-PKi effectively inhibited HCT116 colon cancer cell growth via crystal violet assay ($p < 0.01$). In addition, DNA-PKi also induced programmed cell death in the HCT116 cell line ($p < 0.05$). ***Conclusion:*** DNA-PKi NU7441 suppressed cell proliferation and induced apoptosis in the HCT116 colon cancer cell line.

Keywords: DNA-PK; DNA-PKi; DNA damage repair; Non-homologous end joining; Colon cancer.

---

[1]**Laboratory Animal Research Center, Vietnam Military Medical University**
[2]**Department of Pathophysiology, Vietnam Military Medical University**
[*]**Corresponding author: Bui Khac Cuong (buikhaccuong@gmail.com)**
Date received: 23/01/2024
Date accepted: 15/3/2024
http://doi.org/10.56535/jmpm.v49i4.726

INTRODUCTION

DNA damages are caused by either endogenous factors (oxi-dative damages, mismatches, altered chromatin structures, and missing, or modified nucleotides) or exogenous factors, i.e., UV radiation, IR, and gen-otoxic chemicals, or drugs [1]. IR is thought to exert a variety of biological effects by causing damage to DNA. DNA damage repair (DDR) is a complex of different mechanisms including DDR, DNA damage tolerance mechanisms, and cell-cycle control checkpoint control. This complex system regulates the proper efficiency of DNA replication, proliferation, and cell survival. The role of the DDR pathway is crucial in maintaining genome integrity and stability by repairing DNA damage. If the damage is not repaired, it will cause instability and gene mutation, which is one of the hallmarks of cancer. In eukaryotes, DSBs are repaired mainly through homologous recombination (HR) and NHEJ [2]. DSBs are considered the most dangerous among the different types of DNA damage. Unlike HR, NHEJ does not require a DNA template (sister chromatid) for repair. Instead, NHEJ operates by modifying the free ends of DNA located on either side of the break by using various nucleases so that the ends become compatible (i.e. 3'-hydroxyl and a 5'-phosphate), followed by ligation with the enzyme DNA ligase 4. However, NHEJ is a relatively quick but intrinsically error-prone process, and its excessive use can lead to gene rearrangements, deletions, and mutations, all of which can cause post-replicative cells to be more vulnerable to DSBs [2].

DNA-PK is a serine/threonine protein kinase located in the nucleus. Its activation occurs upon interaction with its target DNA. DNA-PK forms a complex consisting of a sizable catalytic subunit, DNA-PKcs, and a regulatory factor, Ku proteins (Ku70/80), which form a heterodimer. Numerous studies highlight the pivotal role of mammalian DNA-PK in responding to DNA damage, particularly in the repair and recombination of DNA DSBs. It collaborates with ATM and ATR to phosphorylate related proteins, contributing to the DNA damage response and subsequent processes [3]. Furthermore, DNA-PK participates in modulating chromatin structure and maintaining telomeres [4].

The human genome encodes Ku70 and Ku80 (also known as Ku86), which are products of the XRCC6 and XRCC5 genes, respectively. These

proteins exhibit a strong affinity for the exposed ends of double-stranded DNA, and their binding is independent of the DNA sequence, focusing on the sugar backbone rather than the bases. Ku, particularly in its heterodimeric form (Ku70/80), plays a crucial role in NHEJ. Ku70/80 senses and binds double-strand breaks, which initiates NHEJ. Acting as a scaffold, it recruits the NHEJ machinery to the damaged DNA site and directly interacts with canonical NHEJ factors such as DNA-PKcs, XRCC4, DNA ligase IV, and XLF [5], along with most DNA end processing factors. Beyond its primary recruitment function, the Ku heterodimer serves a secondary role in maintaining the stability of the broken DNA molecule's ends when a double-strand break occurs. Forming a ring-shaped protein structure, the Ku heterodimer slides onto the ends of the fractured DNA, keeping them together and preventing nonspecific processing.

After induction of the DNA-strand break, the Ku70/80 heterodimer promptly identifies and binds to the damaged DNA, forming a ring-like protein complex at the site of the lesion. This complex plays a crucial role in stabilizing the broken double strands of DNA. Simultaneously, the Ku heterodimer recruits various processing proteins, including DNA-PKcs (the other component of DNA-PK), XRCC4, DNA ligase IV, XLF, and APL [6, 7].

The Ku heterodimer also contributes to maintaining the stability of the NHEJ complex at the DNA damage site. The NHEJ complex, once assembled, bridges the DNA ends and further enhances end stability. The interaction between DNA-PKcs and the Ku heterodimer triggers the inward translocation of the Ku heterodimer along the double-stranded DNA, ultimately activating the kinase activity of DNA-PKcs. The activated DNA-PKcs then phosphorylates numerous factors beyond the Ku heterodimers, including Artemis, polynucleotide kinase/ phosphatase (PNKP), Werner syndrome ATP-dependent helicase (WRN), DNA polymerase, and Aprataxin [8].

DNA-PK plays a crucial role in repairing DSBs through NHEJ. Cells lacking DNA-PK exhibit heightened sensitivity to IR and various DNA-damaging agents. The inhibition of DNA-PK further intensifies cellular susceptibility to IR and DNA-damaging agents. Therefore, inhibition of DNA-PK could impact the cell fate. Several small molecules that inhibit DNA-PK have been developed. This study aimed: *To evaluate the effect of DNA-PKi NU7441 on the HCT116 cell line.*

MATERIALS AND METHODS

1. Materials

** Cell line and cell culture condition:*

In this experiment, HCT116 cells were used as an experimental model to evaluate the antitumor activity of DNA-PKi NU7441 (Catalog No.S2638; purity: 99.94%; Selleckchem), subsequently referred to as DNA-PKi. HCT116 cells originated from an American Type Culture Collection, Manassas, Virginia, USA. These cells were cultivated in Dulbecco's Modified Eagle Medium (DMEM) obtained from Cytiva, Massachusetts, USA, supplemented with 10% fetal bovine serum (FBS) also from Cytiva, Massachusetts, USA, and 1% Penicillin-Streptomycin sourced from Sigma-Aldrich, Missouri, USA. The cells were grown in an environment with 5% CO_2 and 95% air at 37ºC.

2. Methods

** Crystal Violet:*

After harvesting, cells were transferred to 12 wells plate, each well with a density of 300 cells/well and 5mL medium, and cultured in an incubator with 37ºC and 5% CO_2. After 24 hours, cells were treated with control, 0.125µM or 0.250µM of DNA-PKi, and monitored until the cell colonies were visible by eye (approximately 7 - 8 days), then proceed to stain the cells with a specialized purple dye (Crystal Violet). Then, the plates were scanned to obtain cell colony images. Cell images were analyzed using ImageJ software and histograms were constructed based on the measured number of cell colonies and color intensity (n = 4).

** FACS apoptosis assay:*

Cells were treated and stained according to the procedure included with Annexin V Apoptosis Detection kit: HCT116 cells were cultured in 6-well plates of 300,000 cells per well for 2h. After the cells had reached the appropriate number, the DNA-PKi was treated with different concentrations (0.125µM; 0.250µM), and the control group was cultured without treatment. After treatment, the cells were washed with PBS (phosphate-buffered saline), and counted the cell number. Cells were scraped off the plate, stained with Propidium Iodide (PI, 10 ug/mL) and Annexin V, and incubated for 15 min to label the cells. After incubation, cells were analyzed on a flow cytometer.

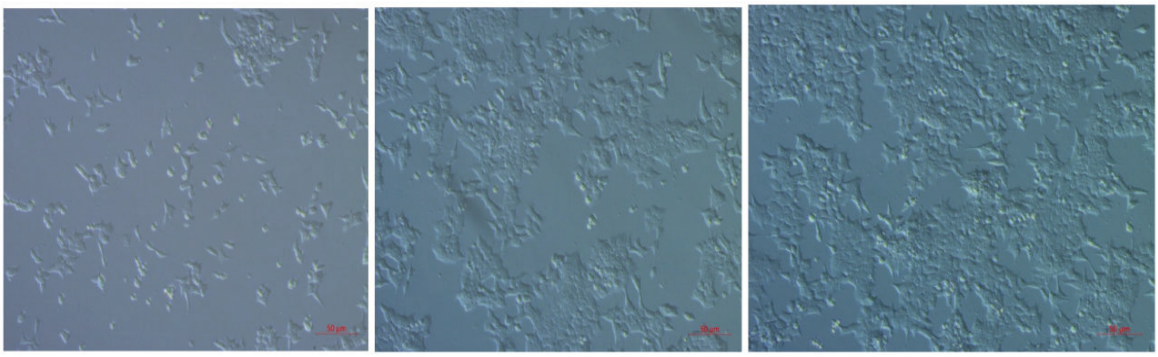
** Statistical analysis method:*

GraphPad Prism version 8.4 (GraphPad Software, Inc., California,

USA) was used for statistical analysis. The study results were presented as Mean ± Standard Deviation (SD). Using One-Way ANOVA to test the difference of mean when comparing more than 2 groups. The difference is considered statistically significant when $p < 0.05$.

RESULTS

1. Cell culture and proliferation



A B C

Figure 1. Morphological characteristics of HCT116 cell line in culture.

(A: HCT116 cells in day 1; B: HCT116 cells in day 2; C: HCT116 cells in day 7. After 24h, cells adhered to the bottom 40 - 50% of the culture area. After 7 days, the cultured cells had covered 80% of the culture area.)

The images in figure 1 recorded the status, form and density of HCT116 cultured after 1 day, 2 days, and 7 days. HCT116 cells appeared as basal epithelial cells, monolayer growing, having many different shapes from oval to polygonal, were about 20 - 25µM in size, although this size could vary depending on the stage of the cell cycle. In addition, HCT116 cells had large nuclei occupied most of the cytoplasm. After 24h of culturing, the HCT116 cells adhered to the bottom of the culture dish and showed robust proliferation. The proliferation rate of HCT116 was about 40 - 50% within 24 hours. After 7 days, the cultured cells had covered 80% of the flask area. The cell proliferation rate was monitored, and when it reached approximately 80% of the plate area, the cells were transferred to a new culture plate.

2. Evaluation of cell proliferation by Crystal Violet assay

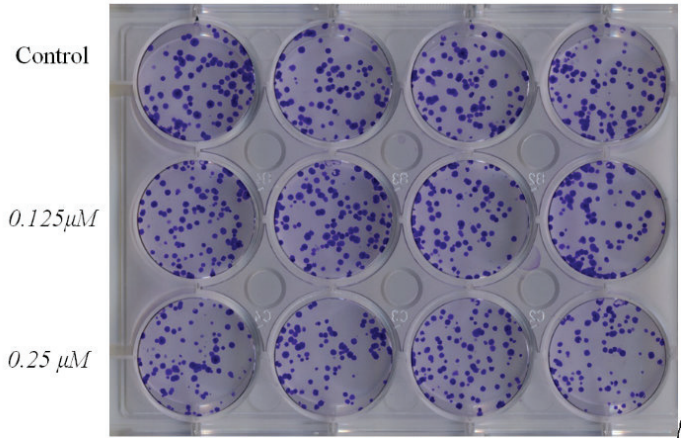


Figure 2. Changes in the results of staining HCT116 cells with Crystal violet between the control and DNA-PKi treatment groups after 2 weeks.

Cells were treated with control, 0.125μM or 0.250μM of DNA-PKi. After that, treatment with DNA-PKi was maintained until the cell colonies were visible by eye (approximately 7 - 8 days), then proceed to stain the cells with a specialized purple dye (Crystal Violet).

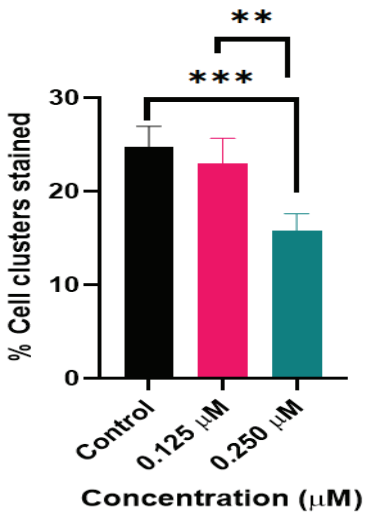


Figure 3. Quantitative analysis of cell of Crystal Violet assay after 2 weeks between control and treatment groups at concentrations: 0.125μM and 0.250μM.

*(p** < 0.0008, p*** < 0.003. Relative staining intensities were measured by using ImageJ software)*

The results of Crystal Violet assay were presented in figure 2 and 3. In figure 2, after stained with Crystal Violet, the control group had large, intensely colored, and densely packed cell clusters, whereas the group treated with DNA-PKi at a concentration of 0.125µM showed smaller, paler, and sparser cell clusters. Meanwhile, the group treated with DNA-PKi at 0.250µM appeared lighter and smaller clusters compared to the control group. We observed that HCT116 at concentrations of 0.250µM exhibited proliferation inhibitory activity on HCT116 cells *in vitro* especially at concentrations 0.250µM (the average stained area of cell clusters for the control group was 24.78%, significantly higher than 0.250µM treatment group (15.75%), with p*** < 0.001). At a concentration of 0.125µM, there was inhibition of proliferation but it is not really clear. Furthermore, the inhibitory effect on proliferation was dose-dependent when comparing the 0.125µM treatment group and the 0.250µM treatment group (the average stained area of cell clusters for the 0.125µM treatment group was significantly higher than the corresponding value for the 0.250µM treatment group, with p** < 0.01, *Figure 3*).

3. Evaluation of the ability of DNA-PKi to induce programmed cell death (apoptosis)

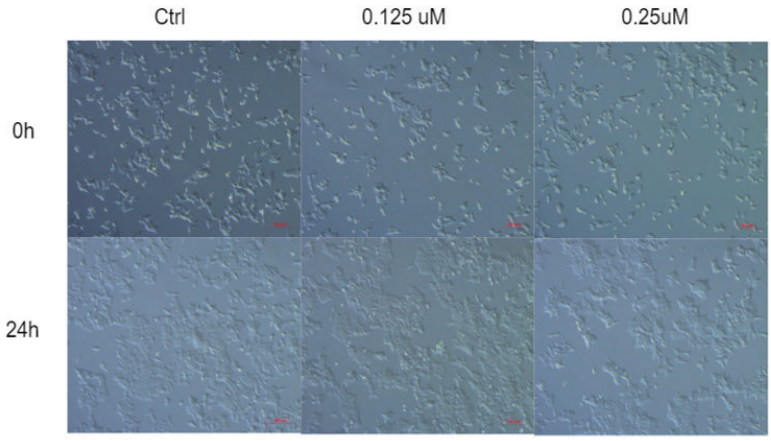


Figure 4. DNA-PKi stimulates apoptosis on HCT116 cells. The cells were treated with DNA-PKi at different concentrations: 0; 0.125µM; 0.250µM.

(At 0h, the cells grew in small dicrete cluster while cells at 24h on all group grew in large patches, spreading evenly on the surface).

HCT116 cells were treated with DNA-PKi at concentrations of 0.125µM, 0.250µM for 48h to evaluate the stimulation of DNA-PKi to apoptosis. After 24h, the number of dead cells increased significantly in both treatment groups compared with the control group (*Figure 4*). The cells were then analyzed on a flow cytometer with the AnnexinV/PI indicators.

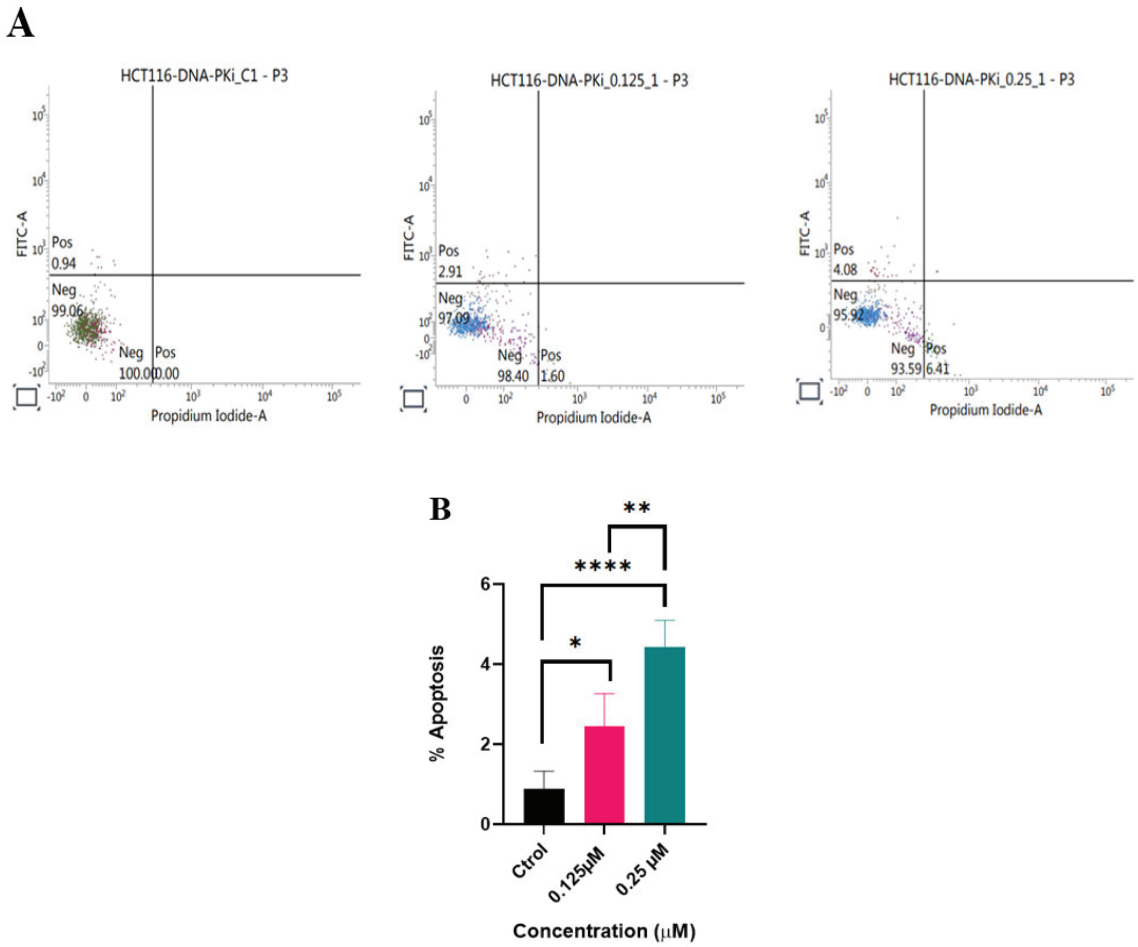


Figure 5. DNA-PKi induces apoptosis on HCT116 cells.

(A: HCT116 cells were treated with DNA-PKi at different concentrations for 24h and stained with Annexin V - FITC; cells were then counted by flow cytometry for apoptosis analysis. Upper right quadrant: Late apoptosis; upper left quadrant: Early apoptosis. Lower right quadrant: Necrosis; lower left quadrant: Viable cells.

B: Quantification of apoptotic cells. Data were analyzed by one-way ANOVA test and post-hoc Tukey test, $^{*}p < 0.01$, $^{****}p < 0.001$).

Cells were treated with DNA-PKi, evaluated with FITC Annexin V-PI staining, and analyzed by flow cytometry. Cells in the upper right quadrant represent late apoptosis, and cells in the upper left quadrant represent early apoptosis. Besides that, cells in the lower right quadrant represent necrosis cells, and cells in the lower left quadrant represent viable cells.

The impact of DNA-PKi on apoptosis was demonstrated in figure 5. The statistical analysis results revealed that the group treated with DNA-PKi at a concentration of 0.125µM after 24 hours had an average apoptosis rate of 2.46%, significantly higher than the corresponding value of the control group at 0.88% ($p = 0.0196$). However, a 4-fold increase in the total number of apoptosis cells was observed when treatment with DNA-PKi 0.25µM ($p < 0.0001$, *Figure 5*). The results of this study serve as preliminary data for future investigations into the anticancer potential of DNA-PKi.

DISCUSSION

The apoptosis process in cancer cells leads to the destruction of the cell's nuclear DNA, rendering the cells incapable of division, thereby reducing the proliferative potential of cancer cells. For cancer, promoting the apoptosis cell death pathway has been considered a strategy for anticancer drug development. In this regard, studies on the anticancer have shown KU-57788 to be possible to prevent cancer cell growth through activation of cell death pathways apoptosis. The results showed that DNA-PKi initially suppresses cell proliferation by induction the apoptosis pathway. A study indicated that inhibition of DNA-PK kinase activity increases apoptosis without affecting DNA repair in proliferating cancer cells [9]. These results were surprising because the percentage of apoptotic cells significantly varied with cell conditions. The presence of NU7026 DNA-PKi, which significantly decreased the ability to repair DNA damage, will likely undergo cell death. These studies corroborate DNA-PK's ability to inhibit apoptosis without affecting DNA repair activity in proliferating cells, where many DNA repair mechanisms are in use. However, in neural cells, where NHEJ is primarily responsible for repairing DNA damage (more precisely, DSBs), DNA-PK complex repair activity may be crucial to the survival of the cell.

Targeting DNA holds promise as an approach for future cancer therapies; however, DNA-PKi also presents certain

limitations. DNA-PKi have failed to induce significant changes in animal studies despite promising laboratory findings. One reason for these observations may be related to the limited solubility and poor pharmacokinetic properties of DNA-PKi. For instance, NU7441 exhibits poor absorption and rapid metabolism in mice, hindering its clinical application as a DNA-PKi [10]. Animal studies have shown that the concentration of NU7441 required for sensitizing cells to chemotherapy and radiation *in vitro* can be achieved and maintained within tumor tissue for at least 4 hours after administration. However, the compound's limited aqueous solubility has impeded further dose escalation. Based on promising pharmacokinetics, combination efficacy studies have been conducted, revealing that NU7441 effectively doubles the delay in tumor growth caused by etoposide without increasing toxicity to unacceptable levels. Similar results have been reported when using the colorectal cancer xenograft system, where IC86621 resulted in a fourfold enhancement of IR, leading to slowed tumor development and increased survival rates. However, due to its pharmacokinetic properties, this compound requires dosing every 4 hours, limiting its dose escalation potential [10].

CONCLUSION

DNA-PKi NU7441 suppressed cell proliferation and induced apoptosis in the HCT116 colon cancer cell line.

Acknowledgment: This research is funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 108.02-2019.324. The funder had no role in the study design, data collection, analysis, or decision to publish or prepare the manuscript. The authors declare to have no potential conflicts of interest.

REFERENCES

1. S Hu, F Lirussi, C Garrido, XY Ye, and T Xie. Small molecule DNA-PK inhibitors as potential cancer therapy: A patent review (2010-present). Feb 2021. DOI: 10.1080/13543776.2021.1866540.

2. Y Matsumoto. Development and evolution of DNA-Dependent Protein kinase inhibitors toward cancer therapy. *Int. J. Mol. Sci.* Jan 2022; 23(8). DOI: 10.3390/ijms23084264.

3. Double-stranded DNA induces the phosphorylation of several proteins including the 90 000 mol. wt. heat-shock protein in animal cell extracts. Accessed: Jan. 17, 2024. [Online]. Available: https://www.embopress.org/doi/epdf/10.1002/j.1460-2075.1985.tb02328.x.

4. BL Ruis, KR Fattah, and EA Hendrickson. The catalytic subunit of DNA-dependent protein kinase regulates proliferation. Telomere length, and genomic stability in human somatic cells. *Mol. Cell. Biol.* Oct 2008; 28(20):6182-6195. DOI: 10.1128/MCB. 00355-08.

5. JM Sekiguchi and DO Ferguson. DNA Double-strand break repair: A relentless hunt uncovers new prey. *Cell*. Jan 2006; 124(2):260-262. DOI: 10.1016/j.cell.2006.01.010.

6. M O'Driscoll et al. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. *Mol. Cell.* Dec 2001; 8(6):1175-1185. DOI: 10.1016/S1097-2765(01)00408-7.

7. Identification of a defect in DNA ligase IV in a radiosensitive leukaemia patient - ScienceDirect. Accessed: Jan. 17, 2024. [Online]. Available: https://www.sciencedirect.com/science /article/pii/S096098229980311X.

8. D Moshous et al. Artemis, a Novel DNA Double-Strand Break Repair/V(D)J recombination protein, is mutated in human with severe combined immune deficiency. *Cell*. Apr 2001; 105(2):177-186. DOI: 10.1016/S0092-8674(01)00309-9.

9. A Cardinale et al. DNA repair protein DNA-PK protects PC12 cells from oxidative stress-induced apoptosis involving AKT phosphorylation. *Mol Biol Rep*. Feb 2022; 49(2):1089-1101. DOI: 10.1007/s11033-021-06934-5.

10. Y Zhao et al. Preclinical evaluation of a potent novel DNA-dependent protein kinase inhibitor NU7441. *Cancer Res*. May 2006; 66(10):5354-5362. DOI: 10.1158/ 0008-5472.CAN-05-4275.

STUDY ON *STAT6* rs324015 POLYMORPHISM IN HEPATITIS B VIRUS-RELATED HEPATOCELLULAR CARCINOMA PATIENTS

Duong Quang Huy[1], Le Quang Nhut[1,2], Nguyen Xuan Kien[1]*

Abstract

Objectives: To determine the genotype frequency of the *STAT6* rs324015 polymorphism and its association with cancer risk in hepatitis B virus (HBV) - related hepatocellular carcinoma (HCC) patients. ***Methods:*** A cross-sectional descriptive study on 118 HBV-related HCC patients, compared to 86 HBV-related cirrhosis patients and 195 healthy people at 108 Military Central Hospital, Military Hospital 103, and Can Tho General Hospital from July 2017 to August 2020. Polymorphism analysis of the *STAT6* rs324015 gene was conducted from peripheral blood samples of subjects using the Sanger sequencing method at Apical Scientific Sequencing Company (Malaysia). ***Results:*** The AG/GA heterozygous genotype of the *STAT6* rs324015 polymorphism accounted for the highest rate in HCC patients at 51.7%, higher than the corresponding index in the cirrhosis group at 39.5%, and healthy people (48.2%); the GG genotype was the highest in cirrhosis patients (40.7%), the difference was not statistically significant, $p > 0.05$. ***Conclusion:*** *STAT6* rs324015 polymorphism is not associated with cancer risk in patients with HBV-related HCC.

Keywords: *STAT6* gene polymorphism; Hepatocellular carcinoma (HCC).

INTRODUCTION

Hepatocellular carcinoma is the most common type of cancer, with the 6th highest prevalence and the 3rd highest mortality rate, following lung cancer and colorectal cancer [1]. There are several causes of HCC, of which HBV is the main one, accounting for over 50% of HCC cases. However, HBV infection can be asymptomatic or

[1]Vietnam Military Medical University

[2]Tay Do University

[*]Corresponding author: Duong Quang Huy (huyduonghvqy@gmail.com)

Date received: 05/12/2023

Date accepted:12/3/2024

http://doi.org/10.56535/jmpm.v49i4.573

cause acute hepatitis, chronic hepatitis, cirrhosis, etc, and partly be able to form HCC [2]. The pathophysiological mechanism of these clinical disease manifestations is still controversial, depending closely on HBV characteristics (genotype, gene mutations, replication level, etc.) as well as the interaction between HBV and other pathogens as related factors of the host body (genes and signaling pathways).

Notably, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a signal transduction pathway of many cytokines and growth factors, responsible for cellular functions such as cell proliferation, stem cell maintenance, cell differentiation, as well as regulation of immune and inflammatory responses, and therefore this signaling pathway is closely related to many infectious diseases and cancers including HCC [3, 4]. Among the seven members of the STAT family, *STAT1, STAT2*, and *STAT4* exhibit inhibitory effects on HCC formation both in vitro and in vivo; on the contrary, *STAT3* is a carcinogenic agent, stimulating angiogenesis, maintaining cancer stem cell populations, thereby promoting the development, invasion and metastasis of HCC, while *STAT5* (including *STAT5a* and *STAT5b*) has a higher expression level in HCC tissue than in non-tumor liver tissue and has significance in disease prognosis [4, 5].

The *STAT6* gene is located on the long arm of chromosome 12, includes 23 exons and more than 10 gene polymorphisms have been identified, of which the polymorphisms at exon 23, such as rs324015, rs703817, etc, are the most studied because exon 23 is the transcriptional activation region and contains important information that affects the structure and function of STAT6 protein [6, 7]. However, new studies only focus on their role in some allergy-related diseases because the *STAT6* gene plays a role in the IL4/IL13/*STAT6* signaling pathway, activating mastocytes and increasing IgE production [7]; study on cancer patients is still limited, especially there has been no study on the *STAT6* rs324015 polymorphism in relation to HBV-infected HCC. Therefore, we conducted the study: *To determine the genotype rate of STAT6 rs324015 polymorphism and its relationship with cancer risk in patients with HBV-related HCC.*

MATERIALS AND METHODS

1. Subjects

The study was conducted on 3 groups of patients:

- Group of patients with HCC: 118 patients were diagnosed with HCC

according to the standards of the Vietnam Ministry of Health in 2012 and HBsAg (+) tested [8].

Excluded criteria: Patients with HCC who had anti-HCV (+), anti-HIV (+) tests; had combined cancer; did not have a test to determine the *STAT6* rs324015 polymorphism; cirrhotic patients with alcohol abuse; use of hepatotoxic drugs, etc.

- Cirrhosis group: 86 patients diagnosed with cirrhosis based on clinical and laboratory tests with portal hypertension syndrome, liver failure and changes in liver morphology or F4 fibrosis, and HBsAg (+).

The group of HCC patients and cirrhosis was selected at Military Hospital 103, 108 Military Central Hospital, and Can Tho City General Hospital.

- Healthy group: 195 blood volunteers at the Center for Hematology - Blood Transfusion, Military Hospital 103, with no clinical symptoms or history of hepatitis, cirrhosis, or liver cancer. HBsAg, Ani-HCV and Anti-HIV tests were negative

* *Study period:* From July 2017 to August 2020.

2. Methods

* *Research design:* A cross-sectional descriptive study.

All patients eligible for the study were carefully examined for medical history, clinical symptoms, and tests to confirm the diagnosis and stage of the disease.

Analyze the rs324015 polymorphism on *STAT6* from peripheral blood samples of subjects at the Biosafety department of the Institute of Biomedicine and Pharmacy, Vietnam Military Medical University according to the following steps:

- Step 1: Separate the whole DNA from peripheral blood using GenJET Whole Blood Genomic DNA Purification Mini Kit (Thermo; USA), following the manufacturer's instructions. The whole DNA product was measured for concentration and checked for purity by measuring optical absorbance at wavelengths of 260nm and 280nm on a Nanodrop machine.

- Step 2: Amplify the target gene segment. Use PCR (Polymerase chain reaction) technique to amplify the *STAT6* gene segment with the following primer pair:

GCACACTTGCTGCTGCTTC (forward)

CTGCTCTGGACACTTGCTCA (reverse)

Electrophoresis of PCR products to check primer specificity.

- Step 3: PCR products will be purified using GeneJET PCR Purification Kit (Thermo; USA), following the manufacturer's instructions.

- Step 4: Take 20µL of purified PCR product and sequence it using the Sanger method at Apical Scientific Sequencing Company, Malaysia. Sequencing results were then entered into Geneious software to compare with the human standard Genbank, thereby identifying the rs324015 polymorphism on *STAT6*.

* *Data processing and analysing*: Using SPSS 20.0 medical statistical software. Statistical analysis by calculating percentages and average values, comparing proportions using the $\chi 2$ test or Fisher exact test. Calculated percentage values are taken 1 digit after the decimal number. The difference is considered statistically significant when $p < 0.05$.

3. Ethics

The study was reviewed and approved by the Ethical Committee, Vietnam Military Medical University. The study complied with the Declaration of Helsinki principles. All study participants or their legal guardians provided informed written consent before study enrollment. The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethics.

RESULTS

1. Age and gender characteristics of the study group

Table 1. Age and gender characteristics of the study group.

Subjects	n	Male	Female	Male/female ratio	Mean ± SD
HCC	118	104	14	7.4	65.5 ± 11.1
Cirrhosis	86	62	24	2.6	59.5 ± 10.5
Healthy	195	118	77	1.5	19.5 ± 1.2
Total	399	284	115	2.5	41.7 ± 23.2

HCC patients had an average age of 65.5 years, higher than the average age of the cirrhosis group of 59.5 and the healthy group of 19.5.

88.1% of HCC patients were male, and the male/female ratio was 7.4. This ratio in the cirrhosis group was 2.6, and in the healthy group was 1.5.

2. Gene and allele distribution of *STAT6* rs324015 polymorphism

Table 2. Genotype and allele ratio of *STAT6* rs324015 polymorphism in patients with HCC.

Genotype and allele	Number	Percentage (%)
Genotype (n = 118)		
AA	25	21.2
AG/GA	61	51.7
GG	32	27.1
Allele (2n = 236)		
A	111	47.0
G	125	53.0

The majority of HCC patients had the heterozygous AG/GA genotype (51.7%), and the homozygous AA and GG genotypes had a low frequency (21.1% and 27.1%, respectively).

The rate of G allele of *STAT6* rs324015 polymorphism in the HCC group was higher than the rate of A allele (53.0% vs. 47.0%).

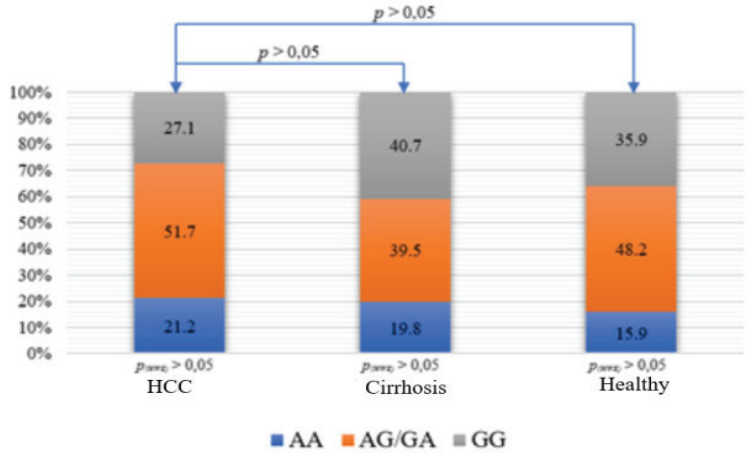


Chart 1. Comparison of genotype distribution of *STAT6* rs324015 polymorphism in HCC, cirrhosis, and healthy people.

The genotype distribution of *STAT6* rs324015 polymorphism in HCC, cirrhosis, and healthy groups all comply with Hardy Weinberg's *equilibrium*, p > 0.05.

The genotype ratio of the *STAT6* rs324015 polymorphism between the HCC group, cirrhosis, and the healthy group was not statistically different, p > 0.05.

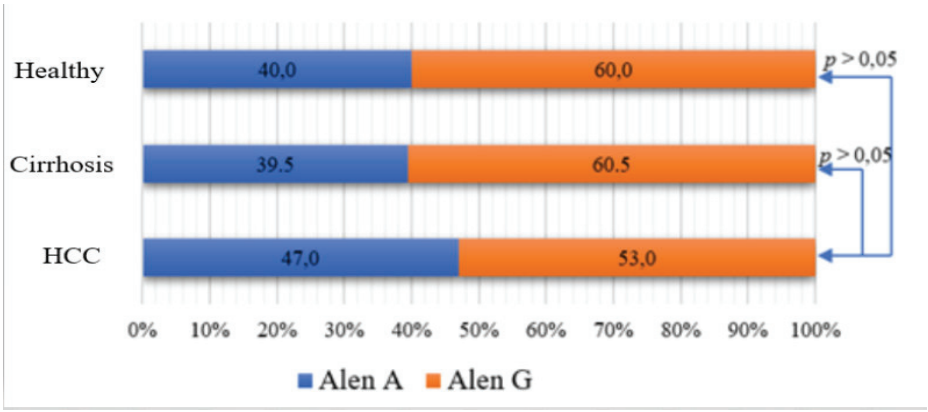


Chart 2. Comparison of allele distribution of *STAT6* rs324015 polymorphism in HCC, cirrhosis, and healthy people.

The allele ratio of *STAT6* rs324015 polymorphism between HCC, cirrhosis, and healthy groups was not statistically different, p > 0.05.

DISCUSSION

1. Patient characteristics by age and gender

* *Age:* The average age of the 118 HCC patients in our study was 65.5 ± 11.1, consistent with the results of domestic study by Phan Thi Hien Luong (2020) on 102 HCC patients with HBV infection at Bach Mai Hospital with the average age of 57.4 ± 9.7 [9]. Thus, in Vietnam, HCC is often detected in middle-aged people because the country is located in an HBV endemic area, with a high rate of mother-to-child infection, while in European countries, the main cause of HCC is alcohol and hepatitis C virus infection. Most authors around the world have noted that the age of HCC depends on many factors such as gender, hepatitis virus infection status, and the difference from region to region [1, 2].

* *Gender:* 88.1% of HCC patients in our study were male, 11.9% were female; the male/female ratio was 7.4/1. This ratio is higher than the results of many previous studies (only ranging from 2 - 8/1, with an average of 4/1), but consistent with the results of Phan Thi Hien Luong (2020), which has a male/female ratio of 11.8/1 [9]. The reason why HCC is more common in men than in women may be because

men are more exposed to risk factors such as alcohol abuse, smoking, and high body mass index, and especially the rate of HBV and HCV infection is higher than in women. In addition, the relationship between sex hormones and the occurrence and progression of HCC has also been confirmed. Testosterone is a factor that plays a role in regulating the liver cell cycle, promoting the signal transduction pathway through the androgen receptor, stimulating the growth of liver cells, and thereby accelerating the pathogenesis of HCC. In contrast, the female sex hormone (oestrogen) inhibits cell cycle regulation and inflammation through Interleukin 6, thereby reducing liver damage and limiting the development of liver cancer [2, 4].

2. Gene and allele distribution of *STAT6* rs324015 polymorphism

HCC is still a malignant disease with a very complex pathogenesis with the impact of many risk factors and the participation of many signaling pathways such as Wnt/β-catenin, PI3K/Akt/ mTOR, Ras/Raf/MAPK, JAK/STAT, and many other genes involved. The JAK/STAT (Janus kinase/Signal transducer and activator of transcription) signaling pathway has been recognized by many studies to play an important role in the formation, emergence, and progression of HCC.

Among members of the STAT family, we found that very few studies have been conducted on *STAT6* polymorphisms in HCC patients (especially polymorphisms at position rs324015).

Our study found that on 195 healthy people, the rate of AG/GA heterozygous genotype of the *STAT6* rs324015 polymorphism (4219 G>A) was the highest at 48.2%, followed by the AG/GA genotype. Homozygous gene GG accounted for 35.9%, and the lowest was genotype AA accounting for 15.9%. The ratio of the G allele was more dominant than the A allele (60.0% vs. 40.0%, respectively) (*Chart 1, 2*).

Results by Ruan Z et al. (2011) on 693 healthy Chinese people with an average age of 39.6 ± 18.3 (varying from 1 - 86 years old) showed similar results to ours. In our study, in the *STAT6* rs324015 polymorphism, the highest rate of genotype was AG (48.9%), while the rate of homozygous genotypes GG and AA was nearly equal at 24.3% and 26.9%, respectively [10]. Research by Duetsch G et al. (2002) analyzing gene polymorphisms on 449 subjects living in Germany and Sweden also showed that the rate of G allele of *STAT6* rs324015 gene

polymorphism was 76.57%, while the rate of allele A was lower at only 23.43% [6]. Thus, according to the above studies, the *STAT6* rs324015 polymorphism has a dominant ratio of the G allele and heterozygous AG genotype compared to the A allele and the remaining genotypes. However, a recently published study by Dai L et al. (2021), when directly analyzing the *STAT6* rs324015 polymorphism by qRT-PCR method on 355 healthy Chinese people, recorded that the AA genotype accounted for the highest proportion. The rate was 56.3%, higher than the remaining two genotypes AG (37.5%) and GG (6.2%); the A allele rate was up to 75.1% compared to the G allele rate, which only accounted for 24.9% [11]. Obviously, the allele and genotype rates of the *STAT6* rs324015 gene polymorphism still seem to largely depend on the human race, so further research is needed.

In the group of HCC patients with HBsAg (+), the results of *STAT6* rs324015 polymorphism analysis were similar to the healthy group: The heterozygous AG genotype had the highest rate of 51.7%, followed by the GG genotype at 27.1% and AA genotype at 21.2%. The G allele was still dominant at 53.0% compared to the A allele at 47.0%. In the group of cirrhotic patients, we noted a slight difference: The proportion of homozygous GG and heterozygous AG genotypes was almost equal (40.7% and 39.5%, respectively). However, we did not observe any difference in the distribution of genotypes and alleles of the *STAT6* rs324015 polymorphism between the 3 study groups. Thus, *STAT6* rs324015 polymorphism does not change the risk of HCC in HBV-infected patients.

Currently, we have not recorded any study published around the world on the relationship of the *STAT6* rs324015 polymorphism with HCC. Most of the studies on *STAT6* rs324015 polymorphism are on subjects with allergies, bronchial asthma, etc, because it is related to the IL4/IL13/*STAT6* signaling pathway that activates mastocytes and increases blood IgE production. A systematic review conducted by Qian X et al. (2014), when subgroup analysis by race (Caucasians and Asians) and age (children and adults), also failed to note an association with asthma. However, this review showed that the *STAT6* rs324015 polymorphism appeared to reduce the risk of allergic asthma with OR = 0.83, 0.68, and 0.79 for the A allele, AA genotype, and AA + AG genotype combination, respectively [12]. Recently, research by Dai L et al. (2021) noted that the *STAT6* rs324015 polymorphism increased the risk of

ulcerative colitis in both homozygous models, dominant models, and allele models. Subgroup analysis also showed a clear association between this polymorphism and alcohol consumption, cigarette smoking, young age < 40, as well as the severity and extent of disease [11].

In a group of cancer patients, we noted the study of Ruan Z et al. (2011) determining the relationship of *STAT6* polymorphisms with brain gliomas. The results show that the *STAT6* rs324015 polymorphism was not associated with the risk of glioma formation when analyzed in both homozygous models, dominant models, and recessive models, as well as when analyzed in subgroups according to smoking status, histopathological results, and disease stage according to WHO [9].

Thus, the relationship between the *STAT6* rs324015 polymorphism and cancer in general and HCC in particular needs to continue to be studied to reach a final conclusion to apply this marker in clinical practice.

CONCLUSION

Studying *STAT6* rs324015 polymorphism in 118 patients with HBV-related HCC, compared with the corresponding polymorphism expression in 86 HBV-related cirrhosis patients and 195 healthy people, we draw the conclusion as follows:

- The AG/GA genotype of the *STAT6* rs324015 polymorphism accounted for the highest proportion in HCC patients at 51.7%, higher than the corresponding index in the cirrhosis group of 39.5% and healthy people at 48.2%. While the GG genotype was the highest in cirrhosis patients (40.7%), the difference was not statistically significant, $p > 0.05$.

- *STAT6* rs324015 gene polymorphism was not associated with HCC risk when compared to the cirrhotic and healthy people groups.

Acknowledgments: The authors thank all the staff members of the Department of Gastroenterology, Military Hospital 103, 108 Central Military Hospital, Can Tho City General Hospital, and the Biosafety Department of the Institute of Biomedicine and Pharmacy, Vietnam Military Medical University for assisting the research group throughout the study process. The authors declare to have no conflicts of interest.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020 GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021; 71:209-249.

2. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2018; 68(2):723-750.

3. Thomas SJ, Snowden JA, Zeidler MP, et al. The role of JAK/STAT signaling in the pathogenesis, prognosis, and treatment of solid tumours. *Br. J. Cancer.* 2015; 113(3):365-371.

4. Alqahtani A, Khan Z, Alloghbi A, et al. Hepatocellular carcinoma: Molecular mechanisms and targeted therapies. *Medicine*. 2019; 55(9): 526-547.

5. Dong Z, Chen Y, Yang C et al. STAT gene family mRNA expression and prognostic value in hepatocellular carcinoma. *OncoTargets and Therapy*. 2019; 12:7175-7191.

6. Duetsch G, Illig T, Loesgen S, et al. *STAT6* as an asthma candidate gene: Polymorphism-screening, association and haplotype analysis in a Caucasian sib-pair study. *Hum Mol Genet.* 2002; 11(6):613-621.

7. Karpathiou G, Papoudou-Bai A, Ferrand E, et al. *STAT6*: A review of a signaling pathway implicated in various diseases with a special emphasis in its usefulness in pathology. *Pathol Res Pract.* 2021; 223:1-8.

8. Bộ Y tế *Hướng dẫn chẩn đoán và điều trị ung thư tế bào gan nguyên phát.* Ban hành kèm theo Quyết định số 5250/QĐ-BYT ngày 28 tháng 12 năm 2012 của Bộ trưởng Bộ Y tế. 2012.

9. Phan Thị Hiền Lương. Nghiên cứu đa hình gen TNF-α-308 và TGF-β1-509 ở bệnh nhân ung thư biểu mô tế bào gan có HBsAg dương tính. *Luận án Tiến sĩ Y học*. Học viện Quân y. 2020.

10. Ruan Z, Zhao Y, Yan L, et al. Single nucleotide polymorphisms in IL-4Ra, IL-13, and *STAT6* genes occur in brain glioma. *Front Biosci (Elite Ed).* 2011; 3:33-45.

11. Dai L, Zhang D, Qian Y, et al. *STAT6* rs324015 Gene Polymorphism increases ulcerative colitis risk: A case-control study. *Pharmacogenomics and Personalized Medicine*. 2021; 14:101-107.

12. Qian X, Gao Y, Ye X, et al. Association of *STAT6* variants with asthma risk: A systematic review and meta-analysis. *Human Immunology*. 2014; 75(8):847-853.

AEROMEDICAL EVACUATION OF VIETNAM'S LEVEL-2 FIELD HOSPITAL IN THE UNITED NATIONS MISSION IN SOUTH SUDAN: A RETROSPECTIVE STUDY

Dinh Van Hong[1], Nguyen Dinh Ta[2], Tu Quang[3], Trinh My Hoa[4]*

Abstract

Objectives: To describe the characteristics of aeromedical evacuation (AE) operations in the United Nations Mission in South Sudan (UNMISS) carried out by Vietnam's Level-2 Field Hospital (L2FH). ***Methods:*** A retrospective, descriptive study on the data from all AE activities of the Aeromedical Evacuation Team (AMET) of Vietnam's L2FH from October 2018 to March 2022 in Bentiu, South Sudan. ***Results:*** 31 AE patients were collected with 1 case of casualty evacuation (CASEVAC), 14 cases of emergency medical evacuation (MEDEVAC), and 16 cases of non-emergency MEDEVAC. The mean age was 38.8 ± 8.4 years old, and the majority were male (83.9%). Patients were mainly from troop-contributing countries (TCCs) (67.7%). All cases belonged to the non-battle injury group, the majority was illness (93.5%). 6 infectious cases underwent AE, of which 2 patients were diagnosed with suspected severe COVID-19. Most patients needed medical officer escorts (29/31). The mean time from AE approval to patient referral for emergency MEDEVAC was 1.8 ± 0.4 hours, and for non-emergency MEDEVAC was 12.5 ± 7.9 hours. All cases were successfully transferred without any complications during AE. ***Conclusion:*** All patients under AE were not due to combat injury and mainly belonged to internal medicine disease, which raises the importance of training and experience exchange in both trauma and non-trauma air transport.

Keywords: Aviation medicine; Aeromedical evacuation; United Nations Mission in South Sudan (UNMISS); Vietnam's Level-2 Field Hospital; CASEVAC; MEDEVAC.

---

[1]ICU, Military Hospital 175, Ho Chi Minh City

[2]Anesthesia Department, Military Hospital 175, Ho Chi Minh City

[3]Military Hygiene Department, Vietnam Military Medical University

[4]Outpatient Department, Military Hospital 175, Ho Chi Minh City

[*]Corresponding author: Dinh Van Hong (dinhvanhong108@gmail.com)

Date received: 16/12/2023

Date accepted: 15/3/2024

http://doi.org/10.56535/jmpm.v49i4.596

INTRODUCTION

Aeromedical evacuation is one of the most important medical activities in the United Nations (UN) Missions to ensure timely implementation of emergency transportation for UN personnel and those involved who are injured/ill during the operations. In the UNMISS, AE is carried out according to the standard operation procedure (SOP) of the UN, in which the AMET of L2FH is directed by the Chief Medical Officer (CMO) to perform this task [1]. To the best of our knowledge, no research has been done on the issue of AE under Vietnam's peacekeeping force. This study aims: *To supplement the theory of Military Medical Management and Aviation Medicine and contribute to improving the quality and operational efficiency of Vietnam's L2FH.*

MATERIALS AND METHODS

Vietnam's L2FH has replaced the UK L2FH since October 2018, performing medical examination and treatment tasks for about 2000 UN soldiers and staff in Bentiu and surrounding areas. This is a descriptive, retrospective study of all AE activities conducted by the AMET of Vietnam's L2FH from October 2018 to March 2022. The data was retrospectively collected from the electronic and handwritten records stored in the deployed L2FH headquarters and used for research purposes only.

** Features of AE in the UNMISS:*

AE at the UNMISS includes two forms: CASEVAC: Evacuation of the casualty/casualties from the site of injury/illness to the closest medical facility and MEDEVAC: Evacuation of ill or injured patients between two medical facilities, either within or outside of the mission area [2, 3].

The term "emergency MEDEVAC" means for the evacuation of seriously ill or injured patients who need to be evacuated to the next level of care as soon as possible, using the most suitable aircraft available near the patients, a diverted aircraft, a specially activated UN flight or commercial air ambulance for that specific reason. On the other hand, "non-emergency MEDEVAC" means a situation in which patients are not responding to treatment at the originating medical facility or the treatment required is not available at the originating medical facility; therefore, they will be transferred to the next available schedule or diverted flight.

** AMET:*

According to UN mandates, every level 2/3 field hospital should have an AMET module that will always be available for the evacuation of casualties/ patients [4]. Vietnam's L2FH has an AMET with 6 members trained in UN air evacuation standards. There are two subteams; each team has 3 members, including one doctor and two nurses.

** Transportation assets:*

Types of aircraft at Bentiu: Rotary aircraft, including 2 Mi-8 helicopters, with a helipad about 500m from Vietnam's L2FH, and Fixed-wing aircraft, including Dash 8, An-26, ATR-72, and L-410. These fixed-wing aircraft used for UN regular flights are available every week from Monday to Friday.

** AME procedure:*

The AME procedure that we are implementing was issued by the UN [3]. The AME process is initiated by UN staff at the point of injury/illness (POI) or by Senior Medical Officers (SMO) in medical facilities. All CAS/MEDEVACs are subject to approval from the CMO, which is then conducted through the MEDEVAC Group (including relevant agencies such as the Air Operations Duty Office, Joint Operations Center, and Movement Control Passenger Booking Unit). For a flight to L3/4FH (outside South Sudan), a permit from the Medical Services Department (MSD) at the UN headquarters is required. When an emergency transfer is required, the Director of Mission Support will authorize medical evacuation pending authorization from Health Services.

** Statistical analysis:*

Descriptive statistics were provided. Continuous data are reported as mean ± standard deviation and categorical variables as numbers (proportion).

RESULTS

After three rotations deployed from October 2018 to March 2022, there were 31 AE cases performed by the AMET of Vietnam's L2FH. There was 1 case of CASEVAC (3.2%), 14 cases of emergency MEDEVAC (45.2%), and 16 cases of non-emergency MEDEVAC (51.6%). The mean age was 38.8 ± 8.4 years old, and the majority was male (83.9%). Patients were mainly from TCCs stationed in Sector Unity (Bentiu) (67.7%). Most of them were from Mongolia (n = 11), followed by Ghana (n = 4), Pakistan (n = 3), and India (n = 3). Half of the non-TCCs cases were UN staff with the nationality of South Sudan (5/10).

Table 1. Characteristics by types of flight.

Characteristics	Routine flight (n = 16)	Special flight (n = 15)	All types (n = 31)
Male, n (%)	14 (87.5)	12 (80)	26 (83.9)
Age, mean ± SD	37.9 ± 7.1	39.7 ± 9.8	38.8 ± 8.4
TCCs, n (%)	11 (68.8)	10 (66.7)	21 (67.7)
Illness, n (%)	14 (87.5)	15 (100)	29 (93.5)
Internal medicine, n (%)	13 (81.3)	10 (66.7)	23 (74.2)
Infectious disease, n (%)	3 (18.8)	3 (20)	6 (19.4)
Medical officer escort, n (%)	14 (87.5)	15 (100)	29 (93.5)
Night flight, n (%)	0 (0)	2 (13.3)	2 (6.5)
Intervention, n (%)			
Oxygenation	4 (25)	10 (66.7)	14 (45.2)
Vasopressor usage	0 (0)	3 (20)	3 (9.7)
Blood transfusion	1 (6.3)	0 (0)	1 (3.2)

(SD: Standard deviation)

All cases belonged to the non-battle injury group, the majority was due to illness (93.5%). There were only 2 cases (6.5%) of eye and limb injuries due to occupational accidents. At the time of transportation, the proportion of patients with internal medicine diagnoses was 74.2%, including respiratory (n = 6), cardiovascular (n = 6), neurology (n = 5), renal medicine (n = 5), and psychiatry (n = 1). The main surgical diagnosis was gastrointestinal disease (n = 6), in which there were 2 cases of severe intestine necrosis after appendicectomy at another medical facility. There were 6 cases of the infectious group who were under AE, of which 2 patients were diagnosed with suspected severe COVID-19, and 1 patient was suspected of bacterial meningitis. Most patients needed medical officer escorts (29/31 cases).

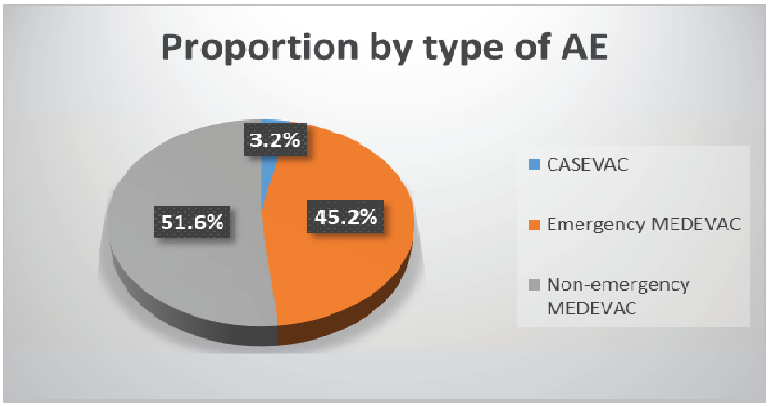


Figure 1. Proportion by type of AE.

Among 30 MEDEVACs, 25 patients were treated at Vietnam's L2FH with a median duration of 1 (1 - 3) day. The mean time from AE approval to patient referral for emergency MEDEVAC was 1.8 ± 0.4 hours, and for non-emergency MEDEVAC was 12.5 ± 7.9 hours. The type of aircraft commonly used in CASEVAC and emergency MEDEVAC was the Mi-8 helicopter (n = 12). The types of fixed-wing aircraft used include Dash 8 (n = 11), AN-26 (n = 5), ATR-72 (n = 2), and L-410 (n = 1). The mean duration of the flight (from Bentiu to Juba) by helicopter was 2.7 ± 0.2 hours, and by fixed wing was 1.7 ± 0.2 hours.

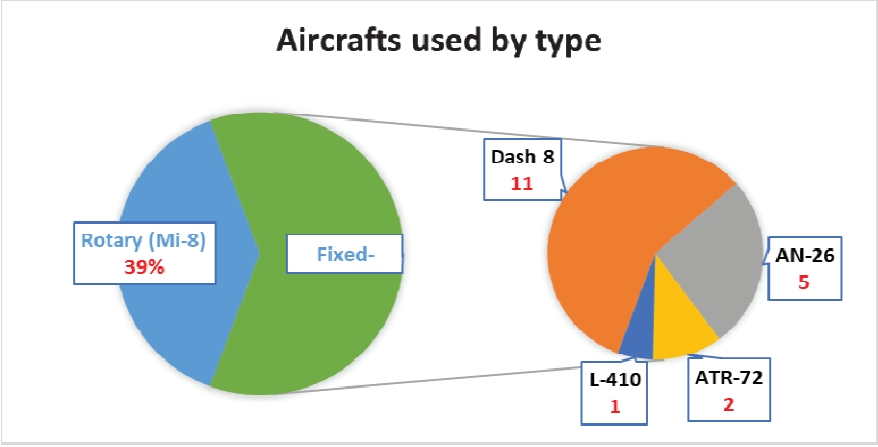


Figure 2. Aircrafts used by type.

During patient transport, the main intervention was oxygenation (n = 14), followed by vasopressor usage (n = 3), and blood transfusion (n = 1). More than half of the patients in this group (55.6%) were referred to L3/4FH outside South Sudan for further diagnosis and treatment. All cases were successfully transferred without any complications during AE.

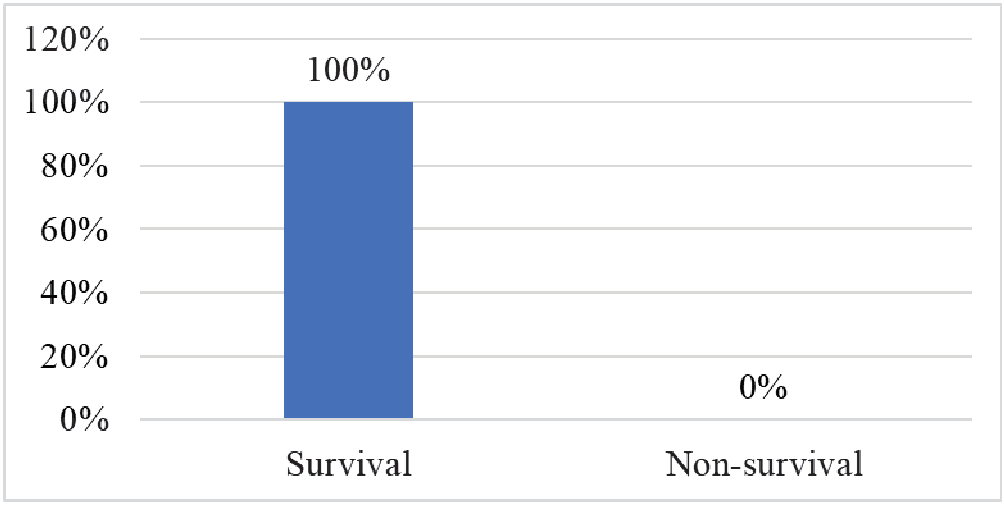


Figure 3. Aeromedical evacuation outcome.

DISCUSSION

AE is one of the essential parts of the UN health care system. This task requires the correct coordination of many agencies and units in the mission, the decision of the CMO, and the effective teamwork of the AMET. Our study showed that the mean age of patients was 38.8 years old, similar to AE research of UK L2FH (36 years old) from June 2017 to October 2018 [5]. Male patients also accounted for the majority due to the gender structure of UN staff being predominantly male. Most of the patients under AE were not due to combat injury, in which internal medicine diseases were predominated. This can be explained by the fact that the war situation in South Sudan has gradually stabilized. The majority of patients with AE required medical officer escorts (93.5%), indicating a very high need for the presence of a doctor as well as a high demand for emergency expertise, and understanding of physiological and pathological changes in AE. This shows the need for intensive training for doctors, nurses, and paramedics participating in AE, especially focusing on internal medicine illnesses and non-battlefield trauma.

In this study, 6 infectious disease patients received AE, while the AMET of UK L2FH did not transport any infectious patients. During the deployment of Vietnam's L2FH, the COVID-19 pandemic was outbreaking globally, meanwhile, South Sudan, with its multinational environment, was also a hot spot in terms of the number of COVID-19 patients. We

applied the SOPs for transporting AE COVID-19 patients according to the UN protocol [6], ensuring good disease prevention as well as patient safety during transportation. However, transporting COVID-19 patients is complicated. In the study by Jean Turc et al., patients with mild and moderate COVID-19 ARDS were transported with an Airbus A330 Multi-Role Tanker Transport plane equipped with the MoRPHEE (Module de Réanimation pour Patient à Haute Elongation d'Evacuation) system, named a "flying ICU" facility that also complies with international aviation security regulations [7]. Madeleine Beaussac et al. also showed that transporting COVID-19 patients requires more oxygen consumption than expected [8]. This demonstrates the need to equip both the escorts and the aircrew with specialized knowledge and medical supplies related to the transport of infectious patients, as well as the exchange of knowledge and experience between the AMETs of the L2/3FH, which is crucial in the situation of limited resources at the UN missions.

Most patients belonged to TTCs, which is consistent with the large number of TTC soldiers compared to individual officers. This result is similar to the UK L2FH study and poses two issues: (1) The selection and health screening of TTC units according to UN standards, and (2) the AE training in the multinational environment, especially a good understanding of countries working in the mission. Some of the AE patients in our study cannot communicate in English, leading to many communication difficulties during AE. We have provided several solutions such as requesting the unit to arrange an interpreter and preparing some question forms suitable for the patient's medical condition in bilingualism (the patient's native language and English). In addition, clinical observations during flights are also very necessary (status, concentration, skin color, and mucous membranes).

In our study, the mean time from AE approval to patient referral for routine AE is much longer than that for urgent AE (1.8 ± 0.4 hours compared to 12.5 ± 7.9 hours). This is because there is only one routine flight from Bentiu to Juba every weekday, so most patients will be hospitalized overnight and transferred the next day. We cooperated well with UN agencies and successfully performed two-night flights by helicopter, ensuring the safety and timely transport of patients to higher medical facilities. In addition, there was 1 case where the routine MEDEVAC had to be delayed for more than 24 hours because of bad weather and

had to use a helicopter to transport from Bentiu to Juba. In addition to the effects of air transportation such as vibration, noise, pressure change, etc. [9], AE at the UNMISS suffers from many other disadvantages. The infrastructure is still underdeveloped. In the rainy season, the roads and the airport are muddy and flooded, AMET may not be able to reach the patients or take them to the airport, or the plane may be unable to land. Language barriers with patients who do not speak English sometimes cause medical escorts to have difficulty taking care of them. The "no flights on Saturdays" policy of UNMISS is also a consideration for medical staff when planning MEDEVAC/CASEVAC. In addition, bad weather can also delay AE, so primary medical facilities must always be ready for this situation. This poses a lesson for primary healthcare facilities in terms of AE training during night flights, as well as being prepared for a situation when a patient needs to retain treatment longer than expected due to a flight delay.

CONCLUSION

AE is a vital medical activity in UN health care policy. This paper raises the importance of AE training on both battle and non-battle illness, especially on infectious diseases. We hope that future AE training will focus more on the characteristics and structure of each UN mission in the current multinational working environment.

Acknowledgments: With special thanks for the hard work of Vietnam's L2FH AMET and UN agencies during the operation. All authors contributed to the preparation of the paper, and there are no competing interests in this paper.

REFERENCES

1. United Nations. United Nations mission in South Sudan standard operating procedure for casualty evacuation and medical evacuation. 2015.

2. United Nations. Casualty evacuation in the field. Department of Operational Support. 2020.

3. United Nations. United Nations mission in South Sudan standard operating procedure for medical evacuation of United Nations personnel. *New York: Aviation Manual*. 2016.

4. United Nations. Medical support manual for United Nations field missions 3rd edition. Department of Peacekeeping Operations. 2015.

5. Eveson LJ, Nevin W, Cordingley N, Almond M. Aeromedical evacuation: Experiences from the UK military level 2 hospital in Bentiu, South Sudan, during Op TRENTON. *BMJ Military*

Health. 2020:bmjmilitary-2020-001448. DOI:10.1136/bmjmilitary-2020-001448.

6. Organization WH. COVID-19 medevac protocols for all WHO, UN and frontline workers/NGOs covered by the COVID-19 medevac arrangement. 2020.

7. Turc J, Dupré H-L, Beaussac M, et al. Collective aeromedical transport of COVID-19 critically ill patients in Europe: A retrospective study. *Anaesthesia Critical Care & Pain Medicine*. 11/01 2020; 40:100786. DOI:10.1016/j.accpm.2020.11.004.

8. Beaussac M, Boutonnet M, Koch L, et al. Oxygen management during collective aeromedical evacuation of 36 COVID-19 patients with ARDS. *Military Medicine*. 11/19 2020; DOI:10.1093/milmed/usaa512.

9. Green N, Gaydos S. Handbook of aviation and space medicine 2019.

EVALUATION OF FACTORS AFFECTING PHARMACISTS' BEHAVIOR REGARDING THE SALE OF VITAMINS AT RETAIL PHARMACIES IN VINH LONG PROVINCE FROM 2022 - 2023

Nguyen Phuc Hung[1], Nguyen Phu Vinh[2], Le My Phung[3], Pham Thanh Suol[1]
Tang Nghiep Minh[4], Pham Thanh Toan[1], Le Thi Thanh Thao[5]*

Abstract

Objectives: To survey the current situation and assess factors affecting pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long province from 2022 - 2023 based on the theory of planned behavior (TPB) research model. ***Methods:*** A cross-sectional descriptive study was conducted on 424 pharmacists at retail pharmacies in Vinh Long province using a set of printed or online questionnaires based on the Google Forms platform. ***Results:*** Among 424 pharmacists participating in the study, females accounted for 72.9%, compared to 27.1% of males; there were 47.9% with intermediate pharmaceutical education, and 45.3% were pharmacy owners. Multivariate analysis indicated that both "Attitude" and "Subjective norm" significantly influenced pharmacists' behavior in selling dietary supplements at retail pharmacies in Vinh Long province from 2022 - 2023. ***Conclusion:*** "Attitude" is a factor that strongly affects pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long province from 2022 - 2023.

Keywords: Vitamin; Behavior; Retail pharmacy.

INTRODUCTION

Nowadays, pharmacists at drugstores strategically play an important role in the delivery of public health services [1]. This strategic position is reflected through the introduction, consultation,

[1]Can Tho University of Medicine and Pharmacy
[2]Ho Chi Minh City University of Medicine and Pharmacy
[3]Vinh Long Department of Health
[4]Can Tho University
[5]Ha Dong Medical College
[*]Corresponding author: Le Thi Thanh Thao (lethanhthao2604@gmail.com)
Date received: 21/12/2023
Date accepted: 10/3/2024
http://doi.org/10.56535/jmpm.v49i4.609

and guidance on the selection and use of pharmaceutical products, dietary supplements, vitamins, etc. in a safe, reasonable, and effective way. Vitamins are very important in maintaining the human health of the human body. However, the human body does not have the ability to synthesize vitamins, so vitamin supplementation is usually done through nutrition and vitamin supplements. As a result, the demand for vitamins has increased dramatically in recent years. Today, the vitamin supplement market is one of the fastest expanding. Worldwide, the vitamin supplement market grew at a rate of 6.8% between 2013 and 2020, from $37.4 billion (2013) to $59.6 billion (2020) [2]. Besides, inappropriate use of vitamins risks potential adverse effects such as neurological disorders, gastrointestinal symptoms, hepatotoxicity, fetal malformations, and drug interactions, which create legal liabilities for healthcare professionals. According to research by Hadi et al. in 2016, people tend to seek nutrition and vitamin advice from pharmacists [3]. Some studies have shown errors in the communication process between pharmacists and people in advising on the selection of pharmaceutical products [1, 4]. Currently, there are very few studies applying the TPB to evaluate factors affecting the knowledge, attitudes, and behaviors of pharmacists at retail pharmacies in Vietnam in general and Vinh Long province in particular. Therefore, the study was carried out with two objectives: *To survey the current condition of vitamin sales by pharmacists at retail pharmacies and assess the factors influencing pharmacists' behavior in selling vitamins at retail pharmacies by using the TPB study model in Vinh Long province from 2022 - 2023.*

MATERIALS AND METHODS

1. Subjects

424 pharmacists at retail pharmacies in Vinh Long province from 2022 - 2023.

* *Inclusion criteria:* Pharmacists agreed to participate in the study.

* *Exclusion criteria:* Pharmacists did not answer the survey in full.

2. Methods

* *Research design:* A cross-sectional descriptive study using data collected from printed or online questionnaires on the Google Forms platform through interviews with pharmacists from June 2022 to February 2023.

* *Sample size:* According to Serena Carpenter, the minimum observation/ measurement ratio is 5:1, meaning that for every measurement variable, there should be a minimum of 5 observed samples. Given that the research scale, after adjustment, consists of 25

measurements, the minimum sample size is, therefore, 125. The number of samples we obtained in this study is 424, which is in line with the sample size requirements [5].

* *Sampling method:* Convenient random sampling using an interview approach with research subjects through a set of printed or Google Forms-based questionnaires.

* *Research content:*

- Characteristics of the research sample: General information about pharmacists, including: Gender, professional qualifications, and job position.

- Evaluating factors affecting pharmacists' behavior regarding the sale of vitamins based on the TPB research model.

- Constructing and evaluating the reliability of measurement scales using Cronbach's Alpha coefficient:

An initial survey of over 100 pharmacists was conducted at various retail pharmacies. The study excluded invalid questionnaires that did not follow a specific order of responses or did not sufficiently answer research questions. A reliability and validity assessment was conducted using Cronbach's alpha coefficient under the conditions that (1) variables with inter-variable correlation coefficients less than 0.3 were excluded, and (2) Cronbach's alpha values of 0.6 or higher were sufficient for the study [6].

* *Research models:*

The study used a model of 4 variables based on Ajzen's TPB (1991) [7] to predict the actual behavioral determinants with high accuracy. The survey questions include Attitude (A); Subjective norm (SN); Perceived behavior control (PBC); and Intention (I). The scale used to evaluate these items is the Likert-5 scale: 1 = "Strongly disagree"; 2 = "Disagree"; 3 = "Partially agree"; 4 = "Agree"; 5 = "Strongly agree".

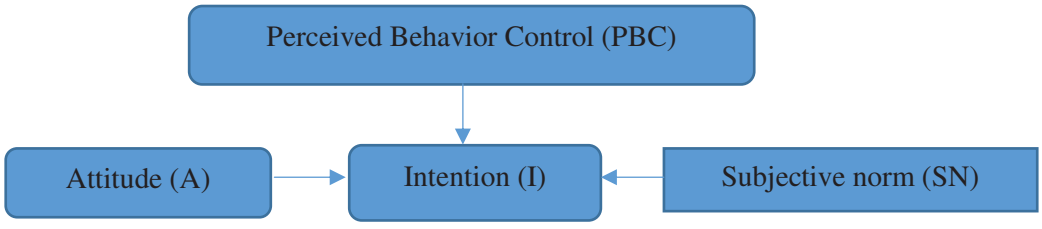


Figure 1. Research model.

Then, the study conducted correlation and regression analysis to build a multivariate regression equation in the form: $I = \beta_0 + \beta_1*A + \beta_2*SN + \beta_3*PBC$.

Coefficients β are Partial regression coefficients. The suitability of the model was tested using F value (ANOVA) with Sig reliability < ± 0.05.

** Data processing:* All research data was synthesized and analyzed using SPSS software version 26.0.

3. Ethics

The study was permitted by the Vinh Long Department of Health. The survey process was based on voluntary participation, ensuring participant anonymity. The authors declare there are no competing interests related to this paper.

RESULTS

1. Characteristics of the research sample

Table 1. Characteristics of pharmacists and retail pharmacies.

Characteristics		Frequency (n = 424)	Percentage (%)
Gender	Male	115	27.1
	Female	309	72.9
Qualifications in pharmacy	Post-graduate	5	1.2
	Bachelor	106	25
	College	96	22.6
	Intermediate	203	47.9
	Others	14	3.3
Job positions	Pharmacy owner	192	45.3
	In charge of professional affairs	93	21.9
	Staff	137	32.3
	Others	22	0.5

Female pharmacists accounted for 72.9%, compared to 27.1% of men; there were 47.9% of pharmacists who have intermediate level of pharmacy; 45.3% were pharmacy owners.

2. Evaluation of factors affecting pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long Province from 2022 - 2023 based on the TPB research model

** Characteristics of the reliability of the scale through Cronbach's Alpha coefficient:*

Table 2. Characteristics of the reliability of the scale through Cronbach's Alpha coefficient.

Survey variables	Variable - total correlation coefficient	Shift coefficient when the type of variable	Cronbach's alpha = 0.813
Attitude			
A1. Currently, most vitamins are being sold by pharmacists to support the treatment of patients in the community	0.727	0.874	0.893
A2. Selling vitamins helps increase sales and profits	0.730	0.873	
A3. Selling vitamins helps save money, time, and effort for patients	0.666	0.880	
A4. The supply of vitamins helps improve patients' current disease and symptoms	0.656	0.881	
A5. Selling vitamins helps increase the level of trust of customers	0.612	0.885	
A6. Because many customers come to buy vitamins regularly	0.714	0.875	
A7. If the pharmacy refuses to sell vitamins, others will sell them	0.501	0.894	
A8. The seller cannot control the use of vitamins by the buyer	0.760	0.871	

Survey variables	Variable - total correlation coefficient	Shift coefficient when the type of variable	Cronbach's alpha = 0.813
Subjective norm			
SN1. Patients often have no objection to me adding vitamins to their prescriptions	0.831	0.887	
SN2. No one objects to pharmacists selling vitamins (registered as prescription drugs) over-the-counter	0.631	0.902	
SN3. Doctors also often prescribe vitamins in inpatient and outpatient prescriptions to support the treatment of some diseases and I also learn from them to sell additional vitamins to patients	0.789	0.890	
SN4. The pressure from patients who require vitamins to improve the immune system and quickly recover from diseases is the reason for selling them	0.539	0.908	
SN5. Pharmacists can freely change the vitamins according to patients' needs	0.810	0.889	0.908
SN6. Pharmacists can enhance the sale of accompanying vitamins	0.407	0.917	
SN7. I noticed that the media is increasingly advertising that vitamins (registered as functional foods) play an important role in supporting the treatment of diseases	0.714	0.896	
SN8. My friends and relatives also advised me to choose vitamins registered as functional foods for sale, limit vitamins registered as prescription drugs	0.783	0.891	
SN9. I realize that pharmacies selling vitamins (registered as prescription drugs or supplements) are very popular today, so it is very normal for me to sell vitamins	0.692	0.898	

Survey variables	Variable - total correlation coefficient	Shift coefficient when the type of variable	Cronbach's alpha = 0.813
Perceived behavioral control			
PBC1. Drug sellers are people with very important positions (skills, knowledge) who provide consultancy and advice on the appropriate use of vitamins to support the treatment of patients	0.604	0.863	0.875
PBC2. I have enough experience to choose vitamins (registered as functional foods) for customers, ensuring safety and effectiveness	0.724	0.852	
PBC3. I will sell vitamins (registered as a prescription drug) if the patient doesn't want to see a doctor	0.459	0.875	
PBC4. The control of the sale of vitamins is loose, so selling them is relatively easy	0.682	0.856	
PBC5. The penalty for selling vitamins (registered as prescription drugs) without a prescription is still lenient, so it is easy to accept	0.424	0.878	
PBC6. The abuse of selling vitamins (registered as prescription drugs) should be more strictly controlled	0.683	0.856	
PBC7. Patients often ask to take a variety of vitamins, so promoting the sale of additional vitamins is inevitable	0.608	0.863	
PBC8. When taking vitamins, patients will have a quick treatment effect due to strengthening the body's immune system	0.725	0.852	
PBC9. Pharmacists should instruct patients to supplement vitamins from food daily to support the treatment of diseases	0.631	0.861	

Survey variables	Variable - total correlation coefficient	Shift coefficient when the type of variable	Cronbach's alpha = 0.813
Intention			
I1. I will sell vitamins to buyers if they are in the healthcare industry and know how to use them properly	0.827	0.853	0.906
I2. I will sell vitamins (registered as a prescription drug) without a prescription at times when I am sure there is no inspection	0.820	0.859	
I3. I will sell vitamins (registered as a prescription drug) to patients without a prescription even if there is a surveillance camera, management	0.791	0.883	

After checking the reliability level by Cronbach's Alpha, there were 4 disqualified variables (A7, SN6, PBC3, PBC5), the remaining 25 observed variables with variable-total correlation coefficient > 0.3 and Cronbach's Alpha reliability coefficients > 0.6 meeting the requirements.

** Multivariate regression analysis of factors affecting vitamin selling behavior:*

Table 3. Multivariate regression analysis of factors affecting vitamin selling behavior of pharmacists.

Variable	Coefficients					
	Non-standardized coefficients		Standardized coefficients	t Sig. combined statistic	Sig. combined statistic	Durbin-Watson
	Beta non-standardized coefficients	Standard Deviation	Beta standardized coefficients			
Constant	1.307	0.253		5.171	0.000	1.362
A	0.324	0.067	0.248	4.812	0.000	
SN	0.677	0.158	0.465	4.290	0.000	
PBC	-0.403	0.134	-0.322	-3.005	0.003	

The results of regression analysis with no variables recorded with variance magnification factor (VIF) > 2; PBC group needs to be eliminated due to poor influence level not reaching the required significance level (p > 0.05), For the remaining 3 component groups, multivariate regression model has not standardized prediction I, Intention is determined: "I = 1.307+ 0.324xA + 0.677xSN + e".

After normalization, the model is collapsed: "I = 0.248xA + 0.465xSN + e".

DISCUSSION

1. Characteristics of the research sample

According to research findings, 424 pharmacists from 2022 - 2023 fulfilled the requirements for the study and were analyzed, in which female pharmacists (72.9%) accounted for a higher proportion than males (27.1%); this is equivalent to the studies of PN Hung et al. (2022) [8]. This can be explained by the fact that retailing pharmacists require meticulousness, carefulness, and patience, so women often meet these requirements better than men. In terms of professional qualifications, many pharmacists are intermediate (47.9%). This result can also be explained by the fact that, according to the Law on Pharmacy of Viet Nam No. 105/2016/QH13, intermediate pharmacists are allowed to establish pharmacies in districts and communes of suburban and suburban districts of provinces and provincial cities. In terms of job position, pharmacists who are pharmacy owners accounted for the highest proportion (45.3%), this result is equivalent to the study of PN Hung et al. (2023) [8], this can explain why there are many private pharmacies in Vietnam.

2. Factors affecting pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long Province from 2022 - 2023 based on the TPB research model

** Reliability of the scale through Cronbach's Alpha coefficient:*

The study has developed a scale of attitudes and factors related to pharmacists' behavior regarding the sale of vitamins based on Ajzen's TPB (1991) [7] and related studies published [2, 8, 9, 10]. The test results were highly reliable with Cronbach's Alpha values of Attitude (α = 0.893); Subjective norm (α = 0.908); Cognitive behavior control (α = 0.875); Intent (α = 0.906), respectively. Compared with previous studies on pharmacists' behavior regarding the sale of vitamins, the study has further analyzed the subjective standard factor; Behavioral control perception; and Intent compared to the study of YK

Emiru et al in Ethiopia (2019) [9] and SA Ghosn et al. in Saudi Arabia (2020) [2]. The construction scale evaluates many aspects related to pharmacists' intention to sell vitamins with relatively high reliability compared to previous studies; along with the use of a 5-level Likert scale, it is a practical, accessible, and time-saving data collection method. Hence, it helps retail pharmacies have objective information in making appropriate and effective strategies to improve public health. The sample size of the study is larger than some previous studies, with a diversity of professional qualifications and working positions at retail pharmacies.

** On multivariate regression analysis of factors affecting pharmacists' behavior regarding the sale of vitamins:*

Research conducted an analysis of pharmacists' behavior regarding the sale of vitamins through regression models, revealing that "attitude" strongly influences pharmacists' behavior regarding the sale of vitamins. This is a crucial point that strategic planners need to consider in enhancing education to elevate the responsibility, ethics, and professionalism of pharmacists in community healthcare. Nowadays, the demand for the use of supplements such as vitamins in healthcare is growing, hence the attitude of pharmacists towards advising and guiding the use of healthcare products plays a significant role in optimizing the treatment outcomes for various illnesses and improving the quality of life for the public. In addition, people tend to seek advice and guidance from pharmacists at retail pharmacies when looking for vitamin supplements, so pharmacists need to have a positive attitude to provide comprehensive and objective information in choosing nutritional products and vitamins for the public. In the study conducted by MS El Hajj [4] and AM Alajmi [1], it was found that the attitude towards advising and guiding healthcare products is crucial in efficiently distributing healthcare products within the community. In this study, participating pharmacists demonstrated a positive attitude toward vitamin supplementation and nutritional substances. Additionally, community pharmacists tend to actively sell healthcare products rather than dispensing them based on prescriptions from doctors, which is a drawback in the current management of retail pharmacies. Therefore, healthcare managers need to establish and improve the legal system for advising and guiding the use of vitamins; retail pharmacies need to collaborate with relevant authorities to develop legal regulations, standards, norms, and related management regulations to protect the health of the community.

CONCLUSION

The study was conducted to assess the factors affecting pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long province from 2022 - 2023 and has basically achieved the set goals. The study also noted that "attitude" is a factor that strongly affects pharmacists' behavior regarding the sale of vitamins at retail pharmacies in Vinh Long province from 2022 - 2023. The study recommends expanding the scope and size of research samples in subsequent phases on similar topics to improve accuracy and reliability.

Acknowledgments: The authors would like to thank all regulatory agencies of retail pharmacies in Vinh Long province for allowing us to collect data and for the support of Vinh Long provincial retail pharmacies in implementing this study.

REFERENCES

1. AM Alajmi, AA Alamoudi, AA Halwani, TA Almangour, NH Almozain, Aal Jedai, et al. Antimicrobial resistance awareness, antibiotics prescription errors and dispensing patterns by community pharmacists in Saudi Arabia. *Journal of Infection and Public Health*. 2023; 16:34-41. https://doi.org/10.1016/j.jiph.2022.11.026.

2. SA Ghosn, B Addison, and MD Ali. Community pharmacist's knowledge, attitude, and practices towards vitamin supplements in Al-Khobar Region, Saudi Arabia: A descriptive cross-sectional study. *J Pharm Bioallied Sci*. 2019; 11:333-340. https://doi.org/10.4103/jpbs.JPBS_99_19.

3. MA Hadi, NA Karami, AS Al-Muwalid, A Al-Otabi, E Al-Subahi, A Bamomen, et al. Community pharmacists' knowledge, attitude, and practices towards dispensing antibiotics without prescription (dawp): A cross-sectional survey in Makkah Province. *Saudi Arabia International Journal of Infectious Diseases*. 2016; 47:95-100. https://doi.org/10.1016/j.ijid.2016.06.003.

4. MS El Hajj, R Mekkawi, R Elkaffash, R Saleh, A El Awaisi, and K Wilbur. Public attitudes towards community pharmacy in Arabic Speaking Middle Eastern Countries: A systematic review. *Research in Social and Administrative Pharmacy*. 2021; 17:1373-1395. https://doi.org/10.1016/j.sapharm.2020.11.013.

5. S Carpenter. Ten steps in scale development and reporting: A guide for researchers. *Communication Methods and Measures*. 2018; 12:25-44. https://doi.org/10.1080/19312458.2017.1396583.

6. O Mansour and R Al-Kayali. Community pharmacists' role in controlling bacterial antibiotic resistance in Aleppo. *Syria Iranian Journal of Pharmaceutical Research: IJPR*. 2017; 16:1612-1620. https://doi.org/10.22037/ijpr.2017.2135.

7. I Ajzen. The theory of planned behavior, organizational behavior and human decision processes. 1991; 50:179-211. https://doi.org/10.1016/0749-5978(91) 90020-T.

8. NP Hung, HL Phu, VTM Huong, TN Phuong, VL Tuong, HN Tram et al. Evaluating attitudes, behaviors, and relevant factors in dispensing antibiotics without prescription by pharmacies: A cross-sectional study in Vietnam, Annali di Igiene. *Medicina Preventiva e di Comunità*. 2023; 35:596-601. https://doi.org/10.7416/ai.2023.2562.

9. YK Emiru. Community pharmacists' knowledge, attitude and professional practice behaviors towards dietary supplements: Results from a multi-center study in Ethiopia. *Value in Health*. 2019; 22:59-68. https://doi.org/10.2147/NDS.S222114.

10. F Lopez-Carmona, A Toro-Ruiz, M Gomez-Guzman, M Valverde-Merino, C Piquer-Martinez, and M Zarzuelo. Community pharmacy is the key to improving vitamin D levels. *Exploratory Research in Clinical and Social Pharmacy*. 2023; 9:100224. https://doi.org/10.1016/j.rcsop.2023.100224.

CORRELATION OF CLINICAL SYMPTOMS AND COMPUTER TOMOGRAPHY SCAN FINDINGS WITH HISTOPATHOLOGY IN PATIENTS WITH CHRONIC RHINOSINUSITIS

Do Lan Huong[1], Nghiem Duc Thuan[1]*
Nguyen Thi Huyen[1], Quan Thanh Nam[1]

Abstract

Objectives: To determine the correlation between clinical symptoms, computer tomography scan (CT-scan), and histopathologic findings of chronic rhinosinusitis (CRS). ***Methods:*** A prospective, case-by-case study on 33 patients with CRS who were diagnosed and treated by functional endoscopic sinus surgery at the Department of Otolaryngology, Military Hospital 103 from January 2022 to August 2022. ***Results:*** There was an inverse correlation between sex and the number of Eosinophil cells/HPF cells, with $p < 0.05$; a moderate correlation between the SNOT-20 score and HPF cells ($r = 0.4$) and the degree of inflammation ($r = 0.39$), with $p < 0.05$; a moderate correlation between sneezing symptoms and smell disorders with HPF cells, $r = 0.33$ and $r = 0.39$ ($p < 0.05$); a low or moderate correlation between other functional symptoms and histopathological indicators ($p < 0.05$); a moderate correlation between the Lund-Kennedy score and the inflammation of the mucosa with $r = 0.47$, $p < 0.05$; a correlation between the degree of nasal polyps and histological indicators, but not statistically significant $p > 0.05$; a correlation between the average level of Lund-Mackay score and the degree of inflammation ($r = 0.35$), $p < 0.05$. Lund-Mackay score is positively correlated with HPF cells and negatively correlated with epithelial layer thickness, but not statistically significant $p < 0.05$. ***Conclusion:*** Mucosal eosinophilia moderately correlates with signs, but there was no correlation with the Lund-Kennedy score or Lund-Mackay score. Levels of inflammation are moderately correlated with objective disease severity as clinical symptoms, Lund-Kennedy score, and Lund-Mackay score.

Keywords: Chronic rhinosinusitis; Histopathologic; Eosinophil cells.

[1]Military Hospital 103, Vietnam Medical Military University
[*]Corresponding author: Do Lan Huong (huong.89tmh@gmail.com)
Date received: 25/12/2023
Date accepted: 12/3/2024
http://doi.org/10.56535/jmpm.v49i4.626

INTRODUCTION

Chronic rhinosinusitis is one of the most common diseases in otolaryngology. The primary pathogenesis of CRS is the obstruction of the osteo-metal complex (OMC), which is clinically manifested by the main symptoms of nasal congestion, rhinorrhoea, facial pain, sneezing, nasal itching, and loss of smell. The diagnosis of CRS is based on clinical symptoms, endoscopic images, and CT-scan images [1].

Based on the presence of nasal polyps, clinicians classify CRS into two types, including CRS without nasal polyps and CRS with nasal polyps [2]. This classification is mainly based on clinical symptoms rather than histopathology. On histopathology, based on the eosinophil count, some clinicians classify: Eosinophilic CRS (ECRS) and non-eosinophilic CRS (non-ECRS) [3]. Many studies show that ECRS is associated with the severity of symptoms and accomplished asthma, allergies, etc [4, 5]. Thus, there is a relationship between clinical symptoms and histopathology of CRS [6]. There are some studies on this correlation in Vietnam, but there is no comprehensive study on the correlation between clinical symptoms, CT-scan, and histopathologic findings. Thus, we perform this research: *To determine the correlation between clinical symptoms, CT-scan, and histopathologic findings of CRS.*

MATERIALS AND METHODS

1. Subjects

33 patients with CRS who were diagnosed and treated by functional endoscopic sinus surgery at the Department of Otolaryngology, Military Hospital 103 from January 2022 to August 2022.

* *Inclusion criteria:* Patients who were diagnosed with CRS according to the criteria of EPOS 2020; patients who underwent endoscopic sinus surgery and took the sample of mucus membrane sinus at OMC for biopsy during surgery; histopathological examination of the nasal mucosa at the Department of Pathology, Military Hospital 103; full of medical records and research records; patients consented to participate in the study.

* *Exclusion criteria:* Patients who were diagnosed with CRS according to EPOS 2020, but no indication for surgery; using other methods of surgery.

2. Methods

* *Research design:* A prospective, case-by-case study.

* *Study sample size:*

- Sample size: Convenient sample selection.

- Sample selection: Patients aged ≥ 18 years who were diagnosed with CRS and underwent endoscopic sinus surgery at the Department of Otolaryngology, Military Hospital 103.

* *Variables, research targets:*

- Age, sex

- Histopathology of CRS follow Soler's: Eosinophil cells (HPF - A high-power field), epithelial layer thickness, degree of inflammation.

- Signs: SNOT-20, stuff nose, sneezing, sinus pain, eye symptoms, smell disorder.

- Symptoms: Level of polyp, Lund-Kennedy score.

- CT-scan image: Lund-Markay score.

* *Statistical analysis:* Data were collected, entered by Microsoft Excel software and processed according to medical statistical algorithms using SPSS 23.0 software. The correlation shows the relationship between two variables. To determine the strength or weakness of this relationship, the Pearon correlation coefficient (symbol: r) is used.

3. Ethics

This study was approved by the Ethics Committee of Military Hospital 103, Vietnam Medical Military University (Number 192/HDDD, date 15/6/2022).

RESULTS

1. The correlation between clinical symptoms and histopathology

Table 1. The correlation between characteristics and Eosinophil cell count (/HPF).

	Age		**Sex**		**History of allergies**	
Eosinophil	r	p	r	p	r	p
	-0.12	> 0.05	-0.38	< 0.05	0.19	0.29

There was an inverse correlation between sex and the number of Eosinophil cells, with $p < 0.05$. There was no correlation between age and allergy history with Eosinophil cell count.

Table 2. The correlation between clinical signs and Eosinophil cell count (/HPF), epithelial layer thickness and degree of inflammation (n = 33).

Symtoms	Eosinophil cells		Epithelial layer thickness		Degree of inflammation	
	r	p	r	p	r	p
SNOT-20	0.40	< 0.05	-0.39	> 0.05	0.39	< 0.05
Stuffy nose	-0.42	> 0.05	0.05	> 0.05	-0.42	> 0.05
Sneezing	0.33	< 0.05	-0.19	> 0.05	-0.27	> 0.05
Sinus pain	-0.189	> 0.05	0.09	> 0.05	0.05	> 0.05
Eye symptoms	-0.12	> 0.05	-0.1	> 0.05	-0.21	> 0.05
Smell disorder	0.39	< 0.05	-0.2	> 0.05	0.12	> 0.05

There is a moderate correlation between SNOT-20, the number of Eosinophil/HPF cells (r = 0.4) and the degree of inflammation (r = 0.39). This correlation is statistically significant, with $p < 0.05$. Among the functional symptoms, there was a moderate correlation between sneezing symptoms and smell disorders with Eosinophil/HPF cell counts with correlation coefficients r = 0.33 and r = 0.39. This correlation is statistically significant with $p < 0.05$. There is also a low or moderate correlation between other functional symptoms and histopathological indicators, but this correlation has not been statistically significant, with $p < 0.05$.

2. The correlation between endoscopic images and histopathology

Table 3. The correlation between endoscopic image and Eosinophil cell count, epithelial thickness and degree of inflammation (n = 33).

Endoscopic images	Eosinophil		Epithelial layer thickness		Degree of inflammation	
	r	p	r	p	r	p
Level of polyp	0.26	> 0.05	-0.08	> 0.05	0.3	> 0.05
Lund-Kennedy	0.29	> 0.05	0.004	> 0.05	0.47	< 0.05

There is a moderate correlation between the Lund-Kennedy score and the inflammation of the mucosa, with r = 0.47. This correlation is statistically significant, with p < 0.05. There is a correlation between the degree of nasal polyps and histological indicators, but this correlation is not statistically significant, with p > 0.05.

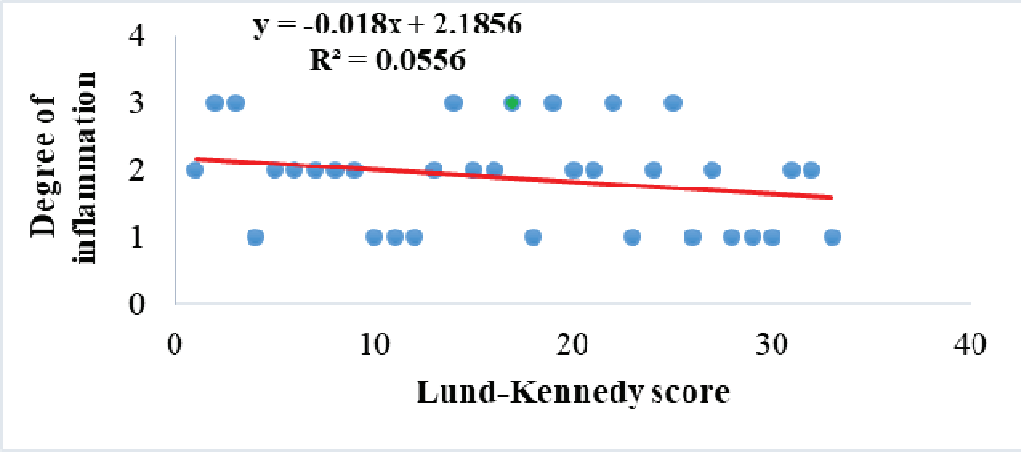


Chart 1. The correlation between the Lund-Kennedy score and the degree of inflammation.

3. The correlation between CT-scan and histopathology

Table 4. The correlation between CT-scan images with Eosinophil cell count, epithelial thickness and degree of inflammation (n = 33).

CT-scan image	Eosinophil		Epithelial layer thickness		Degree of inflammation	
	r	p	r	p	r	p
Lund-Mackay	0.24	> 0.05	-0.92	> 0.05	0.35	< 0.05

There is a correlation between the average level of Lund-Mackay score and the degree of inflammation (r = 0.35). This correlation is statistically significant with p < 0.05; Lund-Mackay score is positively correlated with the number of Eosinophil cells (/HPF) and negatively correlated with epithelial layer thickness, but this correlation is not statistically significant, with p < 0.05.

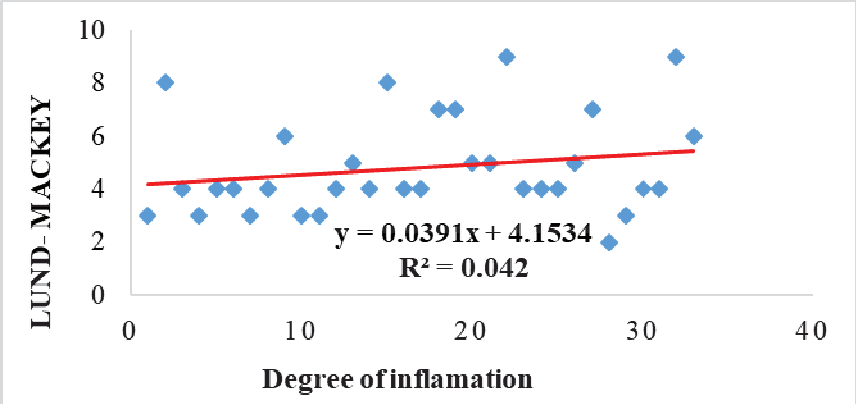


Chart 2. The correlation between the Lund-Kennedy score and the degree of inflammation.

DISCUSSION

1. The correlation between clinical symptoms and histopathology

When comparing the anthropometric characteristics with histopathological characteristics, we found an inverse correlation between sex and the number of Eosinophil cells ($p < 0.05$), but there was no correlation between age and history of allergy with Eosinophil cell counts. Furthermore, according to the study of Zachary M Soler (2009), there is no correlation between the number of Eosinophil cells, Lymphocytes, and mast cells with age, sex, history of endoscopic sinus surgery, and history of other diseases. Allergic diseases included asthma, allergic rhinitis, and aspirin allergy [6].

Many recent studies show an association between asthma and CRS. Both diseases share a similar pathogenesis, with mucosal sensitivity to irritants and eosinophils playing an essential role in this response [2, 4]. Therefore, steroid therapy is considered an effective method in treating CRS, especially in cases with nasal polyps. Steroids relieve symptoms by down-regulating the production of cytokines and lowering the number of eosinophils [4].

In our study, there was a moderate correlation between the number of Eosinophil cells with SNOT-20 score, sneezing symptoms, and smell disorder with the correlation coefficient $r = 0.4$, $r = 0.33$, and $r = 0.39$, respectively. In addition, there was a positive correlation between the SNOT-20 score and the degree of inflammation with $r = 0.39$. This study also showed no correlation between histopathological features (Eosinophil cell count, epithelial layer

thickness, and degree of inflammation) and other clinical symptoms (nasal congestion, nasal discharge, sinus pain, and eye symptoms).

2. The correlation between endoscopic images and histopathology

There is a positive correlation between the Lund- Kennedy score and the degree of inflammation on histopathology, with r = 0.47; however, there is no correlation between the nasal polyps and the Lund-Kennedy scores with the number of Eosinophil cells, epithelium thickness, and degree of inflammation.

In a study by Vo Van Khoa (2000) on the clinical and histopathological characteristics of CRS [7], the rate of headache predominates in the highly active form and the lowest in the less active form, this difference is statistically significant; the rate of stuffy nose is highest in the highly active form and the lowest in the less active form, this difference is statistically significant. However, there was no statistically significant difference between the incidence of nasal polyps at levels of inflammatory activity.

Tomislav Baudoin (2006) performed a study to predict the value of histopathology in the response of CRS by functional endoscopic sinus surgery [8]. The results of the study indicated that there was no correlation between the number of Eosinophil cells and the improvement of functional symptoms.

According to Zachary M Soler's study (2009) on the relationship between clinical symptoms and histopathology of CRS [6], there is no statistically significant correlation between the number of Eosinophil cells, the number of Neutrophil cells, Lymphocytes with demographic characteristics (age, gender) as well as allergy history of the patient; however, the author also showed that there is a correlation between the number of Eosinophil cells with the presence of nasal polyps (r = -0.367), the degree of stromal oedema (r = 0.313), and the severity on endoscopy (r = 0.376).

The results of Figen Aslan's study indicate a correlation between the Lund-Kennedy score and the number of eosinophils (r = 0.444 and p = 0.001) [9].

Thus, other studies have shown a correlation between functional symptoms and endoscopic severity with eosinophil counts. However, the results of our study are in contrast to the results of previous authors. This may be explained by the effect of previous corticosteroid administration on the migration and activation of eosinophils, which significantly affects tissue even at low blood concentrations. The number of eosinophils is a

vital indicator of classifying CRS with eosinophilia or CRS without eosinophilia. However, how tissue eosinophilia is calculated, and its upper limit can be a matter of controversy (eosinophilic count > 70 cells/HPF, > 10 cells/HPF, > 5 cells/HPF).

3. The correlation between CT-scan and histopathology

There was a positive correlation between the Lund-Mackay score and the degree of inflammation on histopathology with r = 0.35 and was not correlated with the number of Eosinophil cells (/HPF), epithelial layer thickness, stromal oedema, and heterochromia.

In the study of Zachary M Soler [6], there was a correlation between the severity of the CT-scan with the number of Eosinophil cells and the degree of stromal oedema with the correlation coefficient r = 0.414, respectively; r = 0.366. In this study, the group of patients with nasal polyps did not correlate with the severity on the CT-scan images and the number of Eosinophil cells, the group of patients with nasal polyps correlated, with r = 0.324. According to the study of Figen Aslan, there is a correlation between the Lund-Mackay score and the number of eosinophils (r = 0.353; p = 0.01) [9].

CONCLUSION

A total of 33 subjects were enrolled with histologic samples available for analysis, there were:

- An inverse correlation between sex and the number of Eosinophil cells, with $p < 0.05$. No correlation between age and allergy history with Eosinophil cell count.

- A moderate correlation between SNOT-20 score and the number of Eosinophil/HPF cells (r = 0.4) and the degree of inflammation (r = 0.39), with $p < 0.05$. Among the functional symptoms, a moderate correlation between sneezing symptoms and smell disorders with Eosinophil/HPF cell counts with correlation coefficients r = 0.33 and r = 0.39 ($p < 0.05$); a low or moderate correlation between other functional symptoms and histopathological indicators ($p < 0.05$).

- A moderate correlation between the Lund-Kennedy score and the inflammation of the mucosa with r = 0.47; $p < 0.05$. A correlation between the degree of nasal polyps and histological indicators, but not statistically significant $p > 0.05$.

- A correlation between the average level of Lund-Mackay score and the degree of inflammation (r = 0.35); $p < 0.05$; Lund-Mackay score is positively correlated with the number of Eosinophil cells (/HPF) and

negatively correlated with epithelial layer thickness, but not statistically significant, $p < 0.05$.

Acknowledgments: We would like to thank all patients participating in this study. We are grateful to all medical staff in the Department of Otorhinolaryngology and Department of Pathology, Military Hospital 103, Vietnam Medical Military University for assisting us in this study. The authors must take full responsibility for any conflicts of interest issues in the research.

REFERENCES

1. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg*. 2003; 129(3 Suppl):S1-S32.

2. Marcus S, Roland LT, DelGaudio JM, et al. The relationship between allergy and chronic rhinosinusitis. *Laryngoscope Investig Otolaryngol*. 2019; 4(1):13-17.

3. Snidvongs K, Lam M, Sacks R, et al. Structured histopathology profiling of chronic rhinosinusitis in routine practice. *Int Forum Allergy Rhinol*. 2012; 2(5):376-385.

4. Soler ZM, Sauer D, Mace J, et al. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg*. 2010; 142(1):64-71.

5. Tosun F, Arslan HH, Karslioglu Y, et al. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. *Ann Otol Rhinol Laryngol*. 2010; 119(7):455-459.

6. Soler ZM, Sauer DA, Mace J, et al. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2009; 141(4):454-461.

7. Võ Văn Khoa. Nghiên cứu đặc điểm lâm sàng, mô bệnh học trong viêm xoang mạn tính. *Luận án Tiến sĩ Y học*. Trường Đại học Y Hà Nội. 2000.

8. Baudoin T, Cupić H, Geber G, et al. Histopathologic parameters as predictors of response to endoscopic sinus surgery in nonallergic patients with chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2006; 134(5):761-766.

9. Aslan F, Altun E, Paksoy S, et al. Could eosinophilia predict clinical severity in nasal polyps?. *Multidiscip Respir Med*. 2017; 12:21.

CHANGES IN CYTOKINES LEVELS IN ASTHMA PATIENTS WITH FREQUENT EXACERBATIONS

Pham Dac The[1,2], Ta Ba Thang[2], Nguyen Huy Luc[2], Dao Ngoc Bang[2]*

Abstract

Objectives: To evaluate changes in serum levels of some cytokines in asthma patients with frequent exacerbations. ***Methods:*** A prospective, descriptive, longitudinal study on 60 asthma patients with frequent exacerbations and 60 ones with few exacerbations, treated as outpatients at the Asthma Management Department, Hai Phong International Hospital from January 2020 to May 2023. Patients underwent clinical examination, chest X-ray, respiratory function test, and assessment of inflammatory markers and serum cytokine levels at the time of the study. ***Results:*** The asthma group with frequent exacerbations had significantly higher IL-4 and IL-13 concentrations than the asthma group with few exacerbations (21.10 and 9.93 pg/mL vs. 16.48 and 3.95 pg/mL). Concentrations of IFN-α, IFN-γ, IL-17, and inflammatory cytokines (IL-12, TNF-α, IL-1β) were not different between the 2 asthma groups. In the asthma group with frequent exacerbations, most serum cytokine concentrations in male patients were insignificantly higher than in females, except for IL-12. IL-17, IFN-α, IL-4, and IL-12 concentrations in patients aged ≥ 60 years were insignificantly higher than those in the group < 60 years old. ***Conclusion:*** There are significantly higher serum levels of IL-4 and IL-13 in asthma patients with frequent exacerbations compared to those with few exacerbations.

Keywords: Frequent exacerbation asthma; Serum cytokine levels.

INTRODUCTION

Asthma is a heterogeneous disease with the impact of many risk factors and has a very complex pathogenesis. Th2, Th1, Th17, and innate immune cells have been identified to play an important role in determining the pathogenesis of airway inflammation

[1]**Hai Phong International Hospital**

[2]**Military Hospital 103, Vietnam Military Medical University**

[*]**Corresponding author: Pham Dac The (dr.dacthebmh@yahoo.com)**

Date received: 28/02/2024

Date accepted: 02/4/2024

http://doi.org/10.56535/jmpm.v49i4.760

in asthma patients. In particular, cytokines are the connecting link and factors that directly affect pathogenesis [1]. The result of the synergistic interaction between cells in the immune response leads to a wide variety of clinical symptoms of the disease, as well as the response to different therapies. Although there have been many advances in the prevention of acute exacerbations, there are 10 - 15% of patients with difficult-to-treat and resistant asthma, despite optimal treatment according to GINA guidelines, leading to asthma phenotype with frequent exacerbations. This phenotype is often associated with persistent symptoms and reduced lung function, causing medical and economic burden [2]. To optimally treat this phenotype, it is necessary to understand the pathogenesis of inflammation and immune response to properly evaluate the endogenous phenotype of asthma to help target treatment. There have been studies on changes in cytokine concentrations to determine endogenous phenotypes worldwide, but they are still limited in focusing on the Th2 phenotype group. In Vietnam, there have been no studies on immune characteristics in asthma patients with frequent exacerbations. Therefore, this study was conducted: *To evaluate changes in serum levels of some cytokines in asthma patients with frequent exacerbations.*

MATERIALS AND METHODS

1. Subjects

120 outpatients with stable asthma treated at the Outpatient Asthma Management Department, Hai Phong International Hospital from January 2020 to May 2023, divided into 2 groups:

- Group 1 (research group): Including 60 asthma patients with frequent exacerbations.

- Group 2 (control group): Including 60 asthma patients with few exacerbations.

* *Inclusion criteria:* Patients have a confirmed diagnosis of asthma according to GINA standards (2019), receive outpatient control and management treatment at the Outpatient Asthma Management Department, and are currently out of exacerbation; criteria for frequent exacerbations are determined according to GINA standards (2019) [3]; criteria for patients with few exacerbations are having less than 2 exacerbations in the last 1 year.

* *Exclusion criteria:* Patients with exacerbation; patients who do not comply with treatment, or drop out of treatment within one year of the study.

Healthy group (group 3): This group includes 30 healthy people who currently have no acute or chronic diseases, have a history of allergies, or are receiving immunosuppressive therapy.

2. Methods

* *Study design:* A descriptive, prospective, and longitudinal study. After being diagnosed with asthma, patients were enrolled in the study. These patients were treated to control asthma according to the guidelines of the Ministry of Health (2020) [4] and regularly re-examined monthly. Patients underwent clinical examination, blood count tests, IgE concentrations, chest X-ray, FeNO measurement, respiratory function test, and serum cytokine levels. Determining cytokine concentrations by using the above magnetic particle immunoassay technique Luminex machine system, performed at the Immunology Laboratory, Military Medical and Pharmaceutical Research Institute, Vietnam Military Medical University.

* *Data analysis:* All data were expressed as mean ± standard deviation or median (interquartile range, Q1-Q3) or percentage where available. Differences between groups were examined with either the student's T-test or Mann-Whitney test. A p-value < 0.05 was defined as statistically significant. Data were managed and analyzed with the SPSS version 20.0 (SPSS Inc, Chicago, IL).

3. Ethics

The study was approved by the Hai Phong International Hospital (No. 09/2020/HIH-IRB). The patients signed the consent and commitment forms.

RESULTS

Table 1. Characteristics of the study population.

Characteristics		Group 1 (n = 60)	Group 2 (n = 60)	p
Age ($\overline{X}$ ± SD) (years)		50.73 ± 15.05	50.43 ± 16.56	0.92**
Gender	Female; n (%)	43 (71.7)	34 (56.7)	0.09*
	Male; n (%)	17 (28.3)	26 (43.3)	
Asthma onset	≤ 12 years old; n (%)	34 (56.67)	40 (66.67)	0.26*
	> 12 years old; n (%)	26 (43.33)	20 (33.33)	
Duration of asthma (year) ($\overline{X}$ ± SD)		26.57 ± 18.32	29.55 ± 17.62	0.37**
Allergy history	Family (n = 29); n (%)	14 (23.3)	15 (25.0)	0.83*
	Personal (n = 66); n (%)	44 (73.3)	22 (36.7)	< 0.001*
Step of asthma	Step (2-3); n (%)	8 (13.3)	14 (23.3)	0.16*
	Step (4-5); n (%)	52 (86.7)	46 (76.7)	

(: Chi-Square Test; **: Student's T-test)*

In group 1, the proportion of women was 71.7%, asthma onset after 12 years old was 43.33%; and the average duration of asthma was 26.57 years, insignificantly shorter than that of group 2 ($p > 0.05$). Patients in group 1 had a personal history of allergies of 73.3%, significantly higher than that of group 2 ($p < 0.001$). The proportion of severe asthma (step 4 - 5) in group 1 was higher than that in group 2. There was no difference in the average age between the 2 groups ($p > 0.05$).

Table 2. Medium serum cytokine concentrations in study groups.

Cytokine level Median (p_{25} - p_{75}) (pg/mL)	**Group 1 (n = 60)**	**Group 2 (n = 60)**	**Group 3 (n = 30)**	**p* (1; 3)**	**p* (2; 3)**	**p* (1; 2)**
Non-Th2-dependent inflammatory response cytokines						
IL-17	8.62 (2.88 - 14.92)	4.86 (1.47 - 13.95)	2.78 (1.47 - 9.44)	0.006	0.27	0.11
INF-α	0.57 (0.40 - 1.43)	0.50 (0.40 - 1.43)	0.40 (0.40 - 0.40)	0.028	0.004	0.67
INF-γ	6,54 (5.05 - 11.95)	5.57 (5.05 - 9.96)	5.05 (3.67 - 6.05)	0.005	0.007	0.63
Th2-dependent inflammatory response cytokines						
IL-4	21.10 (15.99 - 33.67)	16.48 (6.75 - 25.54)	10.49 (6.69 - 16.53)	< 0.001	0.06	0.007
IL-13	9,93 (1.73 - 13.83)	3.95 (1.73 - 10.52)	1.73 (1.73 - 10.52)	0.001	0.29	0.01
Cytokines respond to inflammation and inhibit inflammation						
IL-12	55.11 (28.17 - 269.03)	32.24 (17.22 - 271.04)	120.56 (14.88 - 182.16)	0.21	0.83	0.06
TNF-α	10.25 (4.76 - 18.92)	7.30 (3,53 - 17,88)	4.12 (3.53 - 7.98)	0.002	0.08	0.18
IL-1β	1.61 (0.81 - 2.68)	1.39 (0.81 - 3.76)	1.35 (0.81 - 2.15)	0.32	0.23	0.78

(: Manney-White test)*

In group 1, levels of most cytokines were significantly higher than those of group 3 ($p < 0.05$), except for IL-12 concentrations. Besides, levels of IL-4 and IL-13 were significantly higher compared to group 2 ($p < 0.05$).

Table 3. Medium serum cytokine concentrations in the asthma group with frequent exacerbations by gender

Cytokine level Median (p_{25} - p_{75}) (pg/mL)	**Male (n = 17)**	**Female (n = 43)**	**p***
Non-Th2-dependent inflammatory response cytokines			
IL-17	10.67 (5.92 - 17.38)	8.19 (1.47 - 13.07)	0.23
IFN-α	0.68 (0.40 - 1.85)	0.57 (0.40 - 1.22)	0.32
IFN-γ	8.98 (5.05 - 12.43)	6.05 (5.05 - 10.95)	0.37
Th2-dependent inflammatory response cytokines			
IL-4	21.10 (14.98 - 33.52)	21.10 (16.53 - 34.23)	0.85
IL-13	10.52 (3.48 - 22.52)	9.60 (1.73 - 11.49)	0.46
Inflammation and inhibited inflammation cytokines			
IL-12	45.09 (31.53 - 258.22)	78.19 (27.68 - 271.83)	0.90
TNF-α	13.16 (8.62 - 22.80)	8.88 (3.53 - 17.19)	0.05
IL-1β	1.64 (0.81 - 2.68)	1.61 (0.81 - 2.68)	0.26

(: Manney-White test)*

In the asthma group with frequent exacerbations, the medium serum concentrations of most cytokines in male patients were higher than those in the female group, except for the IL-12 concentration, but the difference was not statistically significant ($p > 0.05$).

Table 4. Medium serum cytokine concentrations in the asthma group with frequent exacerbations by age group

Cytokine level Median (p25 - p75) (pg/mL)	< 60 years old (n = 36)	≥ 60 years old (n = 24)	p*
Non-Th2-dependent inflammatory response cytokines			
IL-17	8.16 (2.13 - 13.07)	10.35 (4.65 - 17.54)	0.30
IFN-α	0.53 (0.37 - 1.31)	0.68 (0.40 - 1.47)	0.31
IFN-γ	7.02 (5.05 - 19.14)	5.57 (5.05 - 10.49)	0.22
Th2-dependent inflammatory response cytokines			
IL-4	21.10 (11.82 - 34.02)	21.84 (16.53 - 33.27)	0.76
IL-13	10.52 (2.96 - 14.94)	9.27 (1.73 - 10.70)	0.29
Inflammation and inhibited inflammation cytokines			
IL-12	45.67 (29.61 - 257.82)	155.36 (28.17 - 323.91)	0.55
TNF-α	10.93 (3.53 - 19.05)	10.23 (5.99 - 17.99)	0.86
IL-1β	1.61 (0.81 - 2.68)	1.61 (0.81 - 2.68)	0.65

(: Manney-White test)*

In the asthma patients with frequent exacerbations, medium serum concentrations of IL-17, IFN-α, IL-4, and IL-12 in the group ≥ 60 years old were higher than those of the group < 60 years old, but the difference was not statistically significant (p > 0.05).

DISCUSSION

1. Characteristics of asthma patients with frequent exacerbations

The study results showed that the asthma patients with frequent exacerbations had insignificantly higher proportions of female and disease onset after age 12, and a shorter average duration of the disease than those of the group with few exacerbations. Asthma patients with frequent exacerbations had a significantly higher personal history of allergies than those of the group with few exacerbations. There was no difference

in age or asthma grade between the 2 groups. Similar results have been proved in many previous studies. In the research by Ten Brinke A (2005), risk factors for exacerbations in patients with difficult-to-treat asthma were evaluated, the results of a younger patient group (the average age was 38 compared to 47 years old) and shorter duration of disease (12 vs. 24.5 years) had a higher risk of exacerbation. In addition, asthma patients with many exacerbations often have a family history of asthma and allergies. Patients with allergic conditions are 10.7 times more likely to have an exacerbation than those without allergic conditions. In particular, patients with increased IgE specific to house dust have a 6.9-fold increased risk of exacerbation [6]. In a cluster study by Kim M (2017), the results showed that the group of patients with non-allergic asthma, late-onset, and poor respiratory function, and the one with allergic asthma, early onset, and poor respiratory function had a higher risk of asthma exacerbation than the one with allergic asthma, early onset, and preserved respiratory function and the one with non-allergic asthma, late-onset, and preserved lung function [6]. With the results of previous studies, it can be seen that most of the results showed that being female, having a history of allergies, having many symptoms, and exhibiting poor respiratory function are risk factors for frequent exacerbations.

2. Changes in serum cytokine levels in asthma patients with frequent exacerbations

* *Serum cytokine concentrations according to the study patient group:*

The results of this study showed that asthma patients had most of the average concentrations of cytokines in serum significantly increased compared to that of the normal ones, except for the concentration of IL-12. In the asthma group with frequent exacerbations, IL-4 and IL-13 concentrations were significantly higher than in the one with few exacerbations. To compare with other previous studies, we realized similarities in the assessment of the role of Th2-dependent cytokines in exacerbations; however, there are differences in the assessment of the role of Th1- and Th17-dependent cytokines in asthma exacerbations. In the research by Wenzel S (2013) on moderate to severe asthma patients with blood eosinophilia, using ICS in combination with LABA, the results showed that Dupilumab (anti-IL-4 receptor alpha) reduced the number of asthma exacerbations (although the patient had previously stopped ICS + LABA), improved respiratory function

and reduced markers of Th2-dependent inflammation [7]. There was a difference in the study by Djukanovic R (2014) to evaluate the effectiveness of IFN-β on patients with asthma exacerbation due to viral infection, with the results showing that inhalation of IFN-β helps reduce the need for additional drug treatment in the management of exacerbation [8]. It can be seen that the results of those studies were not consistent, so identifying the endogenous phenotype that plays a key role in asthma with frequent exacerbations is still challenging.

** Serum cytokine concentrations according to gender characteristics:*

The results of this research showed that men had higher average serum concentrations of most cytokines than women in the asthma group with frequent exacerbations, except for IL-12 concentration which was insignificant. Some previous studies have proved sex hormones relate to the inflammatory status of the airway and treatment response. In the research by Han Y (2020), testosterone was a protective factor for asthma in women and effective against airway inflammation [9]. An analysing study by Yung J (2018) showed that estrogen promotes, while androgen slightly reduces type 2 inflammatory response [10]. Many studies have shown that cytokine production in the lung parenchyma in women is higher than in men. This is associated with increased responsiveness and airway remodeling. In the experimental model, ILC2s in female mice produced significantly higher levels of IL-5 and IL-13 than in male mice. Increased expression of type 2 inflammatory response genes in female mice with ILC2 activated by IL-33 compared to male mice. The research by Newcomb D (2015) showed that patients with severe asthma have increased IL-17A levels in women when compared to men [11]. It can be seen that there have been studies on the impact of gender on the concentrations of cytokines involved in the pathogenesis of asthma. However, the limitation is that most of the studies were carried out on experimental animals, or sex hormones only played a small role in the results of research. More researches are needed to evaluate the impact of sex hormones on asthma patients with frequent exacerbations.

** Serum cytokine concentrations by age group:*

The results of this study showed that patients in the group with frequent exacerbations who are older (≥ 60 years) have higher average concentrations

of IL-17, IFN-α, IL-4, and IL-12 than the younger ones (< 60 years old) insignificantly. Poor prognosis partly comes from underdiagnosis and undertreatment. Changes in the immune system, structural composition, and function of the airways are the main causes of this consequence. When patients become older, there will be a change in the response of the innate immune system and inflammatory response with an increase in IL-1β, IL-6, and TNF-α. Neutrophilic airway inflammation is also a feature of this patient group. In animal experimental models, this group showed the increased expression of IL-8 and Th17-dependent cytokines in the airways. In the research by Ulambayar B (2018), IL-33 and IL-31 concentrations were significantly lower in elderly asthma patients (≥ 60 years old), while there was no difference in IL-8 concentrations, eotaxin-2, TGF-β1, and periostin between young and elderly asthma ones [12]. In conclusion, elderly asthma patients have special physiological characteristics, with many overlapping factors affecting asthma control (comorbidities, the role of sex hormones, changes in the immune system...); it is necessary to have studies with strict selection criteria to homogenize research subjects to help more accurately evaluate these effects.

CONCLUSION

Evaluating changes in the concentrations of some serum cytokines in patients with frequent asthma exacerbations, we initially draw the following conclusion: There are significantly higher serum levels of IL-4 and IL-13 in asthma patients with frequent exacerbations than in those with few exacerbations.

REFERENCES

1. Holgate ST, Holloway J, Wilson S, et al. Understanding the pathophysiology of severe asthma to generate new therapeutic opportunities. *Journal of Allergy and Clinical Immunology*. 2006; 117(3):496-506.

2. Wener RRL and Bel EH. Severe refractory asthma: An update. *European Respiratory Review*. 2013; 22(129): 227-235.

3.GINA-2019-main-Pocket-Guide-wms.pdf. <https://ginasthma.org/wpcontent/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf>.

4. Bộ Y tế. Hướng dẫn chẩn đoán và điều trị hen phế quản người lớn và trẻ em ≥ 12 tuổi. Số 1851/QQĐ-BYT, ngày 24 tháng 4 năm 2020.

5. Ten Brinke A. Risk factors of frequent exacerbations in difficult-to-treat asthma. *European Respiratory Journal.* 2005; 26(5):812-818.

6. Kim MA, Shin SW, Park JS, et al. Clinical characteristics of exacerbation-prone adult asthmatics identified by cluster analysis. *Allergy Asthma Immunol Res*. 2017; 9(6):483.

7. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013; 368(26):2455-2466.

8. Djukanović R, Harrison T, Johnston SL, et al. The effect of inhaled IFN-β on Worsening of asthma symptoms caused by viral infections: A randomized trial. *Am J Respir Crit Care Med*. 2014; 190(2):145-154.

9. Han YY, Forno E, and Celedón JC. Sex steroid hormones and asthma in a nationwide study of U.S. adults. *Am J Respir Crit Care Med*. 2020; 201(2):158-166.

10. Yung JA, Fuseini H, and Newcomb DC. Hormones, sex, and asthma. *Annals of Allergy, Asthma & Immunology*. 2018; 120(5):488-494.

11. Newcomb DC, Cephus JY, Boswell MG, et al. Estrogen and progesterone decrease Let-7f miRNA expression and increase IL-23/IL-23R signaling and IL-17A production in severe asthma. *J Allergy Clin Immunol*. 2015; 136(4):1025-1034.e11.

12. Ulambayar B, Lee SH, Yang EM, et al. Association between epithelial cytokines and clinical phenotypes of elderly asthma. *Allergy Asthma Immunol Res*. 2018; 11(1):79-89.

A STUDY ON THE MORTALITY PROGNOSTIC VALUE OF NEUTROPHIL TO LYMPHOCYTE RATIO AT ADMISSION IN POLYTRAUMA PATIENTS

Nguyen Trung Kien[1], Pham Thai Dung[1], Dang Van Ba[1], Pham Van Cong[1]
Dao Trong Phuc[1], Tran Quoc Viet[2], Ta Thanh Xuan[3], Nguyen Dac Khoi[1]*

Abstract

Objectives: To evaluate the mortality prognostic value of neutrophil/lymphocyte ratio (NLR) at admission in patients with polytrauma. ***Methods:*** A retrospective, descriptive study on 196 polytrauma patients diagnosed using the criterion of the Berlin Consensus 2014, treated at Military Hospital 103 from June 2020 to June 2023. Severity was assessed based on ISS scales, and NLR was calculated at admission prior to any treatment intervention. ***Results:*** Polytrauma predominantly affected males (80.1%) aged between 20 and 59, polytrauma cases were primarily attributed to traffic accidents (66.8%). The group experiencing mortality exhibited lower Glasgow scores, Revised Trauma Score (RTS) at admission, and length of hospital stay compared to the survival group. Additionally, the mortality group demonstrated a higher Injury Severity Score (ISS), lactate level, INR, and aPTT scores, all statistically significant. The NLR value at admission demonstrated predictive value for mortality in polytrauma patients, with an AUC of 0.724, a cut-off of 10.8, sensitivity of 80%, and specificity of 67.2%. ***Conclusion:*** Polytrauma predominantly affected working-age males, with traffic accidents being the primary cause. The NLR value at admission emerges as a meaningful predictor of mortality in polytrauma patients.

Keywords: Polytrauma; Mortality prognosis; Neutrophil to lymphocyte ratio.

---

[1]Military Hospital 103, Vietnam Military Medical University

[2]Military Hospital 175

[3]108 Military Hospital

[*]Corresponding author: Nguyen Dac Khoi (ndackhoi@gmail.com)

Date received: 18/01/2024

Date accepted: 15/3/2024

http://doi.org/10.56535/jmpm.v49i4.713

INTRODUCTION

Polytrauma stands as the primary cause of severe complications and fatalities among trauma patients. It is defined as a condition wherein a patient sustains two or more severe injuries in distinct body regions or organ systems, with at least one injury, or a combination thereof, posing a life-threatening risk.

The pathophysiological cascade following polytrauma, traumatic shock, and severe trauma typically involves the activation of immune function cells. This process triggers the release of pro-inflammatory and anti-inflammatory chemical mediators at both local and systemic levels, culminating in a systemic inflammatory response syndrome (SIRS), where leukocytes play a pivotal role. Notably, neutrophils, the primary contributors to this mechanism, undergo an increase in both quantity and functional differentiation in response to the severity of the injury. This robust immune cell response occurs promptly post-injury. Conversely, lymphocytes, adaptive immune cells, require time to differentiate and proliferate after receiving activation signals and antigen presentation. In the initial stages following severe injury, the number of lymphocytes may even decrease, disrupting the adaptive immune response. Consequently, during the early days of polytrauma, NLR tends to rise, indicating a higher response in more severe injuries. NLR serves as an objective index that is rapid, cost-effective, repeatable, and covered by health insurance [1]. Therefore, NLR emerges as a simple yet effective predictor of outcomes in polytrauma patients. Despite the scarcity of specific studies on NLR in patients with multiple injuries in Vietnam, it remains an unexplored area. This study aims: *To examine the mortality prognostic value of NLR in polytrauma patients*.

MATERIALS AND METHODS

1. Subjects

196 polytrauma patients who were admitted to the Surgical Intensive Care Unit, Military Hospital 103, from June 2020 to June 2023.

** Inclusion criteria:*

- Patients aged ≥ 18 years;

- Patients diagnosed with polytrauma according to the Berlin Consensus criteria in 2014 [2]: Patients have > 2 lesions with an AIS ≥ 3 and at least one of the following additional conditions:

+ Hypotension (systolic blood pressure ≤ 90 mm Hg);

+ Coma (Glasgow Coma Scale [GCS] ≤ 8);

+ Acidosis (Base Excess [BE] ≤ - 6.0);

+ Coagulation disorders (activated partial thromboplastin time [aPTT] ≥ 50 seconds or international normalized ratio [INR] ≥ 1.4);

+ Age ≥ 70;

- Patients' relatives provided consent to participate in the study.

Table 1. Abbreviated injury scale AIS - 2005.

Point	Injuries
1	Minor injury
2	Average injury
3	Severe injury, not life-threatening
4	Severe injury, life-threatening, still capable of living
5	Severe injury, life-threatening, unlikely to live
6	Injury cannot be survived

* *Exclusion criteria:* Hospitalized > 12 hours after the accident; patients who have had surgery or treatment at previous level hospitals; pregnant woman; have chronic diseases such as cirrhosis, end-stage chronic kidney failure, congestive heart failure, and malignancy; patients who had cardiac arrest before entering the hospital and were successfully resuscitated.

* *Criteria for removal from the study:* Transfer to another hospital before discharge after 30 days; insufficient collection of research data.

2. Methods

* *Research design:* A retrospective, descriptive study.

* *Data collection:* Vital signs, Glasgow score, RTS, Trauma score (TS), and ISS were documented upon admission. Blood samples, including biochemical, complete blood count, and blood gas tests, were obtained within 30 minutes of admission. Patient outcomes were assessed 30 days after admission, considering patients dead if they expired in the hospital or were in serious condition

with a family request for discharge. Compiled information is recorded in the research medical record.

* *Treatment protocols:*

Coma patients (GCS ≤ 8 points) received volume-controlled ventilation (Tidal volume = 8 mL/kg, respiratory rate 16 - 20 breaths/minute, PEEP 5 - 10 cmH_2O, I:E ratio of 1:2, FiO_2 40%), adjusted parameters to keep end-tidal CO_2 pressure ($EtCO_2$) within the range of 35 - 45 mmHg, arterial blood gas PaO_2 80 - 100 mmHg.

Treatment followed the 2014 Berlin Consensus guidelines for polytrauma patients, involving vasopressors (Noradrenalin, Adrenalin, etc.), fluid infusion to maintain mean blood pressure ≥ 65 mmHg, aggressive management of visceral bleeding and cerebral edema (in traumatic brain injury) with 3% hypertonic saline and tranexamic acid, use of antibiotics, analgesics, and sedatives as needed.

Nutritional support targeted 25 - 35 kcal/kg/day, initiated promptly post-injury unless contraindicated.

* *Statistical analysis:* Qualitative variables are presented as percentages. The Kolmogorov-Smirnov test was performed to check the normal distribution of the variables. Quantitative variables that are not normally distributed are presented as medians (interquartile range: Q1 - Q3). Test the difference between two quantitative variables that do not have a normal distribution using the Mann - Whitney test. Kaplan-Meier failure curve and log-rank test were fitted to explore the survival difference among groups. After the bivariable and multivariable Cox regression analysis, an Adjusted Hazard Ratio with 95% Confidence Intervals (CI) was reported to declare the strength of association and statistical significance, respectively.

* *Data processing:* Using the SPSS 26.0 software.

3. Ethics

All patients (without consciousness disorders) in the study were informed and consented by their relatives. Patients' names are kept anonymous. The main variable of the article is NLR, which is an objective paraclinical parameter in complete blood count. This parameter and other clinical characteristics are collected and recorded in the medical record on a regular basis. Obtaining research data does not affect diagnosis, treatment, patient costs, or health insurance. The research has no conflicts of interest among any individual or organization.

RESULTS

Table 2. General characteristics of research subjects.

Characteristics		Quantity (n)	Proportion (%)
Age	< 20	24	12.2
	20 - 40	76	38.8
	41 - 59	64	32.7
	≥ 60	32	16.3
	Mean age	41.75 ± 18.2	
Gender	Male	157	80.1
	Female	39	19.9
Causes	Traffic accidents	131	66.8
	Occupational accidents	32	16.3
	High fall	23	11.7
	Others	10	5.1
ISS	18 - 25	38	19.4
	26 - 40	98	50.0
	41 - 75	60	30.6
Outcome	Survival	116	59.2
	Death	80	40.8
Total		196	100

The patients with multiple injuries in the study were mainly working age, with an average age of 41.75 ± 18.2 years old. The lowest age was 18, and the highest was 82. The majority were men (80.1%).

The main cause of multiple injuries was traffic accidents (66.8%). The mortality rate due to multiple injuries in hospitalized patients was 40.8%.

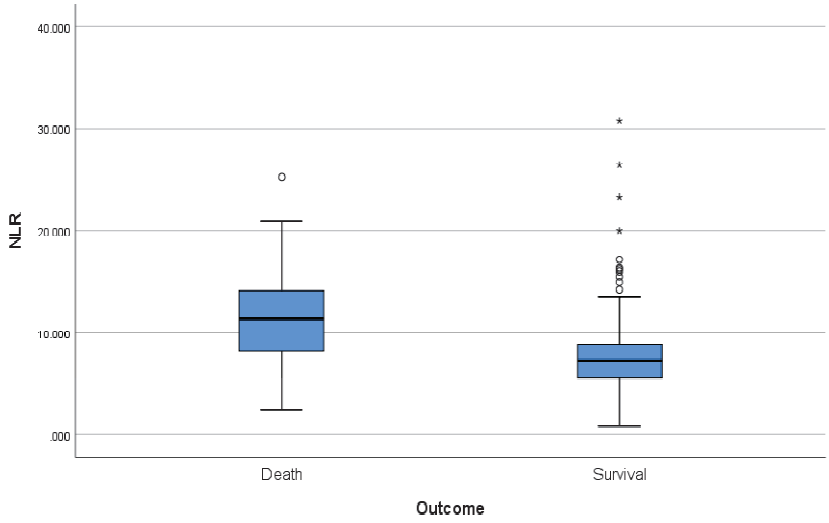
Most patients with multiple injuries had ISS scores ranging from 26 to 40 (50%). The lowest ISS score was 18 (4 patients accounting for 2%), and the highest ISS score was 75 (1 patient).

Table 3. Comparing the survival group with the death group.

Characteristics	Survival group (n = 116)	Death group (n = 80)	p
Age	37.0 (25.0 - 56.0)	45.0 (28.0 - 58.0)	0.16
Glasgow score	8 (7 - 9)	5 (4 - 5)	< 0.001
RTS	11 (10 - 12)	8 (6 - 10)	< 0.001
ISS	32 (25 - 35)	41 (34 - 45)	< 0.001
Lactate	3.7 (2.5 - 5.5)	6.6 (3.7 - 9.3)	< 0.001
INR	1.13 (1.04 - 1.27)	1.34 (1.12 - 1.60)	< 0.001
aPTT	29.6 (27.0 - 36.4)	38.1 (30.3 - 53.0)	< 0.001
Time elapsed until care (hours)	3.0 (2.0 - 4.0)	3.0 (2.0 - 3.0)	0.241
Duration of mechanical ventilation (days)	5.0 (1.0 - 8.0)	2.0 (1.0 - 6.0)	0.37
Length of intensive care (days)	6.5 (3.0 - 13.0)	2.0 (1.0 - 6.8)	< 0.001
Length of hospital stay (days)	21.5 (11.7 - 30.0)	2.0 (1.0 - 6.8)	< 0.001

The Glasgow scores, TS, and RTS at admission and the length of recovery and hospital stay of the death group were smaller than those of the survival group. In addition, the death group's ISS, creatinine at admission, lactate, blood glucose, INR, and aPTT were statistically significantly greater than those of the survival group.

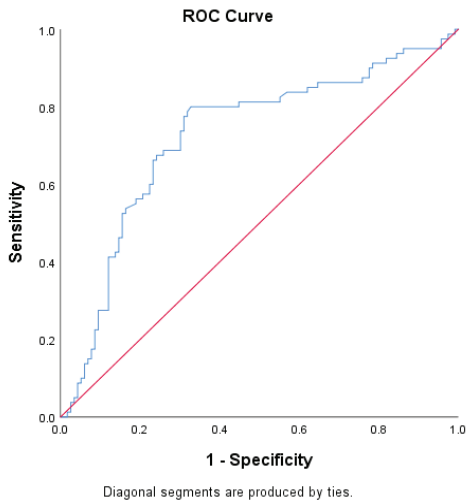
Figure 1. NLR value is in the survival group and death group.



	Survival group (n = 116)	Death group (n = 80)	p
NLR	8.21 (7.36 - 9.05)	11.08 (10.1 - 12.05)	p < 0.05

The mean admission NLR value in the death group was 11.08 ± 0.48 (95%CI: 10.1 - 12.05), in the survival group, it was 8.21 ± 0.42 (95%CI: 7.36 - 9.05); the death group had a higher NLR at the time of admission than the survival group, which was statistically significant with p < 0.05.

Figure 2. ROC curve predicting mortality by NLR at the time of hospitalization in patients with polytrauma.



	AUC	Cut - off	Specificity	Sensitivity
NLR	0.724	10.8	0.672	0.8

The NLR value at the time of admission has a predictive value for mortality in polytrauma patients with $p < 0.01$, area under the curve AUC = 0.724, cut-off point = 10.8 with 80% sensitivity (Se), specificity (Sp) 67.2%.

DISCUSSION

1. General characteristics of the patients

Our study was performed on 196 polytrauma patients with an average age of 41.75 ± 18.2 years. The male patient group accounted for 80.1%, most of whom were of working age. Up to 66.8% of the total patients in the study suffered multiple injuries due to traffic accidents. Research by Farzad Rahmani et al. on 374 multiple trauma patients admitted to the emergency department also found that most multiple trauma patients were men (82.1%), and the average age was 40.42 ± 18.05 years [3], quite similar to our research results. This is because young and middle-aged men are the main group of workers in most occupations, including occupations with heavy, intense labor, with a higher risk of accidents. Moreover, men also account for a high rate of traffic accidents, and is related to alcohol use while driving, etc.

The survival rate at 1 month after hospitalization for treatment in the study patient group was 59.2%, and the death rate was 40.8% (death cases were removed from the study patient population); death before the first 24 hours after admission). The study of Sauaia A et al. on 289 trauma patients showed that the mortality rate was 20%, lower than that of our study [4]. This difference was due to many reasons; it may caused by the larger number of patients studied, and at the same time, the patient population selected for this study was trauma in general; in addition to multiple trauma patients, there were also patients with multiple injuries. The injury was only in one organ, and the level of injury was not severe. In addition, it may also be due to first aid steps at the accident site, patient transportation, the capacity of doctors and hospitals, and good coordination between emergency, resuscitation, and surgical departments than in Western countries.

RTS in the death group were lower than in the survival group, and ISS in the death group were higher than in the survival group. The difference

between the two groups is statistically significant, with p < 0.001 (*Table 3*). This result is equivalent to the study of Diwakar Verma et al. on 88 multiple trauma patients from June 2016 to November 2016 in New Delhi, India, finding that ISS and RTS had a statistically significant difference between the two groups of living and dead patients, and research also shows that ISS and RTS are highly effective factors in predicting death for patients with multiple injuries [5].

Lactate is a product of anaerobic metabolism, reflecting hypoxia. Research results showed that blood lactate concentration at admission was statistically significantly higher at p < 0.001. This result is equivalent to the study by Divya Jyoti et al. (2022) on 90 patients with polytrauma, showing that lactate concentration at the time of admission is valuable in predicting both severity and the possibility of death in internal hospitals [6]. Normalization of lactate in polytrauma patients within the first 48 hours after injury significantly improves in-hospital mortality.

Coagulation disorder is one of the three deadly triads in polytrauma patients. The parameters assessing basic coagulation status at the time of hospitalization of most patients with multiple injuries are disordered. The study results showed that PT/INR and APTT at the time of admission in the group of patients who died were higher than those who survived; this difference was statistically significant with p < 0.001. This was similar to the results of a study by Gururaj N Puranik, et al. on 142 polytrauma patients in the pathology department of a tertiary care center for 20 months from December 2012 to July 2014, PT/INR, aPTT, and D-Dimer were independent predictors of mortality in polytrauma patients [7].

2. The mortality prognostic value of NLR at the time of hospitalization in polytrauma patients.

NLR at the time of hospitalization in the death group was higher than the survival group, with a statistical significance of p < 0.001. This result was similar to the study by Jinghong Xu et al. on 3865 trauma patients at 335 ICU centers in 208 hospitals, showing that the NLR at many time points between the polytrauma patients who died and survived group had different statistical significance [8].

NLR at the time of hospitalization could predict the outcome of polytrauma patients on a moderate level with p < 0.001 and AUC = 0.724. The cut-off point at NLR value = 10.8 because it has the highest J index with Se = 0.8 and Sp = 0.672.

This result is quite similar to the study by author Soulairman ES et al. on 566 patients with multiple injuries from July 2017 to November 2017: NLR at the time of admission has the ability to predict the outcome of the disease. Multiply the moderate level by AUC = 0.63. The cut-off point of NLR at time T_0 that best predicts the risk of death in this study is at NLR T_0 = 4 with Se = 0.70, Sp = 0.56 [9]. There are differences in the location of the cutting point that can be caused by many reasons. The subjects and design of the two studies are quite different. In Soulairman's study, subjects with ISS $\geq$ 15 were selected, while in our study, patients with ISS $\geq$ 18 were selected. Differences in acute conditions research and treatment in the two centers, study race, and tumor size also make a difference.

Our research results are also quite like the results of Jinghong Xu et al. in 2022: NLR at the time of hospitalization is a factor in predicting outcomes in trauma patients. With the area under the curve AUC = 0.681 and the optimal cut-off point of 9.75, Se = 65.3% and Sp = 65.8%. Meanwhile, in patients with traumatic brain injury, the area under the curve is 65.8%. Under the curve of NLR at the time of hospitalization, predicting outcomes is AUC = 0.725, and the optimal cut-off point is 7.439, Se = 77.7%, and Sp = 60.2%, respectively [8]. This shows that the value of NLR at the time of admission predicts mortality in patients with traumatic brain injury better than in patients with trauma. However, the time of death assessment in the two studies is different. Our study assessed death after 30 days, while the study by Jinghong Xu et al. was 15 days with many patients. In multicenter settings, this resulted in differences in the two study results.

In patients with severe TBI, research by Weiqiang Chen and colleagues on 688 patients from January 2007 to March 2012 found that NLR at the time of admission may be an effective new marker to predict mortality in patients with severe TBI with AUC = 0.704 (95%CI = 0.66 - 0.744), Se = 60.1% and Sp = 72.5%, respectively. The optimal cut-off point of the NLR value at the time of admission is 16.23 [10]. This result was like our study on the group of patients with polytrauma but with a higher NLR cut-off point.

CONCLUSION

Patients with multiple injuries were mainly men in the working age group, with traffic accidents being the main cause of multiple injuries. NLR at the time of admission in the group of patients who died was higher than that

of the group who survived, with $p < 0.001$. NLR at the time of hospital admission is meaningful in predicting mortality in patients with polytrauma. The higher the NLR at the time of admission, the greater the mortality rate of polytrauma patients.

REFERENCES

1. H Fouladseresht, S Bolandparvaz, HR Abbasi, et al. The neutrophil-to-lymphocyte ratio at the time of admission: A new prognostic indicator for hospital mortality of trauma patients. *Iran J Allergy Asthma Immunol*. 2021; 20(1):33-45.

2. HC Pape, R Lefering, N Butcher, et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg*. 2014; 77(5):780-786.

3. Farzad Rahmani, Hanieh Ebrahimi Bakhtavar, Samad Shams Vahdati, et al. Evaluation of MGAP and GAP trauma scores to predict prognosis of multiple-trauma patients. *J Trauma Monthly*. 2017; 22(3).

4. A Sauaia, FA Moore, EE Moore, et al. Epidemiology of trauma deaths: A reassessment. *J Trauma*. 1995; 38(2):185-193.

5. HF Watts, Y Kerem, E B Kulstad. Evaluation of the revised trauma and injury severity scores in elderly trauma patients. *J Emerg Trauma Shock*. 2012 5(2):131-134.

6. D Jyoti, A Kumar, T Halim, et al. The association between serum lactate concentration, base deficit, and mortality in polytrauma patients as a prognostic factor: An observational study. *Cureus*. 2022; 14(8):e28200.

7. GN Puranik, TYP Verma, GA Pandit (2018). The study of coagulation parameters in polytrauma patients and their effects on outcome. *J Hematol*. 2018; 7(3):107-111.

8. J Xu, S Li, KY Lui, et al. The neutrophil-to-lymphocyte ratio: A potential predictor of poor prognosis in adult patients with trauma and traumatic brain injury. *Front Surg*. 2022; 9:917172.

9. SE Soulaiman, D Dopa, AT Raad, et al. Cohort retrospective study: The neutrophil to lymphocyte ratio as an independent predictor of outcomes at the presentation of the multi-trauma patient. *Int J Emerg Med*. 2020; 13(1):5.

10. W Chen, J Yang, B Li, et al. Neutrophil to lymphocyte ratio as a novel predictor of outcome in patients with severe traumatic brain injury. *J Head Trauma Rehabil*. 2018; 33(1): 53-59.

MATERNAL SERUM LEPTIN LEVELS IN SUBJECTS WITH GESTATIONAL DIABETES MELLITUS

Phan Thi To Nhu[1,2], Hoang Trung Vinh[2]*
Vu Ba Quyet[3], Pham The Tai[4]

Abstract

Objectives: To determine serum leptin levels and its correlation with pre-pregnancy BMI, BMI, and insulin resistance at 24 - 28 weeks of gestation and before delivery in subjects with gestational diabetes mellitus (GDM). ***Methods:*** A cross-sectional descriptive, longitudinal follow-up study with a control group on 115 pregnant women with GDM and 115 pregnant women with normal glucose tolerance (NGT) enrolled at 24 - 28 weeks of gestation and completed the study. The subjects' serum leptin levels were measured using the enzyme-linked immunosorbent assay (ELISA) method at 24 - 28 weeks of pregnancy and before delivery. The clinical characteristics, serum insulin levels, and homeostatic model assessment of insulin resistance (HOMA-IR) were also performed at both study time points. ***Results:*** Serum leptin levels in subjects with GDM were significantly higher than those in normal pregnant women at 24 - 28 weeks of gestation and before delivery ($p < 0.001$). At both study time points, there was a positive correlation between serum leptin levels and pre-pregnancy BMI, maternal weight, serum insulin levels, and HOMA-IR index in subjects with GDM ($p < 0.05$). Multivariable logistic regression showed that pre-pregnancy BMI and serum insulin levels were associated with hyperleptinemia ($p < 0.05$). ***Conclusion:*** Serum leptin levels were higher in GDM and had a positive correlation with pre-pregnancy BMI, BMI, and insulin resistance at the time of the study. Pre-pregnancy BMI and serum insulin levels were independent factors related to increased serum leptin levels.

Keywords: Gestational diabetes mellitus; Leptin; Insulin resistance; Adipokines.

[1]**Hanoi University of Pharmacy**

[2]**Military Hospital 103, Vietnam Military Medical University**

[3]**National Hospital of Obstetrics and Gynecology**

[4]**Institute of Biomedicine and Pharmacy, Vietnam Military Medical University**

[*]**Corresponding author: Phan Thi To Nhu (phantonhu.hup@gmail.com)**

Date received: 13/12/2023

Date accepted: 20/3/2024

http://doi.org/10.56535/jmpm.v49i4.584

INTRODUCTION

Pregnancy is a hyperglycemic period of life, with hyperglycemia serving a highly important role in the nutrition and development of the fetus by providing it with adequate glucose levels. GDM is a condition associated with maternal hyperglycemia to a lesser degree than overt diabetes but is associated with an increased risk of adverse obstetric outcomes [1]. Like all forms of hyperglycemia, GDM is characterized by insulin levels that are insufficient to meet insulin demands.

Adiposity is an important modifiable risk factor for the development of GDM, although mechanisms linking excess adiposity to elevated risk of GDM are not completely understood. Leptin is one of the adipocyte-derived hormones involved in energy homeostasis and plays an important role in insulin and glucose metabolism [2]. Most of the literature data have associated hyperleptinemia with the development and progression of GDM, while only a few studies have shown reduced or unchanged levels of this protein in affected women. Such varieties might be ascribed to the utilization of a one-step bio-sample together with immense contrasts within leptin estimation circumstances, which are liable to the active variations in leptin levels during pregnancy. However, very few studies described the longitudinal changes in leptin concentration related to GDM. A longitudinal monitoring of maternal leptin concentrations in relation to insulin resistance during pregnancy may help to gain a better understanding of the development of GDM. Therefore, we conducted this study: *To determine serum leptin levels and its correlation with pre-pregnancy BMI, BMI, and insulin resistance at 24 - 28 weeks of gestation and before delivery in GDM subjects.*

MATERIALS AND METHODS

1. Subjects

230 pregnant women with a single fetus, at 24 - 28 weeks gestation, examined at the Hanoi Obstetrics and Gynecology Hospital from 2019 to 2021, who have not been diagnosed with diabetes before.

** Inclusion criteria:*

- GDM group: Single pregnant women, gestational weeks 24 - 28, diagnosed with GDM according to the criteria of the American Diabetes Association 2011 guidelines.

- NGT group: Single pregnant women, gestational weeks 24 - 28 with NGT according to the criteria of the American Diabetes Association 2011 guidelines.

** Exclusion criteria:*

- GDM group: Multiple pregnancies, diagnosed with diabetes before 24 - 28 weeks of gestation, GDM requiring insulin treatment, currently suffering from endocrine disorders, currently using

drugs that affect glucose metabolism, currently suffering from infectious diseases acute or malignant disease.

- NGT group: Multiple pregnancies, diagnosed with diabetes before 24 - 28 weeks of gestation, history of GDM in a previous pregnancy, family history of diabetes, bad obstetric history (stillbirth, multiple miscarriages, giving birth to babies over 4000g), currently suffering from endocrine disorders, currently using drugs that affect glucose metabolism, currently suffering from infectious diseases acute or malignant disease.

2. Methods

* *Study design:* A cross-sectional descriptive, longitudinal follow-up study with a control group.

* *Sample size and sample selection:* This study is part of a project investigating the levels of some adipocytokines in subjects with GDM. According to the results of the previous study [3], the estimated number of subjects needed for each group was 113. This sample size still ensures representativeness and reliability when studying leptin levels. In fact, we selected 115 pregnant women for each group.

* *Research tools and information-gathering techniques:*

- Eligible participants were studied longitudinally during the 24 - 28 weeks and prenatal period (≥ 37 weeks, 1 week prepartum) of pregnancy. Each participant carried out a 75g oral glucose tolerance test under a fasting state (> 8h) at 24 - 28 weeks. Pregnant women with normal glucose tolerance were assigned to the NGT group. Participants who were diagnosed with GDM received individual nutritional counseling with instructions on the appropriate restriction of energy intake, daily moderate exercise, and self-monitoring of blood glucose for 2 weeks. If blood glucose cannot be controlled, pregnant women will be hospitalized for insulin treatment and will be removed from the study.

- Demographic information from each participant, including maternal age, parity, gestational weeks, personal, and familial medical history, pre-pregnancy weight (before 1 month), was collected at 24 - 28 weeks gestation.

- During the observation period, blood pressure, heart rate, height, and body weight were measured at 24 - 28 weeks gestation and before delivery.

- Laboratory methods: At 24 - 28 weeks of gestation and before delivery, maternal venous blood samples of 5mL were collected after fasting at least 8h. Samples were processed within one hour of collection. The serum was separated by centrifugation at 4000 rpm for 15 minutes after clotting, then was separated into appropriate tubes and stored at -80°C until leptin and insulin were quantified.

+ Fasting plasma glucose, glucose after 1 hour, and 2 hours after drinking glucose were measured immediately after venous blood collection using colorimetric enzymatic method with reagents and standards from Roche.

+ Serum leptin levels were determined by the ELISA method, using the Human Leptin ELISA Kit (Austria).

+ Serum insulin levels were determined by solid-phase chemiluminescence immunoassay.

- Serum insulin and serum leptin were measured at the Institute of Biomedicine and Pharmacy, Vietnam Military Medical University.

- Standards and assessments used in research:

+ Diagnostic criteria for GDM according to the criteria of American Diabetes Association 2011 guidelines (fasting plasma glucose (FPG): 5.1 - 6.9 mmol/L, 1-hour glucose ≥ 10.0 mmol/L, or 2-hour glucose ≥ 8.5 mmol/L, if any of the three criteria met or exceeded), using a 75-g OGTT [1].

+ BMI pre-pregnancy and at each time of the study is calculated according to the formula: Weight (kg)/(height)^2 (m). It is called overweight/obese when BMI ≥ 23 kg/m^2.

+ Increased leptin is identified when the leptin level is greater than the 75% quartile of the NGT group in this study.

+ Hyperinsulinemia is identified when the insulin level is greater than the 75% quartile of the NGT group in this study.

+ Insulin resistance was calculated using the homeostasis model assessment of insulin resistance index (HOMA-IR), using the formula [fasting glucose (mmol/L) x fasting insulin (µU/mL)]/ 22.5. It is called insulin resistance when HOMA-IR is greater than the 75% quartile of the NGT group in this study.

* *Statistical analysis:* Results are expressed as mean and standard deviation or median, and interquartile range. The data was compiled and analyzed by SPSS 27.0 using appropriate statistical methods. For comparisons of means, Student's T-test was used to determine the significance between GDM and controls. For the assessment of the correlation between variables, Pearson's correlation was used; $p < 0.05$ were considered statistically significant.

3. Ethics

The study has been approved by Hanoi Obstetrics and Gynecology Hospital for implementation. All research subjects were specifically explained about the purpose and content of the study and agreed to voluntarily participate in the study. All research subject information is kept confidential and used for research purposes only.

RESULTS

230 pregnant women were selected for the study, including 115 pregnant women with GDM and 115 pregnant women with NGT.

Table 1. General characteristics of research subjects.

Parameter	GDM group (n = 115)	NGT group (n = 115)	p
Maternal age (year) ($\overline{X}$ ± SD)	31.48 ± 5.09	29.37 ± 4.94	0.002
Pre-pregnancy BMI (kg/m^2) ($\overline{X}$ ± SD)	21.24 ± 2.68	20.59 ± 2.21	0.045
24 - 28 weeks of gestation			
Maternal weight (kg) ($\overline{X}$ ± SD)	58.8 ± 8.3	56.5 ± 5.8	0.016
Fasting plasma glucose (mmol/L)	5.01 ± 0.41	4.68 ± 0.25	< 0.001
Glucose after 1h of OGTT (mmol/L)	9.99 ± 1.52	7.48 ± 1.25	< 0.001
Glucose after 2h of OGTT (mmol/L)	8.91 ± 1.55	6.84 ± 0.96	< 0.001
Insulin (µU/mL) (Median) (Quartile)	14.08 (8.4)	10.79(6.2)	< 0.001
HOMA-IR (Median) (Quartile)	3.08 (1.82)	2.23 (1.32)	< 0.001
Leptin (ng/mL) (Median) (Quartile)	9.03 (9.25)	4.27 (3.41)	< 0.001
Before delivery			
Maternal weight (kg) ($\overline{X}$ ± SD)	65.4 ± 8.5	62.9 ± 5.9	0.01
Fasting plasma glucose (mmol/L)	4.88 ± 0.76	4.63 ± 0.56	0.005
Insulin (µU/mL) (Median) (Quartile)	18.36 (8.68)	15.05 (6.44)	< 0.001
HOMA-IR (Median) (Quartile)	3.93 (2.27)	3.02 (1.36)	< 0.001
Leptin (ng/mL) (Median) (Quartile)	10.55 (13.17)	6.13 (4.76)	< 0.001

Pregnant women in the GDM group had significantly higher maternal age, pre-pregnancy BMI than the NGT group, $p < 0.05$.

The GDM group had higher blood glucose levels, serum leptin levels, insulin levels, and HOMA-IR index than the NGT group ($p < 0.05$) at 24 - 28 weeks of gestation and before delivery.

Table 2. The proportion of patients with increased leptin levels of study subjects.

Characteristic	GDM group (n = 115)		NGT group (n = 115)		p
	n	%	n	%	
24 - 28 weeks of gestation					
Increased serum leptin	84	73.0	28	24.3	< 0.001
Before delivery					
Increased serum leptin	76	66.1	28	24.3	< 0.001

The GDM group had a higher rate of patients with increased leptin than the NGT group ($p < 0.001$) at 24 - 28 weeks of gestation and before delivery.

Table 3. Serum leptin levels in the GDM group according to assessment indicators.

Evaluation index		Serum leptin levels (ng/mL)	p
24 - 28 weeks of gestation			
Pre-pregnancy BMI (kg/m^2)	≥ 23 (n = 42)	17.46 (13.38 - 20.5)	< 0.001
	< 23 (n = 73)	7.22 (4.92 - 9.58)	
Increased serum insulin	Yes (n = 55)	15.06 (9.11 - 19.43)	< 0.001
	No (n = 60)	6.99 (4.34 - 9.23)	
Insulin resistance	Yes (n = 62)	13.82 (8.38 - 18.99)	< 0.001
	No (n = 53)	6.67 (3.99 - 9.31)	
Before delivery			
Pre-pregnancy BMI (kg/m^2)	≥ 23 (n = 42)	23.22 (17.57 - 26.26)	< 0.001
	< 23 (n = 73)	9.03 (6.99 - 12.12)	
Increased serum insulin	Yes (n = 55)	17.98 (9.94 - 24.62)	< 0.001
	No (n = 60)	8.19 (6.53 - 11.35)	
Insulin resistance	Yes (n = 62)	16.72 (9.34 - 24.22)	< 0.001
	No (n = 53)	7.98 (5.97 - 11.94)	

Serum leptin levels increased significantly in GDM subjects with pre-pregnancy overweight/obesity, increased serum insulin and insulin resistance ($p < 0.001$), at 24 - 28 weeks of gestation and before delivery.

Table 4. The correlation between increased serum leptin and some indicators in GDM group.

Evaluation index		Increased serum leptin (n, %)	p
24 - 28 weeks of gestation			
Pre-pregnancy BMI (kg/m^2)	≥ 23 (n = 42)	40 (95.2)	< 0.001
	< 23 (n = 73)	44 (60.3)	OR = 13.18
Increased serum insulin	Yes (n = 55)	50 (90.9)	< 0.001
	No (n = 60)	34 (56.7)	OR = 7.65
Insulin resistance	Yes (n = 62)	55 (88.7)	< 0.001
	No (n = 53)	29 (54.7)	OR = 6.5
Before delivery			
Pre-pregnancy BMI (kg/m^2)	≥ 23 (n = 42)	41 (97.6)	< 0.001
	< 23 (n = 73)	35 (47.9)	OR = 44.51
Increased serum insulin	Yes (n = 61)	52 (85.2)	< 0.001
	No (n = 54)	24 (44.4)	OR = 7.22
Insulin resistance	Yes (n = 70)	57 (81.4)	< 0.001
	No (n = 45)	19 (42.2)	OR = 6.0

In the GDM group, there was overweight and obesity before pregnancy, increased serum insulin levels and insulin resistance. The rate of increase in serum leptin levels was higher than in the normal weight group; there were no increase serum insulin levels and no insulin resistance statistically significant ($p < 0.05$).

Table 5. The correlation between leptin levels and some indicators in the GDM group.

Evaluation index	Leptin levels at 24 - 28 weeks		Leptin levels before delivery	
	r	p	r	p
Pre-pregnancy BMI	0.735	< 0.001	0.747	< 0.001
BMI at the time of the study	0.723	< 0.001	0.71	< 0.001
Maternal weight at the time of the study	0.653	< 0.001	0.643	< 0.001
FPG at the time of the study	0.123	0.189	- 0.02	0.835
Insulin levels at the time of the study	0.763	< 0.001	0.734	< 0.001
HOMA-IR at the time of the study	0.774	< 0.001	0.695	< 0.001

At gestational weeks 24 - 28 and before delivery: There were a significant, fairly close positive correlation between serum leptin levels and BMI, maternal weight, serum insulin levels and HOMA-IR index in patients with GDM, $p < 0.001$.

There were no significant correlation between serum leptin levels and fasting plasma glucose levels at the time of the study ($p > 0.05$).

Table 6. The correlation between increased serum leptin and some indicators in GDM group.

Evaluation index	Increased leptin at 24 - 28 weeks		Increased leptin before delivery	
	OR	p	OR	p
Pre-pregnancy BMI	1.75	0.006	1.63	0.007
Maternal weight gain	1.09	0.541	0.95	0.648
Fasting plasma glucose	4.81	0.31	1.33	0.42
Insulin levels at the time of the study	2.85	0.039	1.23	0.047
Insulin resistance at the time of the study	0.43	0.369	0.42	0.304

Among the related factors, pre-pregnancy BMI and serum insulin levels were independent factors related to increased serum leptin levels, $p < 0.05$.

DISCUSSION

Leptin is a protein secreted from adipocytes, which is believed to play a role in the pathogenesis of GDM [2]. Except for adipocytes, leptin can also be produced by non-adipose tissues such as the stomach, intestine, and, in particular, the placenta in humans. As pregnancy progresses, because of the increased fat mass and the presence of placenta, maternal leptin levels increase 2 to 3-fold above non-pregnant concentration, with the peak occurring around 28 weeks of gestation [2]. However, GDM induces more weight gain as it creates chronic hypoxia in the placental environment, leading to compensatory hyper-perfusion and thereby increasing the placental weight more as compared to normal pregnancy [4]. As a result, the serum leptin levels of women with GDM were higher than that of healthy pregnant women. This is in concordance with our findings in this study. Our study shows that pregnant women with GDM have higher serum leptin levels (*Table 1*) and a significantly higher rate of serum leptin increase (*Table 2*) compared to normal pregnant women, in both study times ($p < 0.001$). These results are generally consistent with studies that assessed maternal serum leptin levels in pregnancies complicated by GDM. In a case-control study, Fatima et al. [5] reported that maternal serum leptin levels were higher in GDM women compared with the control group (20.38 ± 12.7 ng/mL vs. 3.41 ± 2.17 ng/mL, $p < 0.001$). Andleeb et al. [6] and Yang Mei et al. [7] also showed similar results of elevated values of leptin in GDM at 24 - 28 weeks of gestation. Florian et al. [8] found significantly increased leptin levels in pregnant women with GDM and a higher probability of developing GDM in women with serum leptin concentrations > 16 ng/mL at 11 - 13 weeks of gestation ($p < 0.001$). However, in contrast to the findings reported above, Mosavat et al. [9] reported a decrease in leptin levels and soluble leptin receptor in 53 GDM women compared with 43 women with NGT. These inconsistencies among the results might arise from the different sample sizes of the population and timing of maternal blood collection: Many previous studies were conducted in non-pregnant women, but the regulation of leptin might be very different during pregnancy.

The classic perception of adipose tissue merely as a lipid storage site has changed significantly over the past decade. Now, adipose tissue can act as an endocrine organ that regulates systemic metabolism. Leptin is produced mainly in mature cells of white adipose

tissue. Leptin biosynthesis and secretion depend on white adipose tissue mass and adipocyte size. In obese people, there is an increase in adipose tissue mass and fat cell size. Hypertrophied and excess adipose tissue tends to enhance leptin release. Therefore, leptin levels is closely correlated with the body's BMI; the higher the body fat mass, the higher the leptin levels. In pregnant women, increased body weight and accumulation of visceral fat can increase adipose tissue mass, thereby stimulating leptin production. As a result, serum leptin levels increased in overweight and obese pregnant women. This is consistent with our research results. In this study, women with GDM had significantly higher pre-pregnancy BMI than the NGT group ($p < 0.001$) (*Table 1*). We found strong positive correlations between serum leptin levels and pre-pregnancy BMI, BMI, and weight at each study time point in the mother ($p < 0.001$) (*Table 5*). Overweight/obese women with GDM had higher leptin levels (*Table 3*) and higher rates of leptin elevation (*Table 4*) compared with non-overweight/obese pregnant women. This suggests that obesity is a major factor in insulin resistance and increased leptin levels. Our results are supported by Yang Mei et al. [7], who studied 357 GDM at 24 - 30 weeks of gestation and found a positive correlation between leptin levels and maternal pre-pregnancy BMI ($r = 0.45$, $p < 0.001$). Our results are supported by Yang Mei et al. [7], who studied 357 GDM at 24 - 30 weeks gestation and found a positive correlation between leptin levels and maternal pre-pregnancy BMI ($r = 0.45$, $p < 0.001$).

GDM is associated with reduced responsiveness of maternal body tissues to insulin. Therefore, increased serum insulin levels and high HOMA-IR values are expected in GDM patients. The same thing was also described in our study when serum insulin levels and HOMA-IR index in the GDM group were significantly higher than the NGT group ($p < 0.001$) (*Table 1*). As mentioned in previous studies, leptin inhibits insulin secretion from pancreatic beta cells in obese or pregnant people. Chronic increases in leptin levels cause the leptin receptor system on the pancreatic beta cell membrane to become less sensitive to leptin. Therefore, insulin synthesis increased. This is a condition of dysregulation of the endocrine-pancreas adipose tissue axis. If this axis is deregulated, more insulin is secreted. Increased insulin levels have a positive feedback effect on adipose tissue, stimulating fat formation. Increasing fat mass causes more leptin to be

secreted - a vicious cycle. More central obesity is accompanied by a gradual increase in glucose levels and increased insulin response to oral glucose intake. Central obesity increases posthepatic insulin, leading to increased peripheral insulin levels, ultimately causing insulin resistance. According to Fatima et al. [5], leptin levels were positively correlated with serum insulin levels ($r = 0.619$, $p < 0.001$) and HOMA-IR ($r = 0.653$, $p < 0.001$) in GDM women at 24 - 28 weeks of gestation. Yang Mei et al. [7] also noted a positive correlation between serum leptin levels with serum insulin and HOMA-IR. Our study obtained similar results to the above authors. We found that serum leptin levels had a strong positive correlation with serum insulin levels and insulin resistance in GDM patients (*Table 5*). Pregnant women with GDM who have increased serum insulin and insulin resistance have higher serum leptin levels than pregnant women without insulin resistance (*Table 3*).

There are several independent factors associated with increased serum leptin, including pre-pregnancy BMI and serum insulin levels (*Table 4, 6*). As is known, white adipose tissue is the main place to synthesize and regulate leptin secretion. Obese people often have increased BMI, so it often causes increased serum leptin. On the other hand, obesity is a disorder that facilitates the development of chronic inflammation. Excess adipose tissue and hypertrophied adipocytes lead to increased proinflammatory cytokines. The resulting chronic inflammation promotes insulin resistance and increases serum insulin. High blood insulin will increase the expression of leptin synthesis genes and increase leptin levels in the blood. Researchers have documented insulin as an important regulatory factor in the synthesis and secretion of leptin from white adipose tissue.

CONCLUSION

Serum leptin levels were higher in patients with GDM and were positively correlated with pre-pregnancy BMI, BMI, and insulin resistance at 24 - 28 weeks of gestation and before delivery. Pre-pregnancy BMI and serum insulin levels were independent factors related to increased serum leptin levels at 24 - 28 weeks of gestation and before delivery.

Limitations of the study: Small sample size; the study quantified leptin levels at 24 - 28 weeks, coinciding with the time of diagnosis of GDM, so the predictive ability of leptin could not be evaluated. Research needs to be conducted with a larger sample size, at many other times during pregnancy, such as 11 - 13 weeks, postpartum

period to clarify the role of leptin in the pathophysiology of GDM.

Acknowledgments: We would like to thank Hanoi Obstetrics Hospital for coordinating to facilitate the implementation of the study and all patients for agreeing to participate in the study. We declare to have no conflicts of interest in this research.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care.* 2011; 34(1):S11-S61.

2. Mallardo M, Ferraro S, Daniele A, Nigro E. GDM-complicated pregnancies: Focus on adipokines. *Molecular Biology Reports.* 2021; 48:8171-8180.

3. Phan Thị Tố Như, Hoàng Trung Vinh, Vũ Bá Quyết, Phạm Thế Tài. Nồng độ adiponectin huyết thanh ở đối tượng đái tháo đường thai kỳ tuần thai 24 - 28 và trước khi sinh. *Tạp chí Y Dược học Quân sự.* 2024; 49(2):205-216.

4. Goel R, Duhan N, Kumar HD. Maternal serum leptin concentration in gestational diabetes mellitus. *Imp J Interdisp Res*. 2016; 2(2):414-422.

5. Fatima S, Alam F, Chaudhry B, Khan TA. Elevated levels of chemerin, leptin, and interleukin-18 in gestational diabetes mellitus. *The Journal of Maternal-Fetal & Neonatal Medicine.* 2017; 30(9):1023-1028.

6. Andleeb J, Mehboob F, Javaid S, Ali M, Khan MI, Ain QU. Effect of Gestational Diabetes on Serum Leptin during Pregnancy and Postpartum Period: Effect of GDM on S. Leptin. *The International Journal of Frontier Sciences*. 2020; 5(1):1-5.

7. Yang M, Peng S, Li W, Wan Z, Fan L, Du Y. Relationships between plasma leptin levels, leptin G2548A, leptin receptor Gln223Arg polymorphisms and gestational diabetes mellitus in Chinese population. *Scientific reports.* 2016; 6(1):23948.

8. Florian AR, Cruciat G, Pop RM. Predictive role of altered leptin, adiponectin and 3-carboxy- 4-methyl-5-propyl-2-furanpropanoic acid secretion in gestational diabetes mellitus. *Experimental and Therapeutic Medicine*. 2021; 21(5):1-7.

9. Mosavat M, Omar SZ, Tan PC, Razif MFM, Sthaneshwar P. Leptin and soluble leptin receptor in association with gestational diabetes: A prospective case-control study. *Archives of Gynecology and Obstetrics.* 2018; 297:797-803.

MENTAL DISORDER PROPORTION OF RECRUITED INPATIENTS IN THE DEPARTMENT OF PSYCHIATRY, MILITARY HOSPITAL 103 IN 2 YEARS (2022 - 2023)

Nguyen Trong Dao[1], Hoang Thi Hao[1], Nguyen Thi Tam[1]
Pham Thi Thu[1], Dinh Viet Hung[1], Do Xuan Tinh[1], Bui Quang Huy[1]*

Abstract

Objectives: To investigate the proportion of mental disorders and military-related factors among recruited inpatients. ***Methods:*** A retrospective study on 296 recruits treated in the Department of Psychiatry, Military Hospital 103 from 2022 to 2023 compared to 126 military recruiting-naïve participants obtained from community patients treated at the same department and during the same period. Diagnostic criteria were based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition of the American Psychiatric Association. ***Results:*** Most mental disorders had the onset within 6 months of recruitment (51.7%) and were more common in lower military rank (78.3%). Out of several main mental disorders, major depressive disorder and schizophrenia were prominent (22.6% and 17.9%, respectively). However, the proportion of schizophrenia in recruited inpatients was double lesser than in community inpatients (17.9% and 51.6%, respectively). Dissociative disorders and factitious disorders were unique in recruited inpatients compared with community inpatients with mental health disorders (13.5% and 13.9% vs 0.8% and 0%, respectively). ***Conclusion:*** In the military, the proportion of mental disorders of recruited inpatients compared with community control inpatients is different not only by a higher percentage of dissociative disorders and factitious disorders but also by a smaller percentage of schizophrenia.

Keywords: Mental disorder proportion; Recruit; Inpatient.

[1]Department of Psychiatry, Military Hospital 103
[*]Corresponding author: Bui Quang Huy (bacsyhuy2003@gmail.com)
Date received: 03/02/2024
Date accepted: 27/3/2024
http://doi.org/10.56535/jmpm.v49i4.753

INTRODUCTION

Mental disorder is the leading cause of hospitalization among active-duty military personnel [1]. In recent years, the Vietnam Ministry of Defense has attempted to identify people who are already experiencing mental health problems before recruitment. The advantage of not recruiting sick troops is obvious. However, population epidemiological publications have shown that most lifetime mental disorders have childhood-adolescent onsets [2] that are initially too mild to be detected at a routine recruitment screening examination. In fact, troops developing their particular mental disorders during their military training course in the North Vietnam area have been treated in the Department of Psychiatry, Military Hospital 103. However, until now, the prevalence of their hospitalization mental health disorders during military training has not been elucidated.

Military training is a highly stressful undertaking. Recruits undergo training conditions in which they are exposed to the stress of combat force with not only intense mental and physical training but also separation from normal social supports. For some soldiers, this is a motivating prospect, but for many soldiers, this is a challenging condition. It may predispose them towards mental disorders. For example, the incidence of depressive symptoms in recruits was 45% in the US Navy [3], 25.2% in China [4], and 29.9% in Turkey [5]. A follow-up report using data collected from soldiers during basic combat training found that suicidal ideation, suicidal plans, and suicidal attempt rates were 14.1%, 2.3%, and 1.9%, respectively [6]. However, little is known about the extent to which military characteristics of recruits may inform our understanding of the risk of mental disorder onset. Therefore, we conducted this study: *To investigate the proportion of mental disorders among recruits hospitalized in the Department of Psychiatry, Military Hospital 103, and elucidate their military characteristic-related factors.*

MATERIALS AND METHODS

1. Subjects

296 recruits treated in the Department of Psychiatry, Military Hospital 103 from January 2022 to December 2023 were enrolled. The control group included 126 military recruiting-naïve participants obtained from community patients treated at the same department, during the same period, and with the same age range.

* *Inclusion criteria:* All participants met the criteria for diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of the American Psychiatric Association which has been described in detail elsewhere. In brief, we assessed the presence of several main mental disorders, including schizophrenia, major depressive disorder, bipolar disorder, acute brief psychosis, dissociative disorders, factitious disorder, anxiety disorders, game addiction, gambling, and substance-induced psychosis. Patients were diagnosed by at least two independent, certified psychiatrists.

* *Exclusion criteria:* Participants were excluded if they had a severe concurrent illness or a history of a neurological condition such as traumatic brain injury. To investigate the contribution of military training to mental disorder onset, the additional exclusion criterion of military patients was mental disorder onset before military recruiting.

2. Methods

* *Research design:* A retrospective study.

The time of mental disorders onset was measured from the new soldier recruiting time to the onset of mental disorders. The service roles of recruits were divided into support roles and battle roles. The support role included medical, informative, signal, and logistics. The battle role included the navy, land force, and air force. The military origin of recruits was divided into temporal service who were enlisted and served in the military within 2 years, and military students who studied in the military universities.

* *Statistical analysis:* Data were reported as numbers and percentages for categorical variables or mean ± standard deviation (S.D.) for continuous variables. Between-groups variances in categorical correlates were determined by the Chi-square test or Fisher's exact test. For continuous variables, the normality test (Shapiro-Wilk test) was applied to the data before performing the test. Based on the normality result, data in two sample groups were compared using an unpaired Student T-test or Mann-Whitney U test. Statistical differences were established with $p < 0.05$, $p < 0.01$, and $p < 0.001$. A two-tailed test was always performed. Statistical analysis was performed using the SPSS statistical software package (SPSS 20 for Windows; SPSS, Inc.).

3. Ethics

Participants' information was kept confidential and secure throughout the study.

RESULTS

Table 1. Characteristic of study groups.

	Soldier patients (n = 296)	**Community patients (n = 126)**	**p**
Age, mean (S.D.)	20.9 (1.4)	21.0 (1.6)	> 0.05
Gender, n (%)			
Men	296 (100)	126 (100)	
Women	0 (0)	0 (0)	
Service, n (%)			
Battle role	211 (71.3)		
Support role	85 (28.7)		
Rank, n (%)			
Master Sergeant	10 (3.4)		
Sergeant	18 (6.1)		
Corporal	36 (12.2)		
Private first class	142 (48.0)		
Private	90 (30.3)		
Time of mental disorders' onset (months), n (%)			
≤ 3	97 (32.8)		
4 - 6	56 (18.9)		
> 6	143 (48.3)		

Table 1 describes the sociodemographic and military characteristics of those included in the study. The mean age of the soldier patient group was 20.9 ± 1.4 years old. It was not significantly different compared to the community control group (21.0 ± 1.4 years old, p > 0.05). The military characteristics of the soldier patient group were as follows: Battle role (71.3%) and support role (28.7%), had

private first class or lower rank (78.3%). Out of 296 soldier patients, 32.8% had the mental disorder onset within the first 3 months of training, resulting in 51.7% of patients reporting the onset within the first 6 months of military training.

Table 2. Proportion of mental disorders.

	Scz.	MDD	BD	ABD	DD	FD	Others	Total	p
Soldiers n (%)	53 (17.9)	67 (22.6)	21 (7.1)	24 (8.1)	40 (13.5)	41 (13.9)	50 (16.9)	296 (100)	< 0.001*
Community n (%)	65 (51.6)	23 (18.5)	10 (7.9)	3 (2.4)	1 (0.8)	0 (0)	24 (19.0)	126 (100)	

*(Scz: Schizophrenia; MDD: Major depressive disorder; BD: Bipolar disorder; ABD: Acute brief disorder; DD: Dissociative disorder; FD: Factitious disorder. Others included gambling, substance-induced psychosis, and anxiety disorders; *: by Fisher's exact test).*

We then accessed the proportion of mental disorders in recruited patients (*Table 2*). Several main mental disorders were schizophrenia, major depressive disorder, bipolar disorder, acute brief delusion, dissociative disorder, factitious disorder, and others. We found that major depressive disorder had the highest proportion (22.6%), followed by schizophrenia (17.9%). In the soldier group, the proportion of factitious disorder (13.9%) and dissociative disorders (13.5%) were significantly higher than those in the community group. In contrast, schizophrenia in the community group (51.6%) was significantly higher than in the soldier group (17.9%).

Table 3. Time of mental disorders' onset.

	Scz.	MDD	BD	ABD	DD	FD	Others	Total	p
≤ 3 months n (%)	13 (13.4)	21 (21.6)	3 (3.1)	8 (8.2)	15 (15.5)	21 (21.6)	16 (16.5)	97 (100)	< 0.01
4 - 6 months n (%)	5 (8.9)	17 (30.4)	5 (8.9)	5 (8.9)	5 (8.9)	10 (17.9)	9 (16.1)	56 (100)	
> 6 months n (%)	35 (24.5)	29 (20.3)	13 (9.1)	11 (7.7)	20 (14.0)	10 (7.0)	25 (17.5)	143 (100)	

We found that during the first three months, major depressive disorder and factitious disorder had the highest percentages (21.6%). They were still the first and second most common disorders during 4 and 6 months. After 6 months of recruiting, major depressive disorder and factitious disorder became the second and third most common disorders, respectively, while schizophrenia rose to be the most common disorder. Taken together, major depressive disorder and factitious disorder mostly had the onset within the first 6 months, but schizophrenia had the onset after 6 months of recruiting (*Table 3*).

Table 4. Service roles of the soldier group.

	Scz.	**MDD**	**BD**	**ABD**	**DD**	**FD**	**Others**	**Total**	**p**
Batlle n (%)	42 (19.9)	45 (21.3)	14 (6.6)	17 (8.1)	34 (16.1)	25 (11.8)	34 (16.1)	211 (100)	> 0.05
Support n (%)	11 (12.9)	22 (25.9)	7 (8.2)	7 (8.2)	6 (7.1)	16 (18.8)	16 (18.8)	85 (100)	

Overall, around one-third of personnel held a supportive role, such as medical, logistic, or signal, whereas the majority was in battle role. In contrast to previous results, we found that the proportion of mental disorders was not significantly different between the two groups.

Table 5. Origins of soldier patients.

	Scz.	**MDD**	**BD**	**ABD**	**DD**	**FD**	**Others**	**Total**	**p**
Temporal service n (%)	47 (19.4)	59 (24.4)	17 (7.0)	21 (8.7)	34 (14.0)	27 (11.2)	37 (15.3)	242 (100)	< 0.05*
Student n (%)	6 (11.1)	8 (14.8)	4 (7.4)	3 (5.6)	6 (11.1)	14 (25.9)	13 (24.1)	54 (100)	

We found that the proportion of major depressive disorder was much higher in the temporal service group (24.4%) compared to the military student group (14.8%). Meanwhile, the factitious disorder proportion was higher in the military student group (25.9%) than in the temporal group (11.2%). The difference was statistically significant ($p < 0.05$) (*Table 5*).

DISCUSSION

Regarding the ranking of patients, the proportion of enlisted soldiers and non-commissioned officers was 78.3% and 21.7%, respectively. This suggests that soldiers with lower rank had the tendency to have mental disorders compared to those with higher rank. A previous study has shown that higher rank was considered a protecting factor from mental disorder onset [7]. Our result supported this finding. In addition, the onset of mental disorders in recruits was mostly within 6 months of recruitment. The exact mechanism of this issue is still unclear. The possibility would be that military activities, with their stressful characteristics, could make some vulnerable troops prone to mental disorders. Previous studies have also reported a significant correlation of mental disorders with length of military service, worrying about the future, poor coping skills, and inadequate social support [4, 8, 9, 10].

This is the first study reporting the proportion of mental disorders among recruited inpatients in the Vietnam military. Major depressive disorder was the most prevalent mental disorder in recruited inpatients. This finding is consistent with population studies showing that major depressive disorder is the most common mental disorder. It is notable that although schizophrenia was the second most prevalent mental disorder among recruits, its prevalence was half that of the community control group. The possible mechanism might be that the mental screening test conducted before recruitment somewhat ruled out several severe mental disorders, such as schizophrenia. It indicated the valuable effect of mental disorder screening tests before recruitment, which has been intensively conducted by the Vietnam Ministry of Defense in recent years. Interestingly, dissociative disorders and factitious disorders were unique in recruited patients compared to community patients. The cause is unknown, but dissociative disorder and factitious disorder might relate to traumatic events during childhood. Military training with its stressful conditions may thereby predispose them toward stress-related mental disorders.

The principal limitation of this study is that we focused exclusively on recruits who were hospitalized, thereby representing a very small proportion of the total number of soldiers experiencing mental disorders. However, our data was significant as it presented the extent to which mental disorders correlate with disability from military service. It is well known that mental disorder hospitalization is the burden of the military. It is significantly

associated with service-related disability separations, resulting in a reduction of the military's ability to protect the country from enemies. Furthermore, since many recruits were hospitalized during their military training, our results also point out the difficulty in screening for mental disorders before recruitment. It cannot completely identify all vulnerable people and prevent them from being recruited. Therefore, identifying soldiers who are considered healthy but have a propensity to develop chronic mental disorders should be further investigated in future studies.

CONCLUSION

In summary, major depressive disorder and schizophrenia are the most common disorders in recruited inpatients with mental disorders (22.6% and 17.9%, respectively). Factitious disorder and dissociative disorder are more specific in recruited inpatients compared to community inpatients (13.9% and 13.5% vs. 0% and 0.8%, respectively).

Acknowledgments: We extend our sincere gratitude to all nurses and participants in the Department of Psychiatry, Military Hospital 103 for their invaluable support and contribution to this research. None of the authors has any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Hoge CW, Lesikar SE, Guevara R, Lange J, Brundage JF, Engel CC Jr, Messer SC, Orman DT. Mental disorders among U.S. military personnel in the 1990s: Association with high levels of health care utilization and early military attrition. *Am J Psychiatry*. 2002 Sep; 159(9):1576-1583.

2. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustün TB. Age of onset of mental disorders: A review of recent literature. *Curr Opin Psychiatry*. 2007 Jul; 20(4): 359-364.

3. Williams RA, Hagerty BM, Yousha SM, Hoyle KS, Oe H. Factors associated with depression in navy recruits. *J Clin Psychol*. 2002 Apr; 58(4):323-337.

4. Xiong H, Zhang X, Zhang Y, Ma F, Li Y, Li L. An investigation of the prevalence of depressive symptoms in soldiers during military training. *Prev Med*. 2005 Aug; 41(2):642-645.

5. Tekbaş OF, Ceylan S, Hamzaoğlu O, Hasde M. An investigation of the prevalence of depressive symptoms in newly recruited young adult men in Turkey.

6. Nock MK, Stein MB, Heeringa SG, Ursano RJ, Colpe LJ, Fullerton CS, Hwang I, Naifeh JA, Sampson NA, Schoenbaum M, Zaslavsky AM, Kessler RC. Army STARRS Collaborators. Prevalence and correlates of suicidal behavior among soldiers: Results from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS). *JAMA Psychiatry*. 2014 May; 71(5):514-522.

7. Jones M, Sundin J, Goodwin L, Hull L, Fear NT, Wessely S, Rona RJ. What explains post-traumatic stress disorder (PTSD) in UK service personnel: Deployment or something else? *Psychol Med*. 2013 Aug; 43(8): 1703-1712

8. Biederman J, Faraone SV, Hirshfeld-Becker DR, Friedman D, Robin JA, Rosenbaum JF. Patterns of psychopathology and dysfunction in high-risk children of parents with panic disorder and major depression. *Am J Psychiatry*. 2001 Jan; 158(1):49-57.

9. Cronkite RC, Moos RH, Twohey J, Cohen C, Swindle R Jr. Life circumstances and personal resources as predictors of the ten-year course of depression. *Am J Community Psychol*. 1998 Apr; 26(2):255-280.

10. Vilhjalmsson R. Life stress, social support, and clinical depression: A reanalysis of the literature. *Soc Sci Med*. 1993 Aug; 37(3):331-342.

EVALUATION OF SOME COMMON GERIATRIC SYNDROMES AND THEIR RELATIONSHIP WITH THE QUALITY OF LIFE AMONG OLDER PATIENTS WITH KNEE OSTEOARTHRITIS

Tran Viet Luc[1,2], Nguyen Thi Thu Huong[1,2], Nguyen Trung Anh[1,2]*

Abstract

Objectives: To evaluate some common geriatric syndromes and their associations with health-related quality of life (HRQoL) among older people with knee osteoarthritis (OA). ***Methods:*** A cross-sectional descriptive study on 184 older patients with knee OA treated at National Geriatric Hospital from May to August 2022. HRQoL was assessed using the EQ-5D-5L questionnaire. Geriatric syndromes were assessed. ***Results:*** Some common geriatric syndromes in elderly knee OA patients were sleep disorders (72.3%), polypharmacy (54.3%), depression (48.4%), high risk of falls (45.1%), malnutrition and at risk of malnutrition (45.1%), IADL impairment (35.9%), and ADL impairment (32.6%). Cognitive impairment accounted for the lowest proportion (20.7%). There are significant associations between HRQoL and geriatric syndromes (malnutrition, ADL and IADL impairment, high fall risk, cognitive impairment, depression, and sleep disturbance). Patients with the presence of these geriatric syndromes have a poorer quality of life (QoL), in most aspects of HRQoL such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). ***Conclusion:*** There was a high prevalence of geriatric syndromes in older people with knee OA. Most of these geriatric syndromes were related to the aspects of the patients' QoL.

Keywords: Health-related quality of life; Elderly; Geriatric syndromes; Knee osteoarthritis.

---

[1]Hanoi Medical University

[2]National Geriatric Hospital

[*]Corresponding author: Tran Viet Luc (tranvietluc@hmu.edu.vn)

Date received: 08/01/2024

Date accepted: 20/3/2024

http://doi.org/10.56535/jmpm.v49i4.664

INTRODUCTION

Knee OA is the degeneration of cartilage: The pieces of bone and cartilage in the knee are damaged by wear and tear, the surface of the cartilage is rough, with pain inside and around the knee joint, as well as joint stiffness, and decreased range of motion, which ultimately leads to muscle weakness and is the biggest cause of functional disability [1]. Common clinical symptoms include knee pain that is gradual in onset and worse with activity, knee stiffness, and swelling, pain after prolonged sitting or resting, and pain that worsens over time.

A recent analysis of data from the National Health and Nutrition Examination Survey III (NHANES III) found that approximately 35% of women and men aged ≥ 60 years had radiographic OA of the knee. Moreover, OA is recognized as the most common cause of disability in the elderly, with approximately 85% of all knee and hip replacements being due to OA. In Vietnam, roughly 8.5% of people between the ages 40 - 49 had knee OA, compared with 30% between ages 50 - 59, and 61% over the age of 60 [2].

The term "QoL" or more specially "HRQoL" refers to the patient's sense of his or her health or well-being in the broad area of physical, psychological, and social functioning associated with an illness or its treatment. There are many studies demonstrating lower HRQoL scores in patients with knee OA compared to other patients of the same age. Increasing joint pain comorbidity [3] and radiographic disease severity [4] are inversely related to HRQoL in knee OA patients. In addition, population aging increases the occurrence of geriatric syndromes, which also contributes to reducing the QoL of elderly patients. However, data about geriatric syndromes and their associations with HRQoL are still lacking regarding the older population with knee OA in Vietnam. Thus, this study aimed: *To evaluate some common geriatric syndromes and their associations with HRQoL among older patients with knee OA.*

MATERIALS AND METHODS

1. Subjects

184 knee OA patients aged ≥ 60 years old who were being treated at the National Geriatric Hospital from May to October 2022.

* *Inclusion criteria:* Patients aged ≥ 60 years old who were diagnosed with knee OA by doctors with ACR 1986 (American College of Rheumatology) with patients > 50 years old; had the physical and cognitive abilities to do a face-to-face interview.

* *Exclusion criteria:* Patients who have severe or acute diseases, mental diseases, severe dementia, or refuse to participate in this study.

2. Methods

* *Study design:* A cross-sectional descriptive study.

- The sample size is calculated using the formula: $n = (Z_{1-\frac{\alpha}{2}})^2 \frac{p(1-p)}{d2}$

p = 0.95 (Proportion of people with osteoarthritis who have at least one of the 5 dimensions of HRQoL according to EQ-5D-5L) [5].

From the formula, the estimated sample size was 178 knee OA patients.

A total of 184 knee OA patients were recruited in our study.

* *Variables:*

General information: Age, gender, comorbidities.

- Health-related quality of life:

The European Quality of Life-5 Dimensions-5 Level scale (EQ-5D-5L) Questionnaire has two components: the EQ-5D-5L descriptive system and the EQ visual analog scale (EQ-VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/ depression), and each dimension has 5 levels: "1 = extreme problems", "2 = severe problems", "3 = moderate problems", "4 = mild problems" and "5 = no problems". The lower the mean score, the more serious the problem.

The EQ visual analog scale (EQ-VAS) records the patient's self-rated health status on the day of the interview on a 20 cm vertical analog scale with 2 endpoints: "0 = The worst health you can imagine" and "100 = The best health you can imagine".

The EQ-5D-5L was validated in the Vietnamese population [6].

- Geriatric syndromes:

Nutritional status was assessed using The Mini Nutritional Assessment Short Form (MNA-SF). The questionnaire includes 6 questions with answers, and nutritional status scores are calculated in total scores. Evaluation: Malnutrition (0 - 7 points), at risk of malnutrition (8 - 11 points), normal nutritional status (12 - 14 points).

Activities of Daily Living (ADL) were assessed using the Katz Index of Independence in Activities of Daily Living. A total score of less than 6 points classifies the person as dependent. Instrumental Activities of Daily Livings (IADLs) include 8 domains of function. A total score of less than 8 points classifies the person as dependent.

The risk of falling was assessed using the Fall risk index-21, which includes 21 yes-no questions. A total score of ≥ 10 points indicates a high risk of falling.

Cognition status was screened using the Mini-Mental State Examination (MMSE) test 59. MMSE is a 30-point questionnaire with a cut-off point of 24 points: Cognitive impairment (≤ 23 points).

Depression was assessed by the Patient Health Questionnaire (PHQ-9). The range of total score is from 0 - 27 points and is divided into 3 levels: 0 - 4 points (no depression), 5 - 14 points (mild depression), and ≥ 15 points (severe depression).

Sleep status was assessed using the Pittsburgh Sleep Quality Index (PSQI). The total score PSQI is calculated by sum of 7 components. A total score ≥ 5 points indicates a sleep disorder.

Polypharmacy was defined as the concurrent use of five or more five types of medication.

** Tools and data collection method:*

Data were collected using a research questionnaire, interviews, diagnosis tests, and medical records at the National Geriatric Hospital.

** Data processing and data analysis:*

Data coding, entry into REDCap, and analysis were done using Statistical Package for Social Science (SPSS) software (version 22.0). Descriptive statistics were adopted to examine characteristic data: Frequency, percentage, and mean. Student T-test and ANOVA were employed to compare proportions and means between groups. Statistical significance was set at $p < 0.05$.

3. Ethics

Study subjects were clearly explained the purpose of the study, and they were willing to participate. Collected data was used for research. The results of the study were proposed to improve the health of the community, not for other purposes. The authors declare to have no conflicts of interest.

RESULTS

1. General characteristics

Table 1. Socio-demographic characteristics of participants (n = 184).

Characteristics		Frequency (n)	Percentage (%)
Age group	60 - 69	66	35.9
	70 - 79	70	38.0
	≥ 80	48	26.1
Gender	Male	30	16.3
	Female	154	83.7
KOA stages	1	36	19.6
	2	82	44.6
	3	52	28.3
	4	14	7.6
KOA duration (year)	< 1	77	41.8
	1 - 5	79	42.9
	> 5	28	15.2
Comorbidities	Hypertension	106	57.6
	Diabetes	66	35.9
	Dyslipidemia	63	34.2
	Osteoporosis	47	25.5
		$\overline{X}$ ± SD	
Age (year) (Min - max)		73.6 ± 8.3 (60 - 94)	
KOA duration (year)		3.6 ± 5.3	

The mean age of participants was 73.6 years with a minimum of 60 and a maximum of 94. Participants were evenly distributed into 3 age groups, 60 - 69

patients (35.9%), 70 - 79 patients (38%), and patients over 80 years old (26.1%). The majority of study participants were female, accounting for 83.7%. Stage 2 knee OA accounted for the highest rate (44.6%). Most patients have had knee OA for less than 5 years. Hypertension was the co-morbidity with the highest rate (57.6%).

2. Characteristics of some common geriatric syndromes

Table 2. Common geriatric syndromes among older patients with knee OA (n = 184).

Geriatric syndromes		Frequency (n)	Percentage (%)
Nutritional status	Malnutrition	11	6.0
	At risk of malnutrition	72	39.1
	Normal nutritional status	101	54.9
ADL dependence		60	32.6
IADL dependence		66	35.9
High risk of falls		83	45.1
Cognitive impairment		38	20.7
Depression	Severe depression	7	3.8
	Mild depression	82	44.6
	None	95	51.6
Sleep disorder		133	72.3
Polypharmacy	≥ 5 types	100	54.3

The rate of some common geriatric syndromes in elderly knee OA patients was 72.3% for sleep disorders, 54.3% for polypharmacy, 48.4% for depression, 45.1% for high risk of falling, 45.1% for malnutrition and at risk of malnutrition, 35.9% for IADL impairment, and 32.6% for ADL impairment. Cognitive impairment accounted for the lowest proportion (20.7%).

3. Characteristics of HRQoL

Table 3. Health-related quality of life (EQ-5D-5L) among older patients with knee OA (n = 184).

	Mobility		Self-care		Usual activities		Pain/ Discomfort		Anxiety/ Depression	
	n	%	n	%	n	%	n	%	n	%
No problems	22	12	57	31	44	23.9	17	9.2	44	23.9
Mild problems	77	41.8	76	41.3	80	43.5	81	44	104	56.5
Moderate problems	66	35.9	40	21.7	52	28.3	72	39.1	26	14.1
Severe problems	17	9.2	8	4.3	5	2.7	12	5.6	10	5.4
Extreme problems	2	1.1	3	1.6	3	1.6	2	1.1	0	0
					$\overline{X}$ ± SD					
EQ-VAS					63.2 ± 15.8					

The prevalences of participants who reported moderate or severe problems in these dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression were 45.1%, 26.0%, 31.0%, 44.7%, and 19.5%, respectively. The mean EQ-VAS score was 63.2.

4. The association between HRQoL and geriatric syndromes

Table 4. The association between HRQoL and geriatric syndromes (n = 184).

Geriatric syndrome	n	Responding to a problem					EQVAS score $\overline{X}$ ± SD
		Mobility	Self-care	Usual activities	Pain/ Discomfort	Anxiety/ Depression	
Nutritional status							
Malnutrition	11	3.1	3.1	3.3	2.9	3.1	50.0 ± 21.9
At risk of malnutrition	72	3.6	3.8	3.8	3.6	3.9	62.9 ± 13.8
Normal nutrition status	101	3.5	4.1[a]	3.9	3.6[a]	4.1[b]	64.8 ± 15.9
ADL							
Normal	124	3.7	4.2	4.1	3.7	4.1	64.5 ± 16.4
Impaired	60	3.1[b]	3.4[b]	3.3[b]	3.3[b]	3.8[a]	60.6 ± 14.4
IADL							
Normal	118	3.7	4.3	4.1	3.7	4.1	64.5 ± 16.6
Impaired	66	3.2[b]	3.4[b]	3.4[b]	3.3[b]	3.8[a]	61.0 ± 14.3
Fall risk							
Low risks	101	3.8	4.4	4.2	3.7	4.2	67.2 ± 15.5
High risks	83	3.3	3.5[b]	3.5[b]	3.4	3.8	58.4 ± 14.9
Cognitive status							
Normal	146	3.6	4.1	4.0	3.5	4.1	64.1 ± 16.0
Impaired	38	3.3	3.3[b]	3.3[b]	3.6	3.8[a]	59.7 ± 14.7
Depression							
None	95	3.7	4.2	4.1	3.7	4.4	66.9 ± 14.0
Mild	82	3.4	3.7	3.7	3.5	3.7	60.7 ± 14.4
Severe	7	3.1	3.3[b]	3.1[b]	3.57[b]	2.4[b]	41.4 ± 20.3[c]
Quality of sleep							
Normal	51	3.2	3.7	3.7	3.4	4.2	65.7 ± 10.7
Sleep disorder	133	3.7[b]	4.1[b]	3.9	3.6[b]	3.9	62.3 ± 17.3
Comorbidities							
No	7	4.1	4.3	4.3	4.1	4.7	67.9 ± 6.4
Yes	177	3.5	3.9	3.8	3.5	4.0	63.0 ± 16.1
Polypharmacy							
≥ 5 types	84	3.6	4.0	3.9	3.6	4.0	62.9 ± 16.5
< 5 types	100	3.5	3.9	3.8	3.5	4.0	63.5 ± 15.4

(a: $p < 0.05$; b: $p < 0.01$; c: Kruskall Wallis, $p < 0.05$).

There was a significant association between HRQoL and MNA-SF, especially in self-care, pain/discomfort, and anxiety dimensions. Patients who had normal nutrition status got better QoL than the others. Patients who had normal ADL or IADL also had better QoL than the impaired ones. Patients with low fall risks had better QoL than patients with high fall risks, especially in self-care and usual activities. Surveyed participants who had problems with cognitive impairment had a worse QoL than others whose cognitive condition is normal, especially in self-care, usual activities, and anxiety/depression dimensions.

Regarding depression status, there was a significant difference in QoL, the more severe the depression status, the worse the QoL. The more severe the patient's risk of depression, the lower the EQ-VAS score.

There was also a significant difference between QoL and sleep quality in mobility, self-care, and anxiety/depression dimensions. There was no significant difference between QoL and the patient's comorbidities and polypharmacy status.

DISCUSSION

Our study showed the characteristics of geriatric syndromes and their association with HRQoL among older patients with knee OA at the National Geriatric Hospital. In this study, participants who had sleep disorders accounted for the highest proportion with 72.3%. Our results were higher than that of a previous study which showed that 64.9% had deteriorated sleep quality [7]. This difference may be due to the age of participants in the study. The mean age of participants in our study (73.6 ± 8.3 years old) was higher than that in Zheng's study (63.3 ± 7.1 years).

The number of patients using polypharmacy accounted for a higher rate of 54.3%. This is suitable for older people who often have many co-morbidities, so the rate of using multiple drugs at the same time is higher. In our study, some common comorbidities were hypertension (57.6%), diabetes (35.9%), dyslipidemia (34.2%), and osteoporosis (25.5%). This result is similar to the study of Heuberger et al. which showed that 51.1% of the participants used 5 or more drugs [8]. This similarity can be explained that the elderly have many comorbidities, so the use of polypharmacy is understandable.

According to the PHQ-9 scale, the minority of patients suffering from severe depression accounted for 3.8% and 44.6% of patients had mild depression. The results of our study

were different from those of Sugai et al. (2018) in Japan [9]. During a 2-year follow-up of 573 patients with OA aged 65 years and older to evaluate the relationship between knee OA and functional decline and depressive symptoms using the GDS scale, the results showed that 11.9% of patients showed symptoms of depression. The above difference can be explained because our study is a cross-sectional study, while Sugai's study is a longitudinal follow-up study for 2 years. This was an epidemiological study in the community of patients with primary knee OA in Japan.

Nearly half (45.1%) of the participants were presented as high risk of falls. The rate of history of falls within 1 year in our study was lower than in the study of Van Schoor et al. (2020) with 27.7% of patients having a fall once and 9.8% having two falls in the past year in subjects with knee or hip OA [10]. Thus, this could be explained by the fact that this study was conducted in the older population and they had problems with their knee.

People with normal nutritional status accounted for the highest proportion, 54.9% (n = 68). The percentage of patients with malnutrition and at risk of malnutrition were 6.0% and 39.1%, respectively considering the importance of the association among nutritional problems and HRQoL in caring for and promoting the welfare of the elders.

Most subjects had difficulty performing daily living activities and needed support at different levels. The proportion of dependence on the ADL scale was 32.6%, and on the IADL scale was 35.9%. Our results were higher than those reported by Wang et al. with 23.31% of participants having difficulty with ADL/IADL [11]. The difference is because their research subjects are the elderly, who had at least 4 years of knee OA.

In our study, HRQoL was assessed using the EQ-5D-5L. The EQ-5D-5L was validated and can be used in the Vietnamese population. Our results revealed that all these characteristics except polypharmacy affected 1 to 5 dimensions of HRQoL. It all was a negative correlation, which means that the more geriatric characteristics patients experienced, the lower the QoL score patients got. For example, there was a significant difference between QoL and MNA-SF in self-care, pain/discomfort, and anxiety dimensions. Patients who had normal ADL or IADL also had better QoL than the impaired ones. Regarding depression status, there was a significant difference in QoL, the more severe the depression status, the worse the QoL. It was similar to another

study, ADL/IADL difficulty and severe depressive symptoms affected the patient's QoL ($p < 0.01$) [11]. Patients with low fall risks had better QoL than patients with high fall risks, especially in self-care and usual activities. There was also a significant difference between QoL and sleep quality in mobility, self-care, and anxiety/depression dimensions. There was no significant difference between QoL among the patient's polypharmacy status. From all these results, we can understand that each geriatric characteristics such as nutrition status, mental health, or daily activities, etc., all have certain effects on QoL, it can be similar or different to other studies depending on sample size, living conditions, or research subjects.

CONCLUSION

There was a high prevalence of geriatric syndromes in older people with knee OA. Most of these geriatric syndromes were related to the aspects of patients' QoL. This suggests that screening for geriatric syndromes is essential in this population.

REFERENCES

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: A review of community burden and current use of primary health care. *Ann Rheum Dis*. 2001; 60(2):91-97. DOI:10.1136/ard.60.2.91.

2. Ho-Pham LT, Lai TQ, Mai LD, Doan MC, Pham HN, Nguyen TV. Prevalence of radiographic osteoarthritis of the knee and its relationship to self-reported pain. *PLoS One*. 2014; 9(4):e94563. Published 2014 Apr 10. DOI:10.1371/journal.pone.0094563.

3. Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: Data from the Osteoarthritis Initiative. *Rheumatology (Oxford)*. 2013; 52(3): 543-546. DOI:10.1093/rheumatology/kes314.

4. Muraki S, Akune T, Oka H, et al. Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study. *Osteoarthritis Cartilage*. 2010; 18(9):1227-1234. DOI:10.1016/j.joca.2010.06.001.

5. Martín-Fernández J, García-Maroto R, Bilbao A, et al. Impact of lower limb osteoarthritis on health-related quality of life: A cross-sectional study to estimate the expressed loss of utility in the Spanish population. *PLoS One*. 2020; 15(1):e0228398. Published 2020 Jan 24. DOI:10.1371/journal.pone.0228398.

6. Mai VQ, Sun S, Minh HV, et al. An EQ-5D-5L Value Set for Vietnam. *Qual Life Res*. 2020; 29(7):1923-1933. DOI:10.1007/s11136-020-02469-7

7. Zheng S, Tu L, Cicuttini F, et al. Depression in patients with knee osteoarthritis: Risk factors and associations with joint symptoms. *BMC Musculoskelet Disord*. 2021; 22(1):40. Published 2021 Jan 7. DOI:10.1186/s12891-020-03875-1.

8. Heuberger RA, Caudell K. Polypharmacy and nutritional status in older adults: A cross-sectional study. *Drugs Aging*. 2011; 28(4):315-323. DOI:10.2165/11587670-000000000-00000.

9. Sugai K, Takeda-Imai F, Michikawa T, Nakamura T, Takebayashi T, Nishiwaki Y. Association between knee pain, impaired function, and development of depressive symptoms. *J Am Geriatr Soc*. 2018; 66(3):570-576. DOI:10.1111/jgs.15259.

10. van Schoor NM, Dennison E, Castell MV, et al. Clinical osteoarthritis of the hip and knee and fall risk: The role of low physical functioning and pain medication. *Semin Arthritis Rheum*. 2020; 50(3):380-386. DOI:10.1016/j.semarthrit.2020.02.006.

11. Wang L, Lu H, Chen H, Jin S, Wang M, Shang S. Development of a model for predicting the 4-year risk of symptomatic knee osteoarthritis in China: A longitudinal cohort study. *Arthritis Res Ther*. 2021; 23(1):65. Published 2021 Feb 26. DOI:10.1186/s13075-021-02447-5.

SOME FACTORS RELATED TO FATIGUE STATUS IN ELDERLY POST-STROKE PATIENTS

Vu Thi Diu[1], Tran Thi Ha[3], Nguyen Xuan Thanh[2]*
Tran Viet Luc[2,3], Vu Thi Thanh Huyen[2,3]

Abstract

Objectives: To identify factors related to fatigue status in elderly post-stroke patients. ***Methods:*** A cross-sectional study on 157 patients those ages ≥ 60, diagnosed with stroke (according to the World Health Organization - WHO) and examined or treated as inpatients and outpatients at the National Geriatric Hospital, from July to November 2021. Data were collected using designed tools including characteristics of these patients. Entered data on Redcap and used SPSS version 22.0 for analysis. ***Results:*** Relevant factors affecting fatigue in elderly patients after stroke were physical activity daily living, cognitive impairment by Mini-Mental State Examination (MMSE), sleep disturbance by Pittsburgh Sleep Quality Index (PSQI), depression, and malnutrition. Factors that increased the risk of fatigue were age ≥ 60, using medication total, and cognitive decline. ***Conclusion:*** Early detection by performing the Fatigue Severity Scale (FSS) test to screen for fatigue in elderly post-stroke patients can provide appropriate treatment that helps improve treatment effectiveness as well as patients' quality of life.

Keywords: Fatigue; Older patients; Post-stroke.

INTRODUCTION

Stroke is a cardiovascular disease and is defined by the WHO as a clinical syndrome, including "signs of brain dysfunction (focal or general) that develop rapidly, persist for 24 hours or more, or lead to death, with no identifiable cause other than a vascular etiology".

[1]19-8 Hospital, Ministry of Public Security
[2]National Geriatric Hospital
[3]Hanoi Medical University
[*]Correspondence: Vu Thi Diu (vudiu198@gmail.com)
Date received: 16/12/2023
Date accepted: 20/3/2024
http://doi.org/10.56535/jmpm.v49i4.630

Stroke is the third leading cause of death after cancer and cardiovascular disease in the United States, but second worldwide. In France, the mortality rate of stroke is 12% of the elderly and it is the leading cause of death in old age. According to the American Heart Association, there are about 700,000 strokes every year, with 163,000 deaths from stroke [1]. The incidence of stroke fluctuates significantly over a lifetime, for example, the incidence is about 10 - 20 per 10,000 people aged 55 - 64, while this rate rises to 200 per 10,000 people over the age of 85 [1]. In Vietnam, according to information from the Ministry of Health, there are about 200,000 cases of stroke each year, which is the leading cause of death, with a rate of 10 - 20%, many times higher than some other common causes of death.

Fatigue is a general psychophysiological phenomenon that diminishes the ability of the individual to perform a particular task by altering alertness and vigilance, together with the motivational and subjective states that occur during this transition. Mental fatigue is a common symptom following Traumatic Brain Injury (TBI), or stroke. In the case of long-lasting mental fatigue, mental fatigue could be one important factor that keeps people from returning to the full range of activities they pursued prior to their injury with work, studies and social activities. According to Schillinger and Becker, post-stroke fatigue (PSF) can be defined as "a subjective experience of protracted or recurrent tiredness and a reduced capacity for mental and/or physical activity". PSF is a state that is characterized by exhaustion and a considerable depletion of energy that often occurs without prior physical or mental exertion [2].

It is uncertain whether socio-demographic factors such as age, gender, marital status, living situation (living alone or not), education, and returning to paid work are associated with PSF [2]. Previous research findings are also contradictory in terms of the association between PSF and neuropsychological factors, such as the stroke location, type, and severity [2]. Currently, research on fatigue of patients after stroke is limited; there have been few studies on PSF in Vietnam, and these studies often focus on the relationship between depression and other factors of patients after stroke. Post-stroke fatigue acts only as

a risk factor and influences of depression in post-stroke patients. Therefore, we conducted this research: *To identify some factors related to fatigue status in elderly post-stroke patients*.

MATERIALS AND METHODS

1. Subjects

157 patients who were diagnosed with stroke (according to WHO), aged ≥ 60 years old, examined or treated at National Geriatric Hospital.

* *Inclusion criteria:* Age ≥ 60 years; diagnosed with stroke (according to WHO) by doctors and were being treated as inpatients and outpatients at the National Geriatric Hospital; had the physical and cognitive abilities (evaluated by MMSE) to do a face-to-face interview; patients and families agreed to participate in research.

* *Exclusion criteria:* Patients with a history of stroke more than 7 years; cases of dementia severity, inaccessible; aphasia case limiting in describing symptoms; pharyngeal paralysis, severe quadriplegia limits communication; history of pre-stroke psychosis: schizophrenia, major depression, bipolar disorder.

* *Setting and time:* Patients were diagnosed and treated at National Geriatric Hospital from July 12th to November 12th, 2021.

2. Methods

* *Study design:* A cross-sectional study.

* *Sample size and sampling:*

Sampling: Convenience sampling.

The sample size is calculated using the formula: $n = (Z_{1-\frac{\alpha}{2}})^2 \frac{p(1-p)}{d^2}$

n: Study sample size;

α: Statistical significance level, with α = 0,05; $(Z_{1-\alpha/2}) = 1,96$

p = 0.641 (Prevalence of PSF among post-stroke patients in Schepers's study in 2006) [3].

d = expected error (d = 0.075). From the formula, the estimated sample size was 157 post-stroke older patients. The number of post-stroke older patients in our study was 157.

* *Tools and data collection method:* General information including date of interview, contact information, full name, age, gender, level of education, occupation, living status, and living area.

Data were collected using designed tools included: MMSE: A score of 24 - 30 is normal cognitive status, less than 24 points indicates cognitive decline; PSQI: Total score PSQI is calculated by sum of 7 components,

the maximum of a normal sleep is less than 5, if result is more than or equal 5, the participant will get poor sleep; Mini Nutritional Assessment Short Form (MNA-SF): 12 - 14 points (normal), 8 - 11 points (risk of malnutrition), and 0 - 7 points (malnutrition); Barthel Index (BI) for Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) include dependent and independent, Patient Health Questionnaire - 9 (PHQ-9): Interpretation of total score depression severity: 1 - 4 (minimal depression), 5 - 9 (mild depression), 10 - 14 (moderate depression), 15 - 19 (moderately severe depression), and 20 - 27 (severe depression).

Fatigue assessment: Using FSS to assess fatigue status of the participant. The time to evaluate FFS is after the patient has recovered and can be interviewed. Performing: The original FSS is a nine-item unidimensional questionnaire developed by Krupp, LaRocca, Muir-Nash, and Steinberg (1989). The mean score of the items is used as the FSS score. FSS consists of 9 items, each is scored using a Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). The participants were asked to complete the version of FSS, regarding the previous week. Total score is the sum of these items divided by the number of items. Evaluation: High scores indicate high levels of fatigue. A total score of less than 36 suggests that you may not be suffering from fatigue. A total score of 36 or more suggests that you may need further evaluation by a physician.

* *Data processing and data analysis:* The process of data recording, entries into Redcap and analyzed by using Statistical Package for Social Science (SPSS) software version 22 with statically $p < 0.05$. Descriptive statistics were adopted to examine characteristic data: Frequency, percentage, mean. Inferential statistics was done to perform comparisons between groups, using χ^2.

3. Ethics

All data collected was used for research. The results of the study were proposed for improving the health of the community, not for other purposes, and to ensure all ethical issues in biological research. We are committed to have no conflicts of interest in this research.

RESULTS

A total number of 157 patients were recruited for the study from July 12th to November 12th, 2021. Results of this study presented in detail in below.

Table 1. The association between fatigue status and demographic characteristics (n = 157).

Related factors		FSS		p
		Normal n (%)	Fatigue n (%)	
Gender	Male	27 (67.5)	56 (47.9)	0.024
	Female	13 (32.5)	61 (52.1)	
Age	< 60	5 (12.5)	4 (3.4)	0.048
	≥ 60	35 (87.5)	113 (96.6)	
Marital status	Married	36 (90)	98 (83.8)	0.246
	Single/widowed/divorced	4 (10)	19 (16.2)	
Education level	Secondary school and below	19 (47.5)	72 (61.5)	0.266
	High school	9 (22.5)	22 (18.8)	
	College/university and above	12 (30)	23 (19.7)	

Of all male participants, there were 32.5% patients with normal and 47.9% with fatigue status. In terms of age, the age group ≥ 60 had 96,6% with fatigue status, < 60 years old had 3,4% with fatigue status. The difference between these age groups was statistically significant ($p < 0.05$). There were no significant differences between FSS and material status and education level ($p > 0.05$).

Table 2. The association between comorbidities, medication and FSS (n = 157).

Variable		FSS score		p
		Normal n (%)	Fatigue n (%)	
Comorbidities	≤ 4	32 (80)	78 (66.7)	0.080
	> 4	8 (20)	39 (33.3)	
Medication total	≤ 5	28 (71.8)	49 (41.9)	0.001
	> 5	11 (28.2)	68 (58.1)	

The number of comorbidities ≤ 4 had a fatigue rate of 66.7%, > 4 had a fatigue rate of 33.3%. There was no significant difference between these 2 groups

($p > 0.05$). A total number of medications ≤ 5 had a fatigue rate of 41.9%; > 5 had 58.1%. The difference between these groups is statistically significant ($p < 0.05$).

Table 3. The association between quality of life and FSS score (n = 157).

Quality of life		FSS		p
		Normal n (%)	Fatigue n (%)	
Physical activity daily living (ADL)	Dependent	14 (35)	76 (65)	0.001
	Independent	26 (65)	41 (35)	
Instrument activities of daily living (IADL)	Dependent	31 (77.5)	95 (81.2)	0.383
	Independent	9 (22.5)	22 (18.8)	

In terms of physical activity daily living (BI), patients with dependent had 65% fatigue; patients with independent had 65% fatigue, the difference between these age groups was statistically significant ($p < 0.05$). Instrument activities of daily living (IADL) in dependent patients had 81.2% fatigue; independent patients had 18.8% fatigue. There were no significant differences ($p > 0.05$).

Table 4. Association between mental health status and FSS (n = 157).

Characteristics		FSS		p
		Normal n (%)	Fatigue n (%)	
MMSE	Normal	22 (55)	40 (34.2)	0.017
	Cognitive decline	18 (45)	77 (65.8)	
PSQI	Good sleep	13 (32.5)	16 (13.7)	0.01
	Poor sleep	27 (67.5)	101 (86.3)	

MMSE: Patients with MMSE normal had 35.2% fatigue; patients with cognitive decline had 65.8% fatigue. Patients with good sleep had 13.7% fatigue; patients with poor sleep had 86.3% fatigue. The difference between these age groups was statistically significant ($p < 0.05$).

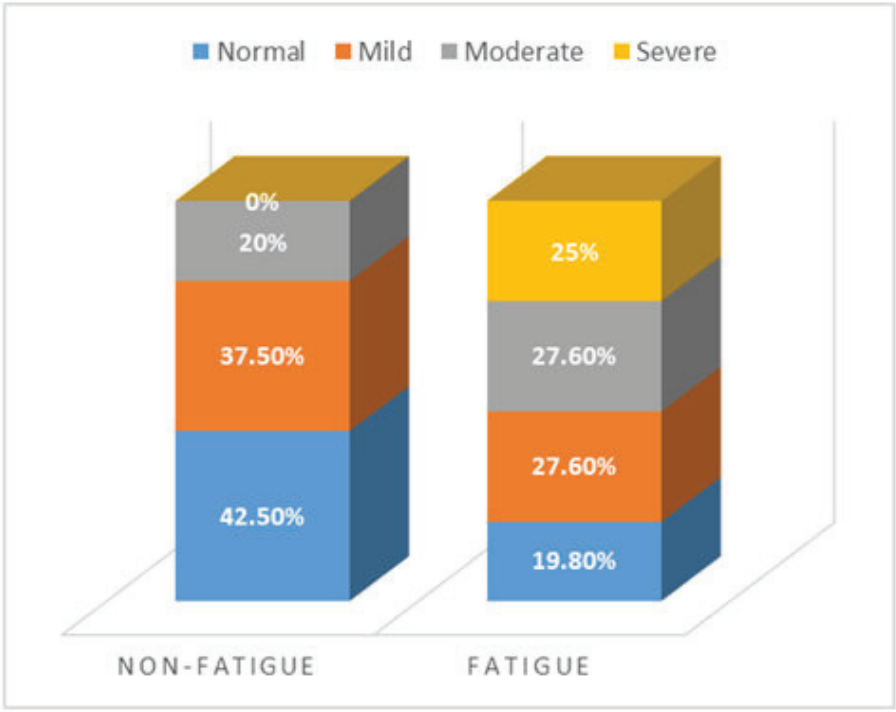


Figure 1. The association between depressive symptoms and FSS (n = 157).

Normal patients had 19,8% fatigue, patients with mild depressive symptoms had 19,8% fatigue; patients with mild depressive symptoms had 27,6% fatigue; patients with moderate depressive symptoms had 27,6% fatigue; patients with mild depressive symptoms had 25% fatigue.

Table 5. The association between nutrition status and FSS (n = 157).

Nutrition status		FSS		p
		Normal n (%)	Fatigue n (%)	
MNA-SF	Normal	7 (17.5)	6 (5.1)	0.014
	Risk of Malnutrition	24 (60)	63 (53.8)	
	Malnutrition	9 (22.5)	48 (41)	

Patients at risk of malnutrition and malnutrition with fatigue were 53.8% and 41%. The difference between these groups was statistically significant ($p < 0.05$).

Table 6. Multivariable regression models on some factors related to fatigue in elderly post-stroke patients.

Characteristic	FSS			
	OR	95%CI		p
		Lower	Upper	
Age (> 60 years)	3.447	0.813	14.620	0.093
Gender (female)	2.121	0.960	4.683	0.063
Medication	3.430	1.532	7.679	0.003
Barthel index (dependent)	0.367	0.138	0.978	0.045
IADL (dependent)	0.277	0.085	0.897	0.032
MMSE (cognitive impairment)	1.226	0.473	3.179	0.675
PSQI (poor sleep)	3.039	1.304	7.083	0.010
PHQ-9 (depression)	2.989	1.376	6.490	0.006
MNA-SF (malnutrition)	3.924	1.233	12.488	0.021

The risk factors for fatigue in patients after stroke were using more than 5 drugs (OR 3.43, 95%CI: 1.532 - 7.679, p = 0.003); dependence in daily activities assessed by Bethel Index scale (OR 0.367, 95%CI: 0.138 - 0.978, p = 0.045) and IADL scale (OR 0.277, 95%CI: 0.085 - 0.897, p = 0.032); patients experiencing depression (OR 2.989, 95%CI: 1.376 - 6.490, p = 0.006), participants had poor sleep (OR 3.039; 95%CI: 1.304 - 7.083; (p = 0.010) and those at risk and/or already malnourished (OR 3.924, 95%CI: 1.233 - 12.488, p = 0.021). There was no statistical significance between fatigue and age, gender and cognitive impairment with p > 0.05.

DISCUSSION

1. The association between post-stroke fatigue and demographic characteristics and comorbidities disease

Complaints of difficulty sleeping increase with age. In this study, there was no statistically significant relationship between fatigue and age. This is similar to an earlier study of 1306 patients in Switzerland between 2005 and 2007 [4]. We found no significant association of FSS with educational attainment and marital status. This is similar to previous research in Sweden. In addition, in the Swedish study, there was a weak association between FSS and gender: The mean difference in FSS in females compared with males was 0.21 ($p = 0.04$); but in this study, no association was found between gender and FSS, with $p = 0.063$ [3]. Differences in results may be explained by differences between sample size, mean age, and cross-sectional studies. In this study, no statistical significance was found between comorbidities and fatigue, with $p > 0.05$. This is in contrast to the study of Kjeverud et al., a study of fatigue in 115 patients after stroke showed that fatigue was also associated with more pre-existing comorbidities ($p = 0.0180$) [5]. Differences in results may be explained by differences between sample size, mean age, and cross-sectional studies. The use of multiple drugs in combination also affects the movement and mental health of the patient related to the side effects of the drug. In this study, we found that the combined use of > 5 drugs had an effect on fatigue, which is a statistically significant relationship with $p = 0.003$.

2. The association between post-stroke fatigue and quality of life

Research by Badaru et al. showed that PSD alone ($p = 0.002$) and both PSF and PSD ($p = 0.02$) were significantly associated with ADL, while PSF alone was not ($p = 0.233$). PSD alone ($p = 0.001$) and both PSF and PSD ($p = 0.001$) significantly negatively affect IADL, while PSF alone had no significant effect ($p = 0.2$) [6]. This is different from our research results, when using the multivariable regression method, there is a significant correlation between fatigue and functional independence in activities of daily living (BI and IADL) with p times of 0.045 and 0.032, respectively. This difference can be explained by sample size and research subjects.

3. The association between post-stroke fatigue and mental health

Out of a total of 157 participants, the percentage of patients with cognitive impairment was 60.5%; the percentage of patients with cognitive impairment with fatigue is 65.8%, after using the multivariate regression method, there is no significant relationship between cognitive impairment and fatigue in post-stroke patients, with p = 0.675. This is in contrast to a previous study in France on the association between fatigue and cognitive decline in 6-month stroke patients, which found a significant association between fatigue and cognitive impairment, with p < 0.001 [7]. Differences in results may be explained by differences between sample size and research objects.

The relationship between fatigue after stroke and sleep disturbance is statistically significant (p < 0.05) because the more sleep disturbances increase, the more physically and mentally the patient is affected. This leads to patients' fatigue getting worse. In the study of Nadal-Nicolás et al. on women with Fibromyalgia, correlations were shown showed a relationship between fatigue and sleep variables (R = 0.411; p = 0.046) [8]. In addition, the study by Badaru et al. also showed a significant association between rates of depression, fatigue, and reduced quality of life [6]. There is a strong link between mental health and fatigue. Careful assessment is required for timely intervention and support, minimizing the impact and improving the patients' quality of life.

4. The association between post-stroke fatigue and nutritional status

In this study, the percentages of patients at risk of malnutrition and malnutrition with fatigue were 53.8% and 41%, respectively. We found a significant relationship between fatigue and the risk of malnutrition in elderly patients after stroke. This is consistent with the results of a previous study in Tehran, which studied malnutrition and some related factors in elderly people living in nursing homes in Tehran. In 119 elderly people over 65 years old, the results of the statistical analysis of data showed a positive relationship between malnutrition and fatigue (p < 0.0001) [9].

5. Multivariable regression association between related factors and post-stroke fatigue

This study indicated that the total amount of medication the patient

was taking, functional status, sleep disturbance, depression, and malnutrition were independently associated features in patients with post-fatigue symptoms. In patients with fatigue, the percentage of patients on maintenance use of > 5 drugs was 1.387 times higher than in patients using 5 or less than 5 drugs, 95%CI: 1.532 - 7.679, p = 0.003. In addition, fatigue also affects dependence on activities and tools of daily living; the proportion of patients dependent on daily living with fatigue increased 1.8536 times (95%CI: 0.138 - 0.978, p = 0.045), and the proportion of patients dependent on tools of daily living was 4.318 times higher than that of patients dependent on tools for daily living for the independents (95%CI: 0.085 - 0.897, p = 0.032). Besides, the proportion of patients with poor sleep was 4.405 times higher than that of patients with good sleep (95%CI: 1.304 - 7.083, p = 0.010). The proportion of patients with signs of depression was 2.83 times higher than those without signs of depression (95%CI: 1.376 - 6.490, p = 0.006). Not only that, the proportion of patients at risk of malnutrition was 11.07 times higher than that of patients without risk of malnutrition (95%CI: 1.233 - 12.488, p = 0.021).

CONCLUSION

After evaluating associated factors among 157 elderly post-stroke patients at the National Geriatric Hospital, the results of the statistical analysis indicated the following remarkable findings: Relevant factors affecting fatigue in elderly patients after stroke are physical activity daily living, cognitive impairment by MMSE, sleep disturbance by PSQI, depression, and malnutrition. Factors that increase the risk of fatigue are age over 60, medication total, and cognitive decline. We suggest the following recommendations: Early detection by performing the FSS test to screen for fatigue in elderly post-stroke patients, thereby providing appropriate treatment, can help improve treatment effectiveness as well as patients' quality of life.

Acknowledgment: We would like to thank all participants in this study and medical staff at National Geriatric Hospital.

REFFERENCES

1. Cao Phi Phong, Nguyễn Bá Thắng. Đột quỵ và các bệnh mạch máu não khác. Điều trị bệnh thần kinh. Đại học Quốc Gia Thành phố Hồ Chí Minh. 2015; 52-96.

2. Schillinger A, Becker F. Fatigue in patients following traumatic brain injury and stroke. *Tidsskr Den Nor Laegeforening Tidsskr Prakt Med Ny Raekke*. 2015;135(4):331-335. DOI: 10.4045/ tidsskr.14.0271.

3. Schepers VP, Visser-Meily AM, Ketelaar M, Lindeman E. Poststroke fatigue: Course and its relation to personal and stroke-related factors. *Arch Phys Med Rehabil*. 2006; 87(2): 184-188. DOI:10.1016/j.apmr.2005.10.005.

4. Valko PO, Bassetti CL, Bloch KE, Held U. Baumann CR. Validation of the Fatigue Severity Scale in a Swiss Cohort. *Sleep*. 2008; 31(11): 1601-1607.

5. Kjeverud A, Østlie K, Schanke AK, Gay C, Thoresen M, Lerdal A. Trajectories of fatigue among stroke patients from the acute phase to 18 months post-injury: A latent class analysis. *PLOS ONE*. 2020; 15(4):e0231709. DOI: 10.1371/journal. pone.0231709.

6. Badaru U m, Ogwumike O, Adeniyi A, Olowe O. Variation in functional independence among stroke survivors having fatigue and depression. *Neurol Res Int*. 2013; 2013:842980. DOI: 10.1155/2013/842980.

7. Graber M, Garnier L, Duloquin G, et al. Association between fatigue and cognitive impairment at 6 months in patients with ischemic stroke treated with acute revascularization therapy. *Front Neurol*. 2019; 10:931. DOI:10.3389/ fneur.2019.00931.

8. Nadal-Nicolás Y, Rubio-Arias JÁ, Martínez-Olcina M, Reche-García C, Hernández-García M, Martínez-Rodríguez A. effects of manual therapy on fatigue, pain, and psychological aspects in women with fibromyalgia. *Int J Environ Res Public Health*. 2020; 17(12): E4611. DOI: 10.3390/ ijerph17124611.

9. Kushkestani M, Parvani M, Kiandokhtmoradi, Moghadassi M. Malnutrition is associated with cognitive function, tiredness and sleep quality in elderly living nursing home. *J Aging Sci*. 2020; 8. DOI: 10.35248/2329-8847. 20.08.233.

SPINAL ANESTHESIA WITH ROPIVACAINE FOR LOWER LIMB SURGERY

Dang Chi Binh[1], Vo Van Hien[2]*

Abstract

Objectives: To evaluate the anesthetic effect and impacts on respiration, circulation, and some undesirable consequences of spinal anesthesia with ropivacaine in patients who are scheduled for lower limb surgery. ***Methods:*** A clinical interventional study, a randomized group with comparative analysis on 70 patients who were indicated for lower limb surgery at the Department of Surgery - Anesthesia and Resuscitation, Military Hospital 121, Military Region 9 (Can Tho province) from November 2022 to June 2023, randomly divided into 2 groups: Group R (35 patients treated with ropivacaine) and group B (35 patients treated with bupivacaine). Evaluate and compare the criteria of anesthetic effects, intraoperative movement inhibition, and postoperative pain relief. Record the effects of some criteria on circulation, respiration, and unwanted effects related to the anesthetic method. ***Results:*** All patients in both groups achieved a good level of anesthesia. In lower limb surgery, the effective pain relief time following spinal anesthesia with ropivacaine was 145.09 ± 7.03 minutes, and the movement inhibition duration was 97.60 ± 7.10 minutes. The effects of ropivacaine on circulation and respiration were minimal, and its side effects, such as bradycardia (5.71%), hypotension (2.86%), and shivering (2.86%), were mild, temporary, and readily managed. ***Conclusion:*** Ropivacaine provided effective and safe spinal anesthesia for lower limb surgery, and short-term mobility, and provided pain relief postoperatively. It caused some modest, temporary side effects that were easily managed, but it had little influence on breathing and circulation.

Keywords: Spinal anesthesia; Ropivacaine; Bupivacaine; Lower limb surgery.

---

[1]Military Hospital 121, Military Region 9

[2]Vietnam Military Medical University

[*]Corresponding author: Vo Van Hien (vanhien103@gmail.com)

Date received: 04/01/2024

Date accepted: 12/3/2024

http://doi.org/10.56535/jmpm.v49i4.659

INTRODUCTION

Spinal anesthesia is often applied for abdominal and lower abdominal surgeries, urology, obstetrics and gynecology, and orthopedic surgeries. The advantage of the spinal anesthetic approach is that it has a high success rate, does not require difficult techniques or equipment, and ensures effective anesthesia and analgesia. Furthermore, spinal anesthesia reduces the duration and expense of postoperative care, allowing for early mobilization postoperatively.

Numerous local anesthetics, such as ropivacaine, levobupivacaine, and bupivacaine, are recommended for spinal anesthesia. Since 1996, ropivacaine, an amide anesthetic, has been utilized in medical clinics. Although it shares characteristics with bupivacaine, the drug causes less bradycardia and hypotension [1]. Due to its limited fat solubility, it also permits an earlier movement recovery period than bupivacaine [2].

There has not been much research in Vietnam to date on spinal anesthesia for low-limb surgery using just ropivacaine. Thus, the purpose of our study was: *To assess the effects of anesthesia, perioperative movement inhibition, and postoperative analgesia duration, as well as the effects of spinal anesthesia with ropivacaine on respiration, circulation, and side effects in patients undergoing lower limb surgery.*

MATERIALS AND METHODS

1. Subjects

70 patients indicated lower limb surgery under spinal anesthesia at the Department of Surgery - Anesthesia and Resuscitation, Military Hospital 121, Military Region 9 (Can Tho province) from November 2022 to June 2023.

* *Inclusion criteria:* Patients age ≥ 18; with American Society of Anesthesiologists (ASA) classification I-II; heights ranging from 160 - 170cm; consent to surgery and study; have no contraindications to spinal anesthesia using ropivacaine or bupivacaine.

* *Exclusion criteria:* Patients with known contraindications to spinal anesthesia; unable to communicate; resting heart rate < 60 bpm; known allergy to amide local anesthetic; pregnancy; history of substance abuse.

2. Methods

* *Research design:* A clinical interventional study, randomized group with comparative analysis. Patients were randomly drawn into one of the two groups of 35:

- Group R (n = 35): Received 10mg of intrathecal ropivacaine.

- Group B (n = 35): Received 10mg of intrathecal bupivacaine.

* *Research process:* Preoperative assessments of each patient's condition were conducted through an examination and testing. Additionally, the anesthetic technique used was explained to the patients.

On arrival in the operating room, an intravenous cannula of appropriate size was placed. 500mL of normal saline was administered. Standard monitors were placed, and baseline readings of heart rate, blood pressure (BP), and oxygen saturation were recorded. Supplemental oxygen was administered in every case.

Under complete aseptic precautions, spinal anesthesia was administered using a 27-gauge spinal needle in the L2-L3 interspace in the sitting position. Patients in group R received a 10-milligram dose of ropivacaine for spinal anesthesia, while patients in group B received a 10-milligram dosage of 0.5% hyperbaric bupivacaine for the same purpose.

* *Data collection:* Patients' general characteristics, such as age (years), height (cm), weight (kg), gender, surgical duration, and type of surgery. Pinprick sensation was assessed using a 20-gauge hypodermic needle. During the tracking of sensory level, the time taken for loss of pinprick sensation at T10 (onset of analgesia) and analgesia duration (from the time spinal anesthesia was given until the patient felt pain at the surgical sites) were recorded. The duration of postoperative pain relief is measured from the completion of surgery until the patient experiences discomfort at the surgical wound (VAS $\geq$ 4) and needs to take their first dose of painkiller. The quality of anesthesia was assessed by the Abouleizh Ezzat scale with three levels: Good, medium, and poor. Motor block was evaluated by the modified Bromage scale (0 = able to raise a leg, 1 = able to flex the knee, 2 = able to flex the ankle, and 3 = no movement). Patients were also observed and noted for side effects such as nausea, vomiting, shivering, bradycardia, hypotension, and respiratory depression.

Time points to collect data: Preoperative time (H_0), perioperative every 5 minutes for the first 30 minutes

corresponding to the values: H_5, H_{10}, H_{15}, H_{20}, H_{25}, H_{30}; then every 10 minutes for the remaining duration until the surgery is finished, according to the values: H_{40}, H_{50}, H_{60},... H_e.

* *Statistical calculation*: The Statistical Package for the Social Sciences 22.0 (SPSS 20.0) software was used for statistical calculation. Data were expressed as either mean ± standard deviation or numbers and percentages. A p-value less than 0.05 is believed to be statistically significant.

3. Ethics

This study received approval from the Medical Research Ethics Committee of Military Hospital 103, Vietnam Military Medical University, according to Decision No. 145/CNChT-HĐĐĐ, dated November 25, 2022. All patients' data was secure throughout the study to protect their anonymity. All patients gave their family members written and informed consent to enter the study. The authors declared no conflicts of interest.

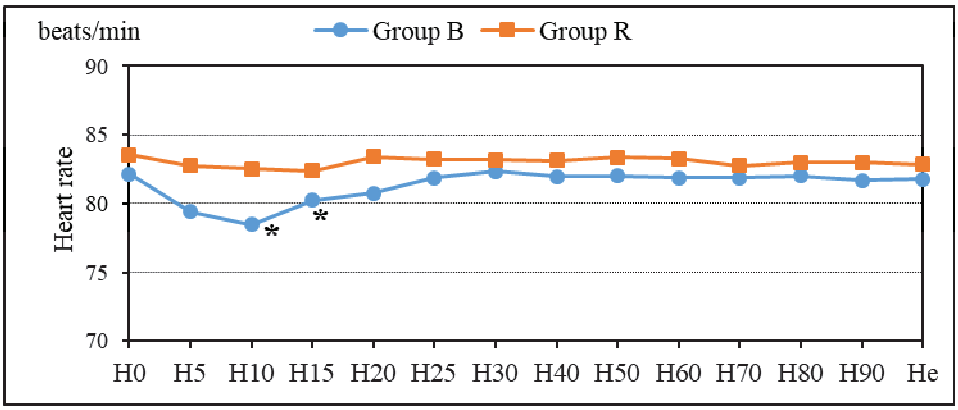
RESULTS

Table 1. Patients' general characteristics.

Criteria		Group R (n = 35)	Group B (n = 35)	p
Age (year)		39.11 ± 15.57	39.29 ± 13.34	> 0.05
Height (cm)		165.20 ± 3.11	165.54 ± 3.35	> 0.05
Weight (kg)		62.29 ± 8.72	63.91 ± 8.62	> 0.05
Gender (%)	Male	77.14	77.14	> 0.05
	Female	22.86	22.86	
Surgical location (%)	Thigh	25.71	11.43	> 0.05
	Knee	34.29	51.43	
	Lower legs and feet	40.0	37.14	
Duration of surgery (minutes)		54.86 ± 20.0	59.77 ± 19.03	> 0.05

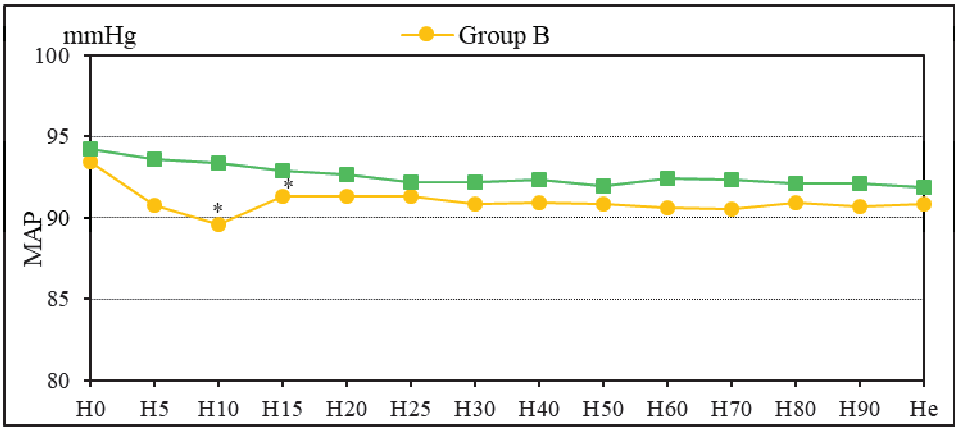
Table 2. Sensory and motor block.

Criteria		Group R (n = 35)	Group B (n = 35)	p
Onset time (minutes)		7.62 ± 0.72	4.90 ± 1.10	< 0.05
Duration time (minutes)		145.09 ± 7.03	178.03 ± 13.02	< 0.05
Duration of postoperative pain relief (minutes)		79.51 ± 22.02	107.89 ± 23.46	< 0.05
Sensory block level at the 10th minute after administering spinal anesthesia (n, %)	T_6	14 (40.0)	20 (57.1)	> 0.05
	T_8	21 (60.0)	15 (42.9)	
Proportion of patients who achieve motor block level at minute 20th after administering spinal anesthesia (n, %)	M_2	26 (74.3)	0	< 0.05
	M_3	9 (25.7)	35 (100)	
Proportion of patients who achieve the quality of good anesthesia (n, %)		35 (100)	35 (100)	> 0.05
Duration of motor block (minutes)		97.60 ± 7.10	158 ± 14.79	< 0.05



(: Statistically different compared with H_0 time-point, $p < 0.05$).*

Figure 1. Heart rate changes during surgery (beats/minute).



(: Statistically different compared with H_0 time-point, $p < 0.05$).*

Figure 2. Changes in mean arterial blood pressure during surgical procedures (mmHg).

After spinal anesthesia, the patients' mean respiratory rate and mean saturation of peripheral oxygen (SpO_2) in both groups were not statistically different ($p > 0.05$). No patient had respiratory depression (respiratory rate < 10 breaths/minute or $SpO_2 < 90\%$).

Table 3. Unwanted effects.

Unwanted effects	Group R (n = 35) n (%)	Group B (n = 35) n (%)	p
Bradycardia	2 (5.71)	8 (22.86)	< 0.05
Hypotension	1(2.86)	6 (17.14)	< 0.05
Shivering	1 (2.86)	3 (8.57)	> 0.05

In addition, we did not encounter any cases of other unwanted effects such as itching, headaches, back pain, nausea or vomiting.

DISCUSSION

The results of our study showed that the onset time for T10-level pain block in group R was 7.62 ± 0.72 minutes, enough pain inhibition to perform lower limb surgery. The onset time of the ropivacaine spinal group in our study was slower than the study by Dar FA et al. (4.90 ± 1.10 minutes [3]) and Boztug N et al. (3.60 ± 1.84 minutes [4]). After 20 minutes, group R patients at the T6 level and the T8

level had achieved pain inhibition in 40% and 60% of cases, respectively. According to Jagtap S et al., the T6 level was the maximum level of pain inhibition that could be attained [5]. The ropivacaine group's maximum level of pain inhibition, according to Kulkarni KR et al. (2014), was primarily T6 [6]. Pain inhibition levels ranged from T8 to T6 in both research groups. This block level ensures sufficient anesthesia for surgery while also having a low risk of affecting respiration and circulation.

The results of our study showed that 100% of patients achieved a good level of anesthesia; no patient had to use additional painkillers or needed to change anesthesia methods. Our research results are consistent with those of Nguyen Anh Tuan (2015) [7] and Jagtap S et al. (2014) [5]. Group R's anesthetic duration time lasted 145.09 ± 7.03 minutes, which was sufficient for lower limb surgery because the average surgical time falls between 60 and 70 minutes. Dar FA et al. (2015) stated that the effective analgesia duration for the patients treated with ropivacaine was 160 ± 12.9 minutes [3], while Nguyen Anh Tuan's (2015) effective pain relief duration for group R is 145.14 ± 5.96 minutes [7]. Boztug N et al. (2005) found that the effective analgesia duration of ropivacaine 10mg was 110.70 ± 31.22 minutes [4]. Huynh Huu Hieu and Phan Ton Anh Vu (2017) showed that the sensory inhibition duration of ropivacaine at the dose of 10mg combined with 25mcg fentanyl was 166.8 ± 12.1 minutes [8].

After 20 minutes of spinal anesthesia, group B had 35 patients (100%) with motor inhibition at the M3 level ($p < 0.05$), while group R had 9 patients (25.7%) with motor inhibition at the M3 level and 26 patients (74.3%) with motor inhibition at the M2 level. According to Gautier PhE et al. (1999), patients in the group treated with spinal anesthesia with 10mg ropivacaine had a motor block level at the M1 level of 3%, a motor block level at the M2 level of 20%, and a motor block level at the M1 level of 20%; M3 level was 77% [9]. Nguyen Anh Tuan (2015), when comparing the effects of spinal anesthesia with a mixture of ropivacaine-fentanyl (group RF) and bupivacaine-fentanyl (group BF) for lower limb surgery, realized that Group BF had 65.78% motor inhibition at the M3 level, and Group RF had 13.15% motor inhibition at the M3 level ($p < 0.05$) [7]. Huynh Huu Hieu and Phan Ton Anh Vu (2017) evaluated the effectiveness of ropivacaine in spinal anesthesia in patients undergoing arthroscopic knee surgery with motor

inhibition levels M1, M2, and M3 of 1.5%, 18.5%, and 80%, respectively [8].

Based on the research findings, it is evident that even with a lower level of motor inhibition than that of 10mg bupivacaine 0.5%, the dosage of 10mg ropivacaine 0.5% still provides adequate muscle softening for lower limb surgery. Group R's motor inhibition period (97.60 ± 7.10 minutes) was significantly shorter than group B's (158 ± 14.79 minutes) ($p < 0.05$). As per the findings of Dar FA et al. (2015), the bupivacaine group exhibited a longer motor inhibition period of 174 minutes compared to the ropivacaine group's motor inhibition period of 126 minutes [3]. According to research by Luck JF et al. (2008), the motor recovery time for the ropivacaine group was 90 minutes, while it was 180 minutes for the bupivacaine group ($p < 0.0001$) [10]. The motor inhibition time of Huynh Huu Hieu and Phan Ton Anh Vu's research (2017) was 88.7 ± 13 minutes [8]. We found that ropivacaine has a shorter motor inhibition period than bupivacaine, which will help patients feel better more quickly and leave the recovery room sooner. It will also lessen the chance of thrombosis following surgical embolization, particularly in patients who are at high risk of thrombosis, and increase patient satisfaction.

Because of the strongest paravertebral sympathetic nerve blockade, heart rate and arterial blood pressure in our study frequently dropped after spinal anesthesia and decreased most from the fifth to the tenth minute (*Figure 1, 2*). In order to identify and treat hypotension early on, it is therefore essential to supplement fluids and keep a closer eye on the patient during this time. The study also discovered that ropivacaine-induced spinal anesthesia had minimal effects on breathing. There were no instances of respiratory failure (respiratory rate < 10 cycles per minute, or SpO_2 < 95%) in either group before or after surgery.

The study resulted in bradycardia, hypotension, and shivering as unfavorable effects (*Table 3*). There were bradycardia patients (beats per minute < 60) in both groups; group R had 2 patients (5.71%) and group B had 8 patients (22.86%) who required medication treatment. Nguyen Anh Tuan (2015) reported that 2 patients (5.88%) had bradycardia in group B, and there was 1 patient in group R (2.94%) [7]. According to research by Dar FA et al. (2015), 5% of patients with bradycardia had bupivacaine, while 9% had ropivacaine [3]. In our study, there were 1 patient (2.86%) in group R and 6 patients (17.14%) in group B who had hypotension. Nevertheless, following

ephedrine treatment and rehydration, the arterial blood pressure in each of these cases recovered to normal levels; no cases of severe hypotension necessitating intensive resuscitation were observed.

Group R had 2.86% of patients who shivered, whereas group B had 3 patients (8.57%) with shivering ($p > 0.05$). According to research by Jagtap S et al. (2014), there was one patient (3.3%) who experienced shivering in the RF group and none in the BF group [5]. Shivering rates were observed to be 16% in the bupivacaine group and 10% in the ropivacaine group by Dar FA et al. (2015) [3]. Chatterjee S et al. (2014) found that the rate of patients with tremors in the ropivacaine group was 22% [11]. Shivering is an unwanted effect after spinal anesthesia, and its mechanism is currently unknown. In our study, tremors only manifested during surgery. The shivering symptoms rapidly subsided and went away after we treated them with warmed fluid infusions and a gradual intravenous injection of 30 - 50mg of diluted dolargan.

We did not experience any other unfavorable side effects during the study, including headaches, nausea, vomiting, back pain, itching, or headaches 24 hours postoperatively.

CONCLUSION

Using 10mg of 0.5% isobaric ropivacaine for spinal anesthesia at the L2-L3 position is a good way to guarantee anesthesia for lower limb surgery. This anesthetic method also inhibits movement in the short term, improves analgesic effects postoperatively, has minimal effects on respiratory and circulation, and has a few mild, temporary side effects that are easily treated.

REFERENCES

1. Malinovsky JM, Charles F, Kick O, et al. Intrathecal anesthesia: Ropivacaine versus bupivacaine. *Anesth Analg.* 2000; 91(6):1457-1460.

2. Hansen TG. Ropivacaine: A pharmacological review. *Expert Rev Neurother.* 2004; 4(5):781-791.

3. Dar FA, Mushtaq MB, Khan UM. Hyperbaric spinal ropivacaine in lower limb and hip surgery: A comparison with hyperbaric bupivacaine. *J Anaesthesiol Clin Pharmacol.* 2015; 31(4):466-470.

4. Boztuğ N, Bigat Z, Ertok E, et al. Intrathecal ropivacaine versus ropivacaine plus fentanyl for out-patient arthroscopic knee surgery. *J Int Med Res.* 2005; 33(4):365-371.

5. Jagtap S, Chhabra A, Dawoodi S, et al. Comparison of intrathecal ropivacaine-fentanyl and bupivacaine-fentanyl for major lower limb

orthopedic surgery: A randomised double-blind study. *Indian J Anaesth.* 2014; 58(4):442-446.

6. Kulkarni KR, Deshpande S, Namazi I, et al. A comparative evaluation of hyperbaric ropivacaine versus hyperbaric bupivacaine for elective surgery under spinal anesthesia. *J Anaesthesiol Clin Pharmacol.* 2014; 30(2):238-242.

7. Nguyen Anh Tuan. Comparing the effects of ablation with bupivacaine or ropivacaine combined with fentanyl for lower limb surgery. *Master's thesis in medicine.* Vietnam Military Medical Academy. 2015.

8. Huynh Huu Hieu, Phan Ton Ngoc Vu. Evaluating the effectiveness of ropivacaine in spinal anesthesia in patients undergoing arthroscopic knee surgery. *Ho Chi Minh City Medical Journal*. 2017; 21(3):47-51.

9. Gautier PE, De Kock M, Van Steenberge A, et al. Intrathecal ropivacaine for ambulatory surgery: A Comparison between Intrathecal Bupivacaine and Intrathecal Ropivacaine for Knee Arthroscopy. *Anesthesiology.* 1999; 91(5):1239-1245.

10. Luck JF, Fettes PD, Wildsmith JA. Spinal anaesthesia for elective surgery: A comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine. *Br J Anaesth.* 2008; 101(5):705-710.

11. Chatterjee S, Bisui B, Mandal A, et al. Effects of intrathecal hyperbaric ropivacaine versus hyperbaric bupivacaine for lower limb orthopedic surgery. *Anesth Essays Res.* 2014; 8(3):349-353.

EVALUATION OF ENDOSCOPIC SURGERY OUTCOMES FOR BENIGN VOCAL FOLD LESIONS AT MILITARY HOSPITAL 103

Quan Thanh Nam[1], Nghiem Duc Thuan[1], Nguyen Quyet Thang[1]*

Abstract

Objectives: To evaluate the endoscopic surgery outcomes for benign vocal fold lesions at Military Hospital 103. ***Methods*:** A prospective, case-by-case descriptive, clinical interventional study was conducted on 45 patients with benign vocal fold lesions who underwent endoscopic surgery at Military Hospital 103 from July 2022 to August 2023. ***Results:*** The disease is common among working-age adults whose ages range from 18 - 60 (77.8%); 100% of patients had hoarseness before surgery at all levels, of which moderate hoarseness accounted for 66.7%; 60.0% of patients had vocal fold nodules; the basic histopathological diagnosis was consistent with the clinical diagnosis. After the surgery, 82.2% of patients had no hoarseness. The average scores of voice handicap index (VHI) and VHI-10 decreased with statistical significance, $p < 0.001$; 80.0% of patients achieved very good results one month after surgery. ***Conclusion:*** Research results show the effectiveness of endoscopic surgery to treat benign vocal fold lesions. Both the VHI and VHI-10 scales are used to evaluate voice disorders, but in clinical practice, the VHI-10 scale may be used instead of the VHI scale.

Keywords: Benign vocal fold lesions; Endoscopic surgery for treatment of benign vocal fold lesions; Endoscopic surgery with suspension laryngoscopy.

INTRODUCTION

Voice is an important means of daily communication, and voice disorders significantly affect a patient's quality of life. Benign vocal fold lesions are the most common cause of chronic hoarseness [1], which can affect work performance, especially in people whose occupation relies on voice use. This group of lesions is very common and

[1]**Military Hospital 103, Vietnam Military Medical University**

[*]**Corresponding author: Quan Thanh Nam (dr.namb6@gmail.com)**

Date received: 01/12/2023

Date accepted: 12/3/2024

http://doi.org/10.56535/jmpm.v49i4.570

applied at a fairly high rate in the professional departments of otorhinolaryngology. It can be found in everyone, including men and women.

Endoscopic surgery to treat benign vocal fold lesions is a complex surgery. The purpose of the surgery is to remove lesions while still ensuring the pronunciation function without causing damage in the future. Traditionally, voice disorders and their treatment assessment protocols have focused on "objective voice measurements" [2]. These objective measures assess only a small component of voice production and do not encompass global vocal function from the patient's perspective. Moreover, neither objective voice nor video perceptual measures can assess the level of handicap that a person experiences as a result of a voice disorder [3]. Therefore, patient-based, voice-specific outcome measures can potentially provide more information than the biological and physiological variables associated with voice and its production.

In 1997, Jacobson et al. [4] proposed a measure of voice handicap known as VHI. This patient-based self-assessment tool consists of a 30-item questionnaire covering the three domains of a voice disorder: Functional, physical, and emotional (*Table 1*). The overall aim of the VHI is to quantify the patient's perception of his handicap due to the alteration in his or her vocal functions. The VHI-10 (*Table 2*) consists of a shortened version of the original VHI, including ten selected questions that were found to be the most clinically robust [5]. Together, they allow both the assessment of the initial voice handicap index and responsiveness to treatment.

Therefore, we conducted this study: *To describe some clinical features of benign vocal cord lesions and evaluate the results of endoscopic surgery to treat benign vocal fold lesions*.

MATERIALS AND METHODS

1. Subjects

45 patients diagnosed with benign vocal fold lesions underwent endoscopic surgery at Military Hospital 103 from July 2022 to August 2023.

* *Inclusion criteria:* Age ≥ 18; diagnosed with benign vocal fold lesions, endoscopic surgery with suspension laryngoscopy was performed.

* *Exclusion criteria:* There are accompanying internal and surgical lesions that contraindicate surgery; benign vocal fold lesions with no indication for surgery; patients did not have a follow-up examination after surgery.

* *Research location and time:* The study was conducted at Military Hospital 103 from July 2022 to August 2023.

2. Methods

* *Research design:* A prospective, case-by-case descriptive, clinical interventional study.

* *Assessment of voice before and after treatment:* The evaluation is based on subjective and objective criteria.

- Subjective criteria:

Patients self-perceived the level of voice disorder before surgery. This was performed between the physician and the patient to evaluate the level of hoarseness after listening to the patient's pronunciation before surgery [6].

Mild hoarseness: Slightly hoarse voice.

Moderate hoarseness: The voice is hoarse, rough, and shrill.

Severe hoarseness: Hoarse voice, unclear pronunciation, like no breath.

Assessed by the VHI and the VHI-10 [4, 5].

Table 1. Voice handicap index.

	Statements	**Scores**				
		0	**1**	**2**	**3**	**4**
	Functional					
F1	My voice makes it difficult for people to hear me.					
F2	People have difficulty understanding me in a noisy room.					
F3	My family has difficulty hearing me when I call them throughout the house.					
F4	I use the phone less often than I would like to.					
F5	I tend to avoid groups of people because of my voice.					
F6	I speak with friends, neighbors, or relatives less often because of my voice.					
F7	People ask me to repeat myself when speaking face-to-face.					
F8	My voice difficulties restrict personal and social life.					
F9	I feel left out of conversations because of my voice.					
F10	My voice problem causes me to lose income.					

	Statements	Scores				
		0	1	2	3	4
	Physical					
P1	I run out of air when I talk					
P2	The sound of my voice varies throughout the day.					
P3	People ask, “What’s wrong with your voice?”					
P4	My voice sounds creaky and dry.					
P5	I feel as though I have to strain to produce a voice.					
P6	The clarity of my voice is unpredictable.					
P7	I try to change my voice to sound different.					
P8	I use a great deal of effort to speak.					
P9	My voice is worse in the evening.					
P10	My voice “gives out” on me in the middle of speaking.					
	Emotional					
E1	I am tense when talking to others because of my voice.					
E2	People seem irritated with my voice.					
E3	I find other people do not understand my voice problem.					
E4	My voice problem upsets me.					
E5	I am less outgoing because of my voice problem.					
E6	My voice makes me feel handicapped.					
E7	I feel annoyed when people ask me to repeat.					
E8	I feel embarrassed when people ask me to repeat.					
E9	My voice makes me feel incompetent.					
E10	I am ashamed of my voice problem.					

Table 2. Voice handicap index-10.

	Statements	Scores				
		0	1	2	3	4
F1	My voice makes it difficult for people to hear me.					
F2	People have difficulty understanding me in a noisy room.					
F8	My voice difficulties restrict my personal and social life.					
F9	I feel left out of conversations because of my voice.					
F10	My voice problem causes me to lose income.					
P5	I feel as though I have to strain to produce a voice.					
P6	The clarity of my voice is unpredictable.					
E4	My voice problem upsets me.					
E6	My voice makes me feel handicapped.					
P3	People ask: “What’s wrong with your voice?”					

The previous statements can be used to describe one’s voice and its impact on his/her life. For each statement, a number (0 - 4) is given corresponding to its frequency. VHI is the mean of all values. Answers: 0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, and 4 = always.

All patients were asked to complete the VHI and VHI-10 questionnaires both before and after endoscopic surgery. The VHI questionnaire includes 30 questions (10 questions each for physical, functional, and emotional items) that patients must answer depending on the frequency of each question. Each question has a score from 0 - 4 in order of increasing frequency. The score of VHI is obtained by adding the values of each question and ranges from 0 - 120 (maximum 4 x 30). According to Giorgio Peretti (0 points: Normal level; 1 - 30 points: Mild level; 31 - 60 points: Moderate level; 61 - 90 points: Severe level; 91 - 120 points: Very severe level) [4].

- Objective criteria: Endoscopic evaluation one month after surgery.

A very good result: All lesions have been removed, there has been no recurrence, the vocal folds are flat, there have been no scarring, no atrophy, no depressions, no tears or mucosal edema, the glottis is closed when pronouncing, the vibration waves of the mucosa of the two vocal folds are regular, and they touch each other when pronouncing.

A good result: Meets the above standards, but there are still a few points that are not perfect.

A not-good result: remaining damage or recurrence, scarring, glottis not closing tightly, and mucous membrane vibrations are few.

* *Data processing and analysis methods:* Data processing by using SPSS 22.0 medical statistical software.

3. Ethics

The procedure of operation was approved by the Institutional Review Board of Military Hospital 103. All participants confirmed their participation in the study by signing the informed consent form before enrollment. The principles of medical ethics are guaranteed to be strictly implemented.

RESULTS

1. Age and gender

Table 3. Distribution age and sex of patients (n = 45).

Content		Quantity (n)	Percentage (%)
Gender	Male	18	40.0
	Female	27	60.0
Age	18 - 39	19	42.2
	40 - 60	16	35.6
	> 60	10	22.2

Male patients accounted for 40% and female patients accounted for 60%. The working age group, from 18 - 60 years old, is the most common (77.8%).

2. Clinical symptoms

Table 4. Clinical symptoms (n = 45).

Symptoms	Quantity (n)	Percentage (%)
Hoarseness	45	100.0
Shortness of breath	7	6.7
Cough	15	33.3
Speak out of breath	40	88.9

The symptom of hoarseness accounted for 100.0%, followed by the symptom of shortness of breath at 88.9%. Other common symptoms, such as coughing and difficulty breathing, were 33.3% and 6.7%, respectively.

Table 5. Classification of benign pathologies (n = 45).

Classification	Clinic		Histopathology	
	n	%	n	%
Vocal fold nodules	27	60.0	27	60
Polyp	8	17.8	4	8.9
Vocal fold cyst	4	8.9	4	8.9
Papillomas	2	0.4	3	6.7
Chronic inflammation	3	6.7	5	11.1
Specific disease	1	0.2	2	4.4
Total	45	100.0	45	100.0

Vocal fold nodules were most common clinically and histopathologically in 27/45 cases (60.0%), vocal fold polyps in 8/45 cases upon clinical assessment, and histopathological results in 4/45 cases. Vocal fold cysts were the same in both clinical and histopathological diagnoses (8.9%), papillomas and specific lesions increased in 1 patient, and chronic inflammation increased in 2 patients compared to the clinical diagnosis.

3. Evaluation of surgical results

Table 6. The level of hoarseness post-operative.

Hoarseness	Pre-operative	%	Post-operative	%
Mild	4	8.9	5	11.1
Moderate	30	66.7	3	6.7
Severe	11	24.4	0	0.0
Not hoarse	45	100.0	37	82.2

Symptoms of hoarseness significantly reduced. Before surgery, 100.0% had hoarseness. After surgery, 82.2% had no hoarseness.

Table 7. Evaluate by VHI and VHI-10 at pre- and post-operation.

VHI	Pre-operative	Post-operative	p
Functional	17.5	1.5	$p < 0.001$
Physical	24.2	1.8	$p < 0.001$
Emotional	17.4	1.3	$p < 0.001$
Average	59.1	4.6	$p < 0.001$
VHI-10	20.5	1.05	$p < 0.001$

The average score on all aspects as well as the overall average score of the VHI and VHI-10 changed after surgery. The difference was statistically significant ($p < 0.001$).

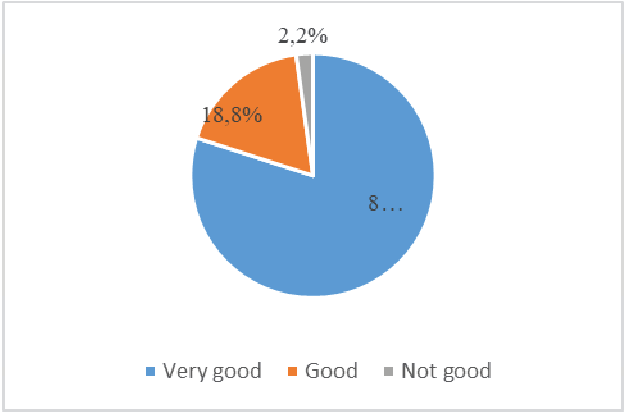


Chart 1. Evaluate the outcomes of endoscopic surgery.

Post-operatively, 80.0% of patients had a very good result, 18.8% had a good result, and 2.2% had a not-good result.

DISCUSSION

1. Age and gender

Our study was conducted on 45 patients; female patients accounted for 60.0%, and male patients accounted for 40.0%. The most common age group was the working age, ranging from 18 - 60 years old (77.8%). This result is consistent with the study by Le Van Diep et al. [7]. The author identifies that this is the age group where communication activities require the most use of voice, and women often do jobs that require more speaking.

2. Clinical symptoms

Symptoms of hoarseness accounted for 100.0%, followed by symptoms of shortness of breath at 88.9%. This is the main symptom that causes patients to go for examination and treatment. The patient's voice is often hoarse and becomes more hoarse when speaking a lot; patients have to work hard to pronounce, so they often feel tired and short of breath. This result is similar to the study by Le Van Diep and Nguyen Van Truong [7, 8]. Patients with accompanying difficulty breathing are those with polyps or large papillomas that partially cover the glottis or who have accompanying inflammation and edema. In addition, coughing is also common in patients with lesions in the larynx due to irritation of the lesions and inflammatory fluid leading to a cough reflex. In our study, this symptom accounted for 33.3%.

3. Pathological classification compared with histopathology

Vocal fold nodules are most common clinically and histopathologically, accounting for 27/45 patients (60.0%), and there is an agreement between endoscopic and histopathological images. This result is consistent with the study by Nguyen Thi Phuong Lam et al. [9] and is also consistent with the characteristics of a higher proportion of female patients and those whose occupations often require the use of voice. There were 8 patients (17.8%) with endoscopy diagnosed with vocal fold polyps, but histopathology results showed only 4 patients (8.9%). 4 patients had histopathology results that were different from the clinical diagnosis. Clinical symptoms include vocal fold papilloma, chronic inflammation, and 1 case of laryngeal tuberculosis. This explains the increased number of patients in this group after surgery. Therefore, in diagnosing benign vocal fold tumors, although endoscopic images give quite accurate results, the definitive diagnosis must be based on histopathological results, which are considered the gold standard for diagnosing tumors.

4. Evaluation of surgical results

** Evaluate the symptoms of hoarseness:*

Pre-operatively, 100.0% of patients had hoarseness to varying degrees. Moderate hoarseness accounts for the highest rate (66.7%), followed by severe hoarseness (24.4%) and mild hoarseness (8.9%). Post-operatively, 82.2% of patients had no hoarseness, the rest had mild and moderate hoarseness, and no patients had severe hoarseness. This result is consistent with Le Van Diep's research [7] when evaluating 105 patients with benign tumors using suspension laryngoscopy, with the result that 100% of patients had hoarseness before surgery, of which the majority was moderate and severe hoarse, accounting for 93.3%. All patients had reduced hoarseness post-operatively, there was no case of increased hoarseness, and 89.5% of patients had voices returned to normal. Author Nguyen Van Truong also had similar results [8].

** Evaluate the VHI and VHI-10 at pre- and post-operation:*

The study evaluated the voice pre-operatively using the VHI showed an average score of 59.1/120, and post-operatively, during a 1-month follow-up period, it showed an average score of 4.6. The research results also show a correspondence between the average score of the two scales and the patient's level of hoarseness (mainly moderate hoarseness); this result is consistent with the observations of Hallak B et al., whose study of voice disorders in patients with Reinke's edema was evaluated before and after surgery. The author believes that the impact of voice disorders on a patient's quality of life is more serious the higher the VHI score [10]. The pre-operative analysis of the different sub-scales showed that the average score for the physical aspect was 24.2/40, the functional aspect was 17.5/40, and the emotional aspect was 17.4/40. Post-operative 1 month for three aspects: Physical, functional, and emotional were 1.8, 1.5, and 1, respectively. According to these results, the physical aspect has the greatest impact on the patient's quality of life before treatment. Using the VHI-10, pre-operative assessment showed an average score of 20.5/40, and post-operatively, at 1 month, it was 1.05/40 (*Table 5*). Analyzing further, we also found that there is also a greater influence from the physical aspect.

In this study, we used the patient-based VHI and VHI-10 self-assessment

questionnaires to provide a subjective assessment of the impact of voice disorders before and after surgery. The results showed a clear difference in both the VHI and VHI-10 obtained before and after surgery and the results were similar in both indexes; both indexes showed great improvement in a clinically significant impact on the quality of life of all patients. However, assessment according to the VHI needs to be more detailed and time-consuming, while the VHI-10 can be used to quickly assess voice disorders, and results can be achieved as quickly and reliably as the VHI questionnaire and have good effectiveness in clinical practice.

** Evaluation of the outcomes of endoscopic surgery:*

Post-operatively, 80% of patients achieved a very good result, 18.8% achieved a good result, and 2.2% achieved a not-good result. Patients with a not-good result were cases of laryngeal papilloma, with one case of early recurrence and one case of scarring. Our research results are similar to Trinh Viet Hong's research, with a very good result reaching 83.71% [6], which is lower than Nguyen Thi Phuong Lam's research, with a very good result reaching 96.2% [9].

CONCLUSION

Endoscopic surgery to treat benign vocal fold lesions had a good result, with 82.2% of patients no longer hoarse and 80% of patients achieving a very good result at one month post-operative. In clinical practice, it can be assessed using the VHI-10 instead of the VHI.

REFERENCES

1. Võ Tấn. Tai Mũi Họng thực hành. Nhà xuất bản Y học Thành phố Hồ Chí Minh. 1994; 111-113.

2. Benninger MS, Atiuja AS, Gardner G, et al. Assessing outcomes for dysphonic patients. *Journal of Voice*. 1998; 12(4):540-550.

3. Woo P. Quantification of videostrobolaryngoscopic indings: Measurements of the normal glottal cycle. *Laryngoscope*. 1996; 106(3):1-16.

4. Jacobson BH, Johnson A, Grywalski C, et al. The voice handicap index (VHI): Development and validation. *American Journal of Speech-Language Pathology*. 1997; 6(3):66-70.

5. Rosen CA, Lee AS, Osborne J, et al. Development and validation of the voice handicap index-10. T*he Laryngoscope*. 2004; 114(9):1549-1556.

6. Trần Việt Hồng. Đánh giá kết quả phẫu thuật nội soi điều trị hạt xơ dây thanh. *Tạp chí Y học TP. Hồ Chí Minh.* 2013; tập 17 (Phụ bản số 1):106-112.

7. Lê Văn Điệp. Đánh giá kết quả điều trị u lành tính dây thanh bằng phẫu thuật nội soi treo. *Tạp chí Y Dược học - Đại học Y dược Huế*. 2017; 7(5):233-238.

8. Nguyễn Văn Trường. Đánh giá kết quả phẫu thuật nội soi vi phẫu các tổn thương lành tính thanh quản tại Khoa Phẫu thuật và Điều trị theo yêu cầu - Bệnh viện Trung ương Quân đội 108. *Tạp chí Y Dược Lâm sàng 108*. 2022; 5:129-134.

9. Nguyễn Thị Phương Lam. Đánh giá kết quả điều trị u lành tính dây thanh bằng phẫu thuật nội soi treo thanh quản tại bệnh viện tai mũi họng cần thơ năm 2016 - 2018. *Tạp chí Y Dược học Cần Thơ*. 2018; 16:1-7.

10. Hallak B, Olivier F, Teiga SP, et al. Subjective voice assessment after endoscopic surgery for an obstructive reinke edema using voice handicap index. *Advances in Otolaryngology*. 2015; 4:1-5.

A CASE REPORT: RECONSTRUCTION OF THE CALCANEAL REGION DEFECT USING THE MEDIAL PLANTAR FREE FLAP

Vu Huu Trung[1], Le Anh Tu[1], Nguyen Ngoc Thach[2]*
Tran Hoang Dat[1], Nguyen Huu Dat[1]

Abstract

Soft tissue defects in the calcaneal region represent a reconstructive challenge because of their complexity and the lack of local flaps. We report a clinical case of using the medial plantar free flap to cover of this area. The advantages of the flaps will be discussed.

Keywords: Medial plantar flap; Medial plantar free flap; Free flap; Reconstruction; Calcaneal region defect.

INTRODUCTION

Reconstructing and covering the calcaneal region is difficult because the heel is a weight-bearing area. Frequently, the tissue defects are covered with pedicle medial plantar flaps. Opoku-Agyeman (2020) [1] reported that medial plantar flaps provided better outcomes than sural flaps. Linkoudis (2013) [2] reported the use of medial plantar free flaps to cover the medial volar of the foot. Xu (2022) [3] noted that the structure of medial plantar free flaps and the finger tissue are compatible so that the flaps can be used to cover finger tissue defects. However, there are few reports about the use of medial plantar free flaps to cover the calcaneal region defect. Our report aimed: *To discuss a case of calcaneal region defect covered with contralateral medial plantar free flaps*.

CASE REPORT

A 25-year-old female patient was admitted with a left plantar and a part of the left calcaneal area skin avulsion; she underwent wound debridement.

[1]General Trauma and Microsurgery Department, Military Hospital 103
[2]Anesthesiology Department, Military Hospital 103
[*]Corresponding author: Le Anh Tu (themummy1207@gmail.com)
Date received: 19/01/2024
Date accepted: 12/3/2024
http://doi.org/10.56535/jmpm.v49i4.721

After the debridement, there was a soft tissue defect with a size of 8 x 5cm. The defect was scheduled to be covered with a contralateral medial plantar free flap; the dimension of the flap was 9 x 6cm (*Figure 1*). The plantar artery, 2 venae comitantes, and some more branches on the donor side were exposed. The posterior tibial artery and 2 veins were exposed in the defect area. After the arterial anastomosis, the vessels were rerouted, but there was no flow in the 2 venae comitantes of the flap, so we decided to connect the posterior tibial vein of the defect area to a branch of the flap. After the anastomosis, the vein was rerouted, and there was a flow in a satellite vein. Then, the 2 satellite veins of the defect area and the flap were connected. The donor site was covered by a full-thickness skin graft, the flap was survival, and the wound healed by primary intention. 3-month follow-up, the flap was good survival, with no necrosis at the edge of the flap. The patient was able to start weight-bearing and there was no ulceration or raw area on the flap. After 3 months, the sensitivity of the flap has not fully recovered.

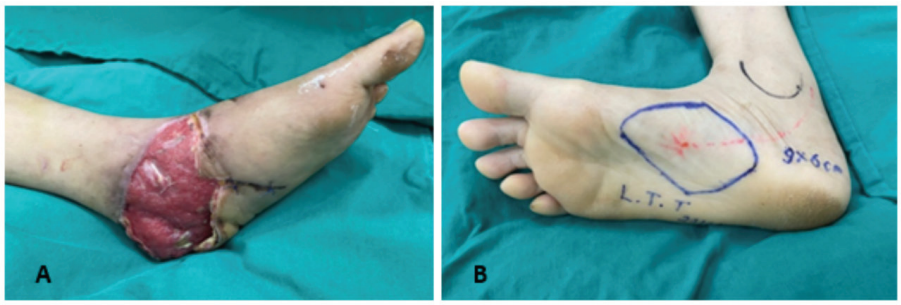


Figure 1. Donor site and defect area before the surgery.
A: Tissue defect; B: Flap design.

Figure 2. Post-operative outcome.
A: 10 days after the surgery; B: 3 months after the surgery.

Figure 3. 3 months after the surgery.
Left foot: Recipient area; Right foot: Donor site.

DISCUSSION

The epithelial tissue of the calcaneal region is thick, so it can bear weight better than other regions of the body. Regularly, local flaps with pedicle, and plantar flaps, for example, are used for tissue defects on the heel. In this patient with plantar complicated wounds, the local flaps were not available. The medial plantar flaps are usually indicated for the defects because the medial plantar area does not bear much weight, so the flaps can be harvested and covered later on by thick skin graft without impeding the function. Lykoudis (2013) [2] reported a case of medial plantar defect successfully covered with the medial plantar flap. Pertea (2018) [4] noted that medial plantar flaps should be the top priority for tissue defects of the calcaneal region defect. However, there are still few reports on the use of the medial plantar free flap to reconstruct the calcaneal region defect.

In case of no backflow in satellite veins after the anastomosis of the flap artery and the posterior tibial artery, the cause should be that the posterior tibial vein is not a dominant efferent vein of the flaps. Corley (2009) [5] reported that there were some cases in which plantar veins are tributaries of the veins of the dorsum of the foot before flowing into a part of the posterior tibial veins. Uhl (2012) [6] reported that plantar superficial veins flow into the veins of the dorsum of the foot; and then, flow into the saphenous vein.

Figure 4. Medial plantar subcutaneous veins flow into the saphenous vein [6].

CONCLUSION

In our case, contralateral medial plantar free flaps are a favorable option for calcaneal or/and foot plantar region defects where medial plantar pedicled flaps can be harvested to cover. The issue of flow veins of the flap should be noted during the surgery.

Acknowledgment: The authors extend our gratitude to members of the General Trauma and Microsurgery Department and Anesthesia Department, Military Hospital 103 for their assistance. We declare to have no conflicts of interest.

REFERENCES

1. Opoku-Agyeman JL, Allen A, Humenansky K. The use of local medial plantar artery flap for heel reconstruction: A systematic review. *Cureus.* 2020; 12(8).

2. E G Lykoudis, K Seretis, and MG Lykissas. Free sensate medial plantar flap for contralateral plantar forefoot reconstruction with flap reinnervation using end-to-side neurorrhaphy: A case report and literature review. *Microsurgery.* 2013; 33:227-231.

3. Xu X, Wang C, Chen Z, et al. Medial plantar artery perforator (MPAP) flap is an ideal option for reconstruction of complex soft tissue defect in the finger: Clinical experience from 11 cases. *Front. Surg*. 2022; 9:934173.

4. Pertea M, Velenciuc N, Grosu O, et al. Reconstruction of heel soft tissue defects using sensate medial plantar flap. *J Mind Med Sci*. 2018; 5(2):250-254.

5. Gavin JC, Barry JB, Sarah MN, et al. The anatomy and physiology of the venous foot pump. *Anat Rec*. 2010; 293:370-378.

6. JF Uhl, C Gillot. Anatomy of the foot venous pump: Physiology and influence on chronic venous disease. *Phlebology.* 2012; 27:219-230.

MORTALITY CHARACTERISTICS OF MULTIPLE TRAUMA PATIENTS AT MILITARY HOSPITAL 103

Le Dang Manh[1], Nguyen Quang Huy[1], Vu Minh Duong[1]*
Le Hong Trung[2], Tran Quoc Viet[3], Le Xuan Thang[3], Nguyen Trung Kien[1]

Abstract

Objectives: To determine mortality characteristics of multiple trauma patients who were treated at Military Hospital 103. ***Methods:*** A prospective, descriptive study on 196 multiple trauma patients who were admitted and treated at the Surgical Intensive Care Unit (SICU), Military Hospital 103. Patients' clinical and subclinical data were collected at the time of admission, during treatment, and at the time of discharge from the SICU. The data were encoded and processed according to statistical methods. ***Results:*** The majority of multiple trauma patients were aged 20 - 40 (38.8%), mainly men (80.1%), and the main cause was traffic accidents (66.8%). The 30-day mortality rate of multiple trauma admitted to the SICU was 40.8%. The mortality rate within 24 and 48 hours after admission was 15.8% and 21.9%, respectively, then it gradually decreased over time. The main causes of death within the first 24 hours were traumatic shock (10.7%) and severe traumatic brain injury (5.1%), but the main cause of death after 24 hours was multiple organ failure (9.7%). Injury Severity Score (ISS) (HR 1.95; 95%CI: 1.05 - 3.64), brain trauma (HR 0.25; 95%CI: 0.09 - 0.70) and shock when arrival (HR 0.41; 95%CI: 0.22 - 0.75) were risk factors for survival over time in multiple trauma patients ($p < 0.05$). ***Conclusion:*** The mortality rate among multiple trauma patients was high. ISS, traumatic brain injury, and shock at the time of admission were risk factors for survival over time in patients with multiple traumas ($p < 0.05$). The main causes of death within the first 24 hours were traumatic shock and severe traumatic brain injury, but after 24 hours was multiple organ failure.

Keywords: Multiple trauma/polytrauma; Mortality.

---

[1]Military Hospital 103, Vietnam Military Medical University
[2]Vinh Phuc Department of Health
[3]Military Hospital 175
[*]Corresponding author: Le Dang Manh (congtuoc412@gmail.com)
Date received: 18/01/2024
Date accepted: 12/3/2024
http://doi.org/10.56535/jmpm.v49i4.714

INTRODUCTION

Trauma is still a leading cause of death and has an enormous impact on patient's life and health systems. Trauma is a major cause of mortality, responsible for 9% of global deaths, and the primary reason for loss of life in young people [1]. Multiple trauma patients who have two or more severe injuries in different areas or organ systems, including at least one injury or a combination of life-threatening injuries. Despite progress in diagnosis and treatment, the mortality rate of patients with multiple traumas remains high [2, 3, 4]. There have been many studies on mortality in patients with multiple injuries, but in Vietnam, data on this issue is insufficient. Therefore, we conducted this study: *To determine mortality characteristics in multiple trauma patients who were admitted to the SICU, Military Hospital 103*.

MATERIALS AND METHODS

1. Subjects

196 multiple trauma patients treated at the SICU, Military Hospital 103 from 6/2020 - 6/2023.

* *Inclusion criteria:* Patients were diagnosed with multiple trauma (polytrauma), which is defined by the New Berlin Definition [5]; patients ≥ 18 years old.

* *Exclusion criteria:* Hospitalized > 24 hours after the accident; patients who have had surgery or treatment at previous level hospitals > 12 hours; pregnant woman; have chronic diseases such as cirrhosis, end-stage chronic kidney failure, congestive heart failure, and malignancy; patients had cardiac arrest before entering the hospital and was successfully resuscitated.

* *Criteria for removal from the study:* Transfer to another hospital before discharge; insufficient collection of research data.

2. Methods

* *Research design:* A prospective, descriptive study.

Vital signs, Glasgow score, and ISS were collected when patients entered the hospital. Blood samples were taken within 30 minutes of admission for biochemical, complete blood count, and blood gas tests. Patients' outcomes were assessed 30 days after admission.

The care of severely injured patients was performed in a structured way according to the A-B-C-D-E scheme and whole-body examination by the interdisciplinary team. Therapeutic decision-making took patients' physiological parameters into account, along with the overall severity of trauma and the complexity of the individual injuries [6, 7]. A patient was considered dead if the patient died in the hospital or was in serious condition and the family

requested to be discharged from the hospital. The above information was compiled in the research medical record.

Qualitative variables were presented as percentages. The Kolmogorov-Smirnov test was performed to check the normal distribution of the variables. Quantitative variables that are not normally distributed are presented as medians (interquartile range: Q1 - Q3). Test the difference between two quantitative variables that do not have a normal distribution using the Mann-Whitney test. Kaplan-Meier failure curve and log-rank test were fitted to explore the survival difference among groups. After the bivariable and multivariable Cox regression analysis, an adjusted hazard ratio with 95% Confidence Intervals (CI) was reported to declare the strength of association and statistical significance, respectively.

All analyses were performed using SPSS version 26.0.

RESULTS

Table 1. General characteristics of patients.

Characteristics		Quantity (n = 196)	Proportion (%)
Age	< 20	24	12.2
	20 - 40	76	38.8
	41 - 59	64	32.7
	≥ 60	32	16.3
Gender	Male	157	80.1
	Female	39	19.9
Causes	Traffic accidents	131	66.8
	Occupational accidents	32	16.3
	High fall	23	11.7
	Others	10	5.1
ISS	18 - 25	38	19.4
	26 - 40	98	50.0
	41 - 75	60	30.6
Outcome	Survival	116	59.2
	Death	80	40.8

Multiple trauma patients were mainly male (80.1%); the majority was in the working age (20 - 40 years old: 38.8%), with the main cause being traffic accidents (66.8%). 40.8% of patients dead.

Table 2. Main causes of death in multiple trauma patients.

Etiologies	Within 24 hours after admission	After 24 hours	Total
Traumatic shock	21 (10.7%)	14	35 (17.8%)
Severe traumatic brain injury	10 (5.1%)	16	26 (13.3%)
Multiple organ failure	0	19	19 (9.7%)
Total	31 (15.8%)	49 (25.0%)	80 (40.8%)

15.8% of multiple trauma patients died within 24 hours after admission. The main causes of death within the first 24 hours were traumatic shock (10.7%) and severe traumatic brain injury (5.1%).

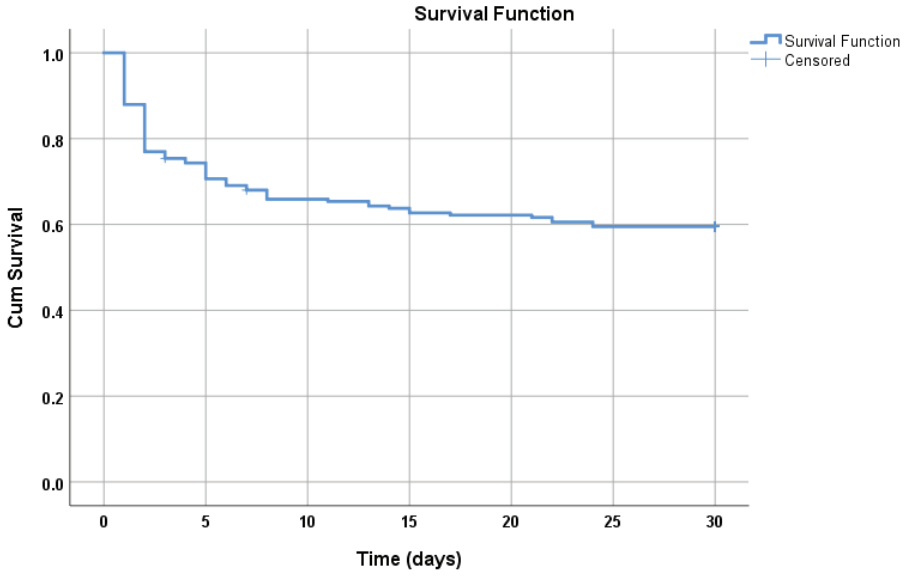


Figure 1. Kaplan-Meier total survival estimates.

21.9% of patients died within 48 hours after admission, then the mortality rate gradually decreased over time.

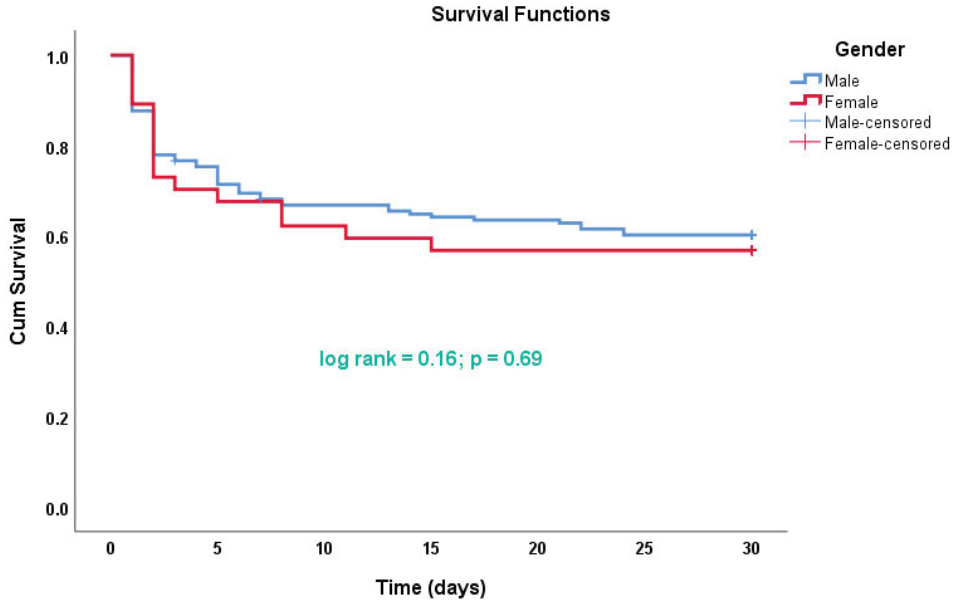


Figure 2. Kaplan-Meier survival estimates by gender.

The mean survival time of male and female patients was 20.2 days and 18.8 days, respectively. The difference was not statistically significant (p > 0,05).

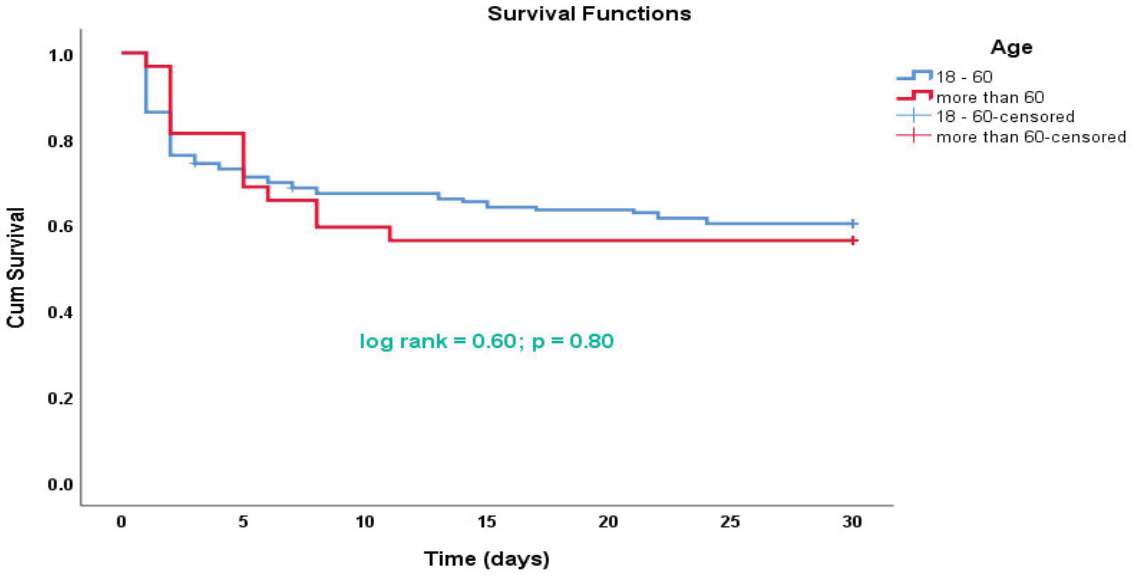


Figure 3. Kaplan-Meier survival estimates by age.

The mean survival time of 18 - 60 and > 61-year-old patients were 20.1 and 18.8 days, respectively. The difference was not statistically significant (p > 0.05).

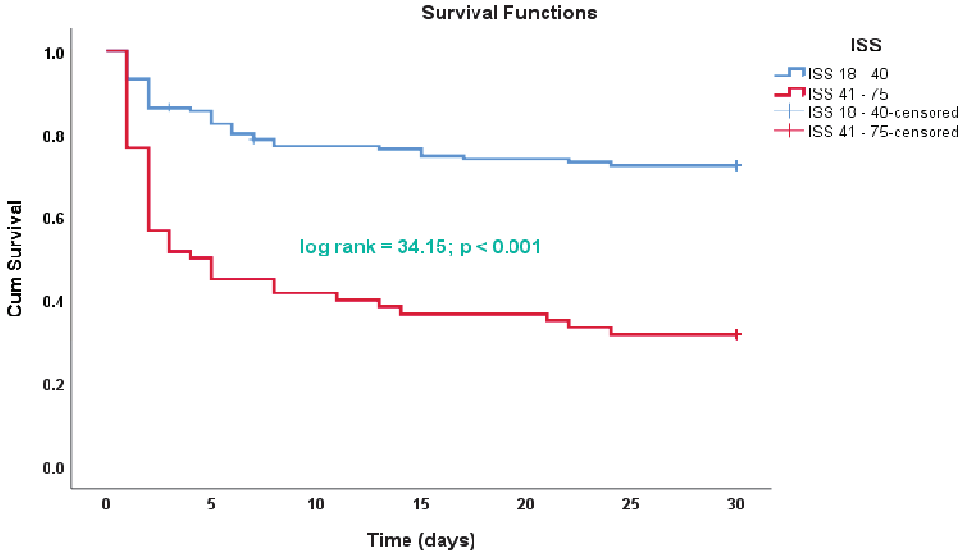


Figure 4. Kaplan-Meier survival estimates by ISS.

The median survival time of the ISS 41 - 75 group was 4.0 (0.7 - 7.3) days, lower than the ISS group, which was 18 - 41: 23.3 (21.3 - 25.2) days. The difference in the survival rate was statistically significant ($p < 0.05$).

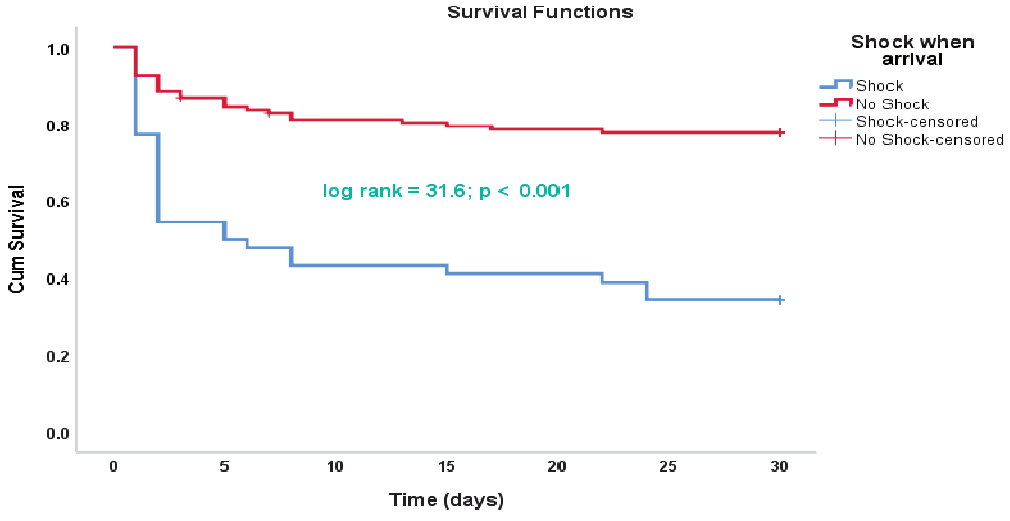


Figure 5. Kaplan-Meier survival estimates by shock when arrival.

The median survival time of shock when arrival was 5.0 (1.9 - 8.0) days, lower than patients with no shock: 24.5 (22.5 - 27.4). The difference in the survival rate was statistically significant ($p < 0.05$).

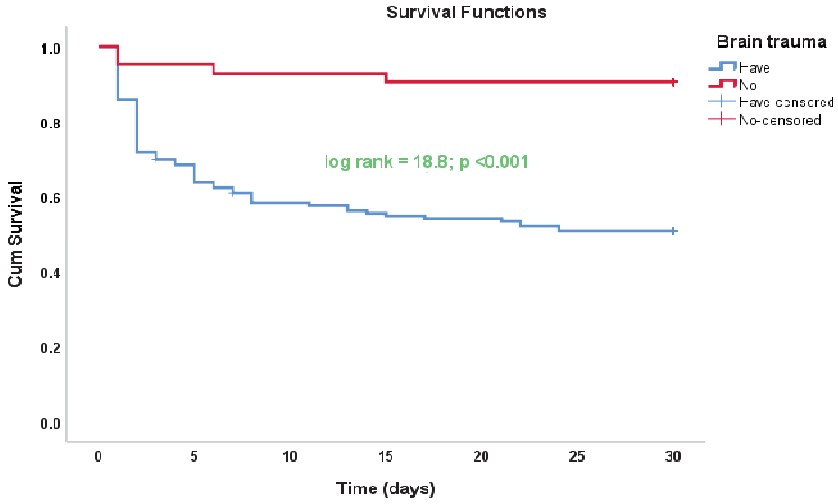


Figure 6. Kaplan-Meier survival estimates by brain trauma when arrival.

The mean survival time of patients who had brain trauma was 17.7, lower than patients with no brain trauma: 27.6 days. The difference in the survival rate was statistically significant ($p < 0.05$).

Table 3. Cox regression analysis on some factors affects the rate of survival in patients.

Characteristics	Unadjusted model		Adjusted model	
	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p
ISS (41 - 75 vs. 18 - 40)	3.38 (2.15 - 5.31)	< 0.001	1.95 (1.05 - 3.64)	0.036
Brain trauma	0.16 (0.06 - 0.42)	< 0.001	0.25 (0.09- 0.70)	0.008
Glucose (mmol/L) (≥ 10 vs. < 10)	2.04 (1.27 - 3.28)	0.003	1.67 (0.93 - 3.00)	0.084
Lactate (mmol/L) (≥ 3 vs. < 3)	1.74 (0.99 - 3.05)	0.056	1.13 (0.55 - 2.33)	0.746
Shock at admission time	0.26 (0.15 - 0.44)	< 0.001	0.41 (0.22 - 0.75)	0.004

ISS, brain trauma, and shock when arrival were risk factors for survival over time in patients with multiple trauma ($p < 0.05$). The hazard of death among

patients with ISS 41 - 70 was 1.95 times higher than those who had ISS 18 - 40. The hazard of death among patients without brain trauma and shock at admission was 0.25 and 0.41 times lower as compared to those who have brain trauma or shock, respectively.

DISCUSSION

Multiple trauma patients were mainly male (80.1%) and working age (20 - 40 years old: 38.8%), with traffic accidents (66.8%) as the main cause (*Table 1*). Similarly, Nguyen Truong Giang (2007) also found that 77.3% of multiple trauma patients were male, young age 35 ± 15, with 81.3% due to traffic accidents [8].

In our study, 15.8% of multiple trauma patients died within 24 hours, and 21.9% of patients died within 48 hours after admission. Kisat MT (2016) demonstrated that the mortality appeared to be highest during patients' first day in the ICU. After surviving for 24 hours, however, trauma patients' proportional mortality more than halved, falling from 9.9% to 3.8% [9]. In our study, the main causes of death within the first 24 hours were traumatic shock and severe traumatic brain injury, and the main cause of death after 24 hours was multiple organ failure (9.7%) (*Table 2 and Figure 1*). This result is similar to research by A Sauaia (1995) that central nervous system injuries and exsanguination were the most frequent cause of death in acute and early phases (within 48 hours and from 3 to 7 days after admission, respectively), and organ failure (7%) was the most common cause of late death (after 7 days) [10]. Nguyen Truong Giang (2006) demonstrated that 23.0% of multiple trauma patients died (72.9% total death) within 24 hours after admission, and the main cause was traumatic brain injury combined with shock or respiratory failure [8]. A study in Dutch by El Mestoui Z (2016) showed that almost 92% of the total population died because of the effects of the accidents (primary trauma). Most patients died because of the effects of severe head injury (63.4%), followed by exsanguination (17.6%) [11]. In 2019, Brohi et al. set a challenge to trauma surgeons, clinicians, and scientists to explain why up to 25% of trauma patients, often admitted to hospitals with normalized perfusion and coagulation status, were still dead despite receiving the best medical care. The first group of early deaths occur 3 - 6 to 24 hours after injury and appear to be associated with profound cardiac and vascular failure. The second group of late deaths occur at 1 to 7 days and appear to be associated with an indolent form of multiple organ failure, immunosuppression, and sepsis,

referred to as persistent inflammation, immunosuppression, and catabolism syndrome (PIICS) [4].

Our research showed that there was no difference in mortality by gender (*Figure 2*) and between two age groups > 60 and < 60 years old (*Figure 3).* In addition, the hospitalized group with ISS scores (41 - 75) had a statistically significant higher mortality rate than the group with ISS scores 18 - 40 (*Figure 4*). Moreover, patients with multiple injuries admitted to the hospital in a state of shock or with traumatic brain injury had a higher mortality rate than the group without shock or without traumatic brain injury, with statistical significance ($p < 0.05$) (*Figures 5 and 6*). Similarly, Kisat MT (2016) found that among patients with an intensive care unit length of stay < 41 days, higher ISS and lower Glasgow score independently predicted mortality [9].

In our study, ISS (HR 1.95; 95%CI: 1.05 - 3.64), brain trauma (HR 0.25; 95%CI: 0.09 - 0.70), and shock when arrival (HR 0.41; 95%CI: 0.22 - 0.75) were independent risk factors for survival over time in patients ($p < 0.05$). The hazard of death among patients with an ISS 41 - 75 was 1.95 times higher than those who had an ISS of 18 - 40. The hazard of death among patients without brain trauma and shock at admission was 0.25 and 0.41 times lower than that of those who had brain trauma or shock, respectively (*Table 3*). Messelu MA et al. (2023) found that the hazard of death among patients with a Glasgow score < 9 was 3.9 times higher than those who had a Glasgow score of 13 - 15 [3]. A study by Jelodar S (2014) showed that Glasgow ≤ 8 (OR 16.5; 95%CI 5.9 - 40.8), head fracture (OR 5.8; 95%CI 3.1 - 9.5) were independent predictors of death in studied patients [12]. Luiz Costa (2017) studied 200 polytrauma patients demonstrated that lactate level (OR 1.06; 95%CI: 1.03 - 1.09; $p < 0.001$), Glasgow Coma Scale score (OR 0.98; 95%CI: 0.97 - 0.99; $p < 0.001$), and presence of traumatic brain injury (OR 6.09; 95%CI: 2.45 - 15.14; $p < 0.001$) were independent early predictors of mortality [13].

CONCLUSION

The overall mortality rate among multiple trauma patients admitted to the SICU was high (40.8%). The main causes of death within the first 24 hours were traumatic shock (10.7%) and severe traumatic brain injury (5.1%), and the main cause of death after 24 hours was multiple organ failure (9.7%). We identified ISS (HR 1.95; 95%CI: 1.05 - 3.64), brain trauma (HR 0.25; 95%CI: 0.09 - 0.70), and shock when arrival (HR 0.41; 95%CI: 0.22 - 0.75) were risk factors for survival over time in multiple trauma patients ($p < 0.05$).

REFERENCES

1. World Health Organization. Injuries and violence: The facts 2014. 2014.

2. R Pfeifer, M Teuben, H Andruszkow et al. Mortality patterns in patients with multiple trauma: A systematic review of autopsy studies. *PLoS One*. 2016; 11(2):e0148844.

3. MA Messelu, AD Tilahun, ZW Beko et al. Incidence and predictors of mortality among adult trauma patients admitted to the intensive care units of comprehensive specialized hospitals in Northwest Ethiopia. *Eur J Med Res*. 2023; 28(1):113.

4. K Brohi, RL Gruen, JB Holcomb. Why are bleeding trauma patients still dying?. *Intensive Care Med*. 2019; 45(5):709-711.

5. HC Pape, R Lefering, N Butcher et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. *J Trauma Acute Care Surg*. 2014; 77(5):780-786.

6. M Frink, P Lechler, F Debus et al. Multiple trauma and emergency room management. *Dtsch Arztebl Int*. 2017; 114(29-30):497-503.

7. Edoardo Picetti, Sandra Rossi, Fikri M Abu-Zidan et al. WSES consensus conference guidelines: Monitoring and management of severe adult traumatic brain injury patients with polytrauma in the first 24 hours. *World Journal of Emergency Surgery*. 2019; 14(1):53.

8. Nguyễn Trường Giang, Đỗ Tất Cường, Nghiêm Đình Phàn. Tử vong do đa chấn thương. *Tạp chí Y học thực hành*. 2006; 547:57-59.

9. MT Kisat, A Latif, CK Zogg et al. Survival outcomes after prolonged intensive care unit length of stay among trauma patients: The evidence for never giving up. *Surgery*. 2016; 160(3):771-780.

10. A Sauaia, FA Moore, EE Moore et al. Epidemiology of trauma deaths: A reassessment. *J Trauma*. 1995; 38(2):185-193.

11. ZEl Mestoui, H Jalalzadeh, GF Giannakopoulos et al. Incidence and etiology of mortality in polytrauma patients in a Dutch level I trauma center. *Eur J Emerg Med*. 2017; 24(1):49-54.

12. S Jelodar, P Jafari, M Yadollahi et al. Potential risk factors of death in multiple trauma patients. *Emerg (Tehran)*. 2014; 2(4):170-173.

13. LGV Da Costa, MJC Carmona, LM Malbouisson et al. Independent early predictors of mortality in polytrauma patients: A prospective, observational, longitudinal study. *Clinics (Sao Paulo)*. 2017; 72(8):461-468.

EVALUATION OF SURGICAL TREATMENT RESULTS FOR FRACTURES IN THE TROCHANTERIC AREA USING LOCKING PLATES AT HA DONG GENERAL HOSPITAL

Nguyen Trong Nghia[1], Tran Quang Toan[1], Nguyen Quang Phu[1]*
Nguyen Minh Hoang[2], Nguyen Cong Duy[3]

Abstract

Objectives: To evaluate the results of surgery to treat adult fractures in the trochanteric area using locking plates at Ha Dong General Hospital. ***Methods:*** A retrospective, cross-sectional descriptive study on 30 patients with fractures in the trochanteric area who underwent surgery with locking plates, followed up, and re-examined at Ha Dong General Hospital from January 2018 to February 2022. ***Results:*** The main cause of injury was daily life accidents (63.3%). Classification according to AO: Type A1 fractures accounted for 13.3%, type A2 fractures were 56.7%, and type A3 fractures were 30%. The average hospital stay was 12.3 days. The anatomical correction results were 90% good and 10% not good. Bone healing results: Good bone healing was 96.7%; poor bone healing was 3.3%, with no cases of osteoarthritis or pseudoarthritis. The results of good and very good walking function were 86.7%, and poor walking function was 3.3%. Overall results: Very good and good accounted for 86.7%, average was 10%, and poor results was 3.3%. ***Conclusion:*** Fractures in the femoral trochanter area are mainly caused by daily life accidents. Bone union with locking plates is a good treatment method for patients with fractures in the trochanteric area helping to firmly fix fractures, allowing patients to exercise and practice early rehabilitation. It is convenient for patients to return to daily life, reducing the rate of complications encountered, thereby improving the quality of life for patients and reducing the burden on families and society.

Keywords: Locking plate; Trochanter facture; Adult.

---

[1]Ha Dong General Hospital
[2]Vietnam University of Traditional Medicine
[3]Ha Noi Medical University
[*]Corresponding author: Nguyen Trong Nghia (nghia.dr@gmail.com)
Date received: 09/12/2023
Date accepted: 12/3/2024
http://doi.org/10.56535/jmpm.v49i4.576

INTRODUCTION

A fracture in the femoral trochanter area is an extra-articular fracture in the transition area between the femoral neck and the femoral shaft. The fracture line is located in the area connecting the greater trochanter to 5cm below the lesser trochanter. Fractures in the femoral trochanter area are quite common, accounting for 55% of upper femoral head fractures, occurring in all ages but are more common in elderly and female patients. Common causes are traffic and work accidents, but the most common are daily life accidents.

In 1935, Boehler proposed that the main treatment method for femoral trochanteric fractures is continuous traction [1]. But after a while, people noticed many complications such as joint stiffness, spleen ulcers, pneumonia due to prolonged lying down, etc., especially, the high death rate.

Due to the development of minimally invasive surgery methods, intramedullary fixation has been recently used to treat femoral intertrochanteric fractures. On the other hand, proximal femoral deformity in adults can be induced by a wide variety of primary diseases, including poliomyelitis sequela, proximal femoral fibrous dysplasia, malunion after fracture, internal fixation implant failure, and the residual deformities from previous osteotomy, which may cause unpredictable pathological and biomechanical changes of the proximal femur and femoral osteotomy. Therefore, total hip arthroplasty for femoral reconstruction and fixation are conventional treatment options for patients without proximal femoral fractures. However, when intertrochanteric fracture and proximal femoral deformity are presented simultaneously, due to the unpredictable fracture pattern, complex proximal femoral geometry and deformity morphology, more accurate clinical decision-making, higher technical requirements for fracture reduction, and a more sophisticated postoperative rehabilitation experience are essential prerequisites for excellent and good clinical outcomes of the patients and is a substantial challenge for intramedullary fixation or total hip arthroplasty and osteotomy for the treatment of femoral intertrochanteric fractures in patients with pre-existing proximal femoral deformities. Orthopedic surgeons are faced with the dilemma of performing a simple and effective internal fixation procedure on these patients to restore optimal hip function. Locking plates have the advantage of firmly fixing the fracture in cases where the patient's bone density is poor

because the thread system on the screw cap is fixed into the locking hole without the need for pressure against the bone surface. Creating a fixed angle with the screw makes the locking plate have the same working principle as an external fixation frame, but is much more stable with axial force and torsional force due to the distance between the brace and the bone is very small. When under pressure, all locking screws have equal and simultaneous effectiveness. This causes the plate structure - the bone to bear the load evenly, avoiding over-loading and reducing the risk of plate fatigue.

Therefore, to clarify the advantages and disadvantages of the locking plate bone combination method, learn from experience, and improve the quality of treatment of trochanteric fractures, we conducted the research: *To evaluate surgical treatment results for fractures in the trochanteric area using locking plates at Ha Dong General Hospital.*

MATERIALS AND METHODS

1. Subjects

30 patients with femoral trochanteric fractures who underwent surgery were enrolled in the study, all these patients underwent osteosynthesis with proximal femoral locking plates at Ha Dong General Hospital from January 2018 to February 2022.

* *Inclusion criteria:* Patients ≥ 16 years old; patients with femoral trochanteric fractures were treated with surgery using locking plates; patients have complete clinical and subclinical information; patients agreed to participate in the study.

* *Exclusion criteria:* Cases of fracture in the femoral trochanter area due to pathology; patients < 16 years old; patients who are paralyzed and unable to walk before surgery; cases of medical record information are incomplete.

2. Methods

* *Research design:* A retrospective, cross-sectional descriptive study was conducted.

* *Definition of variables:* Data on age, sex, and causes of accidents; classification of intertrochanteric fracture according to AO; the total amount of blood transfused before, during, and 48 hours after surgery; the femoral neck angle after surgery, classification of Baumgaertner MR [2], and complications were recorded for each patient.

* *Evaluation methods:*

- Based on subclinical:

+ The femoral neck angle after surgery: Measured on routine pelvic X-rays taken immediately after surgery.

Assessed by measuring the femoral neck angle on the healthy side, the femoral neck angle on the broken side before surgery, immediately after surgery, and when the bone heals. The femoral neck angle is classified according to value groups: 125 - 135 degrees; 120 - < 125 degrees; and < 120 degrees. If the femoral neck angle after surgery reaches a value of 125 - 135 degrees, it is considered good.

+ Time over 6 months since surgery. Evaluate the results of anatomical recovery correction after surgery based on conventional radiographs of the pelvis; based on the classification of Baumgaertner MR [2], divided into 3 levels: Good (the anatomical correction is normal or slightly abducted, anteroposterior flexion displacement is no more than 20 degrees, the fracture gap is no more than 4mm); average (one of the standards is not met at a good level); bad (correction does not meet any standards).

+ The primary postoperative assessment was evidence of osseous consolidation on plain anteroposterior and lateral radiographs. Union was considered present if there was osseous continuity between the greater trochanter and the femur and if there was no evidence of trochanteric migration or broken hardware.

+ All radiographs were reviewed by both authors, and consensus was reached for each patient.

- Based on clinical:

+ Skills and ability to self-solve daily tasks such as living and working activities.

+ Joint range of motion based on Harris hip score [3]. With this tool, functional status can be categorized as excellent (90 - 100 points), good (80 - 89 points), fair (70 - 79 points), or poor (< 70 points). Physical exam was assessed for range of motion, presence of limp, hip abduction strength (tested standing and manually in the lateral decubitus position), and presence of trochanteric pain or crepitation on palpation.

* *Statistical analysis:* Data were processed according to medical statistical methods using SPSS 22.0 software.

3. Ethics

Subjects all agreed and voluntarily participated in the research, with a clear explanation of the purpose of the research to improve the quality of diagnosis and treatment. Information about research subjects is respected and kept confidential.

RESULTS AND DISCUSSION

Table 1. Age and gender distribution (n = 30).

Age	Gender		Total (n)	Ratio (%)
	Male	Female		
16 - 45	2	1	3	10
46 - 59	2	2	4	13.3
60 - 79	2	6	8	26.7
≥ 80	5	10	15	50
Total	11	19	30	100
Ratio (%)	36.7	63.3	100	100

The largest age group was ≥ 80 years old, accounting for 50% of patients. The youngest age was 38 , and the oldest was 98. The average age was 69.6.

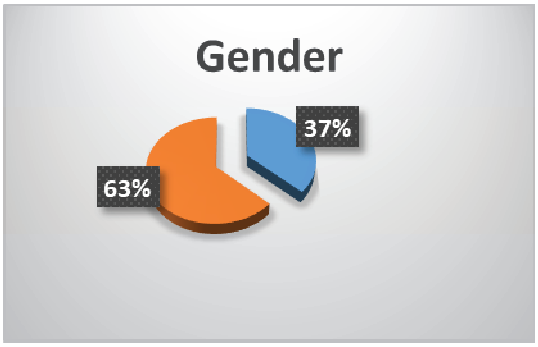


Figure 1. Distribution of patients by gender (n = 30).

Female patients with femoral trochanteric area fractures accounted for 63.3% while male patients accounted for 36.7%.

In most studies, the proportion of female patients with trochanteric area fractures is higher than that of male patients. In our research group, there were 19 female and 11 male patients, and the male-to-female ratio was 1:1.72.

As the age increases, there are more female patients with femoral trochanteric area fracture than male patients. Perhaps because osteoporosis in elderly females is more severe than in males, bone fractures are more common. This result is similar to the study of Le Tat Thang (2023) 1:2.4. [4]

Table 2. Causes of accidents.

Causes	Labor accidents	Traffic accidents	Living accidents	Total
Number (n)	4	7	19	30
Ratio (%)	13.3	23.4	63.3	100

Traffic accidents and work accidents were the main causes of femoral trochanteric area fractures in people whose ages < 60, while daily life accidents were the main cause of trochanteric area fractures in people > 60 years old.

The majority was daily life accidents (19/43 patients, accounting for 63.3%). The most common mechanism of injury is falling and hitting the buttocks on a hard floor (floor, yard, toilet, etc.). Traffic accidents had only 7 cases (23.4%), and work accidents had 4 cases (13.3%) patients of working age.

Nguyen Tien Binh et al. (2002) studied 52 patients, all of whom had femur fractures due to daily life accidents (100%) [5]. In the research by Le Quang Tri, the main cause is also daily life accidents with a rate of 73.2% [6].

The results reflect reality because the elderly (> 60 years old) have thin bones in old age, and even a slight trauma can cause bone fractures. The femoral trochanter is a spongy bone area where bone shape changes, so when osteoporosis occurs, this is a weak spot that can easily cause fractures.

Table 3. Classification of lesions according to AO (n = 30).

Classification	A_1			A_2			A_3			Total
	$A_{1.1}$	$A_{1.2}$	$A_{1.3}$	$A_{2.1}$	$A_{2.2}$	$A_{2.3}$	$A_{3.1}$	$A_{3.2}$	$A_{3.3}$	
Number (n)	0	1	3	3	7	7	2	2	5	30
Ratio (%)		13.3			56.7			30		100

According to AO grading, grade A2 fractures accounted for the highest rate of 55.7%, grade A3 accounted for 30%, and grade A1 accounted for 13.3%.

Table 4. Blood transfusion before, during and 48 hours after surgery (n = 30).

Blood transfusion	0mL	250mL	500mL	750mL	Total
Number (n)	1	13	15	1	30
Ratio (%)	3.3	43.4	50	3.3	100

The proportion of patients requiring blood transfusion before, during, and 48 hours after surgery was 96.7%. The structure of the femoral trochanter area was mainly spongy bone, with rich blood vessels. When a bone fractures in this area, the patient often loses a significant amount of blood in addition to the amount of blood lost during surgery. Therefore, the issue of blood transfusion during and after surgery needs to be raised. However, the amount of blood needed for transfusion is different depending on each case, depending on the type of fracture, early or late surgery, ability to correct, surgery time, etc.

Table 5. The relationship between fracture classification and fracture reduction (n = 30).

Adjust	Classification fracture									Total
	A_{11}	A_{12}	A_{13}	A_{21}	A_{22}	A_{23}	A_{31}	A_{32}	A_{33}	
Good	0	1	3	3	7	6	2	1	4	27
Not good	0	0	0	0	0	1	0	1	1	3
Total	0	1	3	3	7	7	2	2	5	30

Most cases of fracture correction achieve good results, the neck and body angle reach 125 - 130 degrees, accounting for 90%, not good only accounted for 10%.

Table 6. Results of hip joint range of motion (n = 30).

Range motion	Normal	Decrease 10 - 30%	Decrease > 30 - 50%	Decrease > 50%	Total
Number (n)	15	10	3	2	30
Ratio (%)	50	33.3	10	6.7	100

The good range of hip movement after surgery was 50%, the range of hip movement reduced by 10 - 30% was 33.3%, and over 30% was 16.7%. Early treatment is a decisive factor in the ability to restore hip mobility function.

However, this depends heavily on the patient's efforts and the support of family members, so the results are not always as desired.

Table 7. Results of walking function (n = 30).

Function	Very good	Good	Medium	Bad	Total
Number (n)	15	11	3	1	30
Ratio (%)	50	36.7	10	3.3	100

Checking the clinical results, 26/30 patients (86.7%) can walk normally and very well; 3/30 patients (10%) limped, had pain when exerting themselves, and had to use crutches for support; 1 patient (3.3%) had frequent pain and could not walk. Cases of severe, continuous pain are among patients of older age, pre-existing osteoarthritis, and difficulty exercising.

Table 8. Results of a bone union based on X-ray (n).

Bone union	Good	Bad	Septic non-union	Pseudo-arthrosis	Necrosis of the femoral head	Total
Number (n)	29	1	0	0	0	30
Ratio (%)	96.7	3.3	0	0	0	100

In our study, 29/30 patients (96.7%) had good bone union. With complex fractures and elderly patients, the surgery cannot be prolonged for too long, so the problem of adjusting the axis is difficult and it is difficult to achieve the anatomical position. In our opinion, the priority is that the bones remain firm so that the patient can sit up early, avoid complications due to prolonged lying down, and create favorable conditions for the patient.

Table 9. Classification of clinical and radiological results (n).

Classification	Very good	Good	Average	Poor	Total
Number (n)	15	11	3	1	30
Ratio (%)	50	36.7	10	3.3	100

The number of patients with very good and good results accounted for 86.7%, significantly higher than the number of patients with average results of 10% and patients with poor recovery of 3.3%.

Some research projects on the treatment of femoral trochanteric area fractures by other authors have shown the following results:

Dinh The Hai (2016) treated 29 elderly patients with femoral trochanteric area fractures using the locking plate [7], with the following Nguyen Trung Sinh results [8]: Very good: 24.1%; good: 51.7%; average: 20.7%; poor: 3.5%.

Compared with the results of previous studies, it was found that the results obtained in the treatment of intertrochanteric femoral area fractures with locking plates at Ha Dong General Hospital were quite good results.

CONCLUSION

In the study, among 30 patients with femoral trochanteric fractures using a locking plate at Ha Dong General Hospital from January 2018 to February 2022, we found general results according to Nguyen Trung Sinh's standards [8]: Very good: 50%; good: 36.7%; average: 10%; poor: 3.3%.

This treatment method firmly immobilizes the fracture, allowing the patient to mobilize and practice early rehabilitation. It is convenient for patients to return to daily life, reducing the rate of complications encountered. Thus, it improves the quality of life for patients and reduces the burden on families and society.

REFERENCE

1. Bartonícek J. Proximal femur fractures: The pioneer era of 1818 to 1925. *Clin Orthop Relat Res.* Feb 2004; (419):306-310.

2. CSLDKJ Baumgaertner MR. The value of the tip-apex distance in predicting failure of fixation of peritrochanteric fractures of the hip. *J Bone Joint Surg (Am).* Jul 1995; 77(7):1058-1064.

3. Harris W. Traumatic arthritis or the hip after dislocation and acetabular fractures: Treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg [Am].* 1969; 51:737-755.

4. Lê Tất Thắng. Nghiên cứu đặc điểm tổn thương, kết quả điều trị gãy kín vùng mấu chuyển xương đùi bằng kết hợp xương nẹp khoá. *Luận án Tiến sỹ Y học.* Học viện Quân y. 2023:50-51.

5. Nguyễn Tiến Bình. Phân loại gãy đầu trên xương đùi. Phân loại tổn thương do chấn thương. *Nhà xuất bản Quân đội Nhân dân, Hà Nội.* 2009:190-215.

6. Lê Quang Trí. Điều tri gãy liên mấu chuyển xương đùi người già bằng khung cố định ngoài. *Luận án Tiến sỹ Y học. Đại học Y Dược Thành phố Hồ Chí Minh*. 2014:96-97.

7. Đinh Thế Hải. Đánh giá kết quả điều trị gãy liên mấu chuyển xương đùi bằng kết xương nẹp khóa tại Bệnh viện Trung ương Quân đội 108. *Luận văn Bác sỹ chuyên khoa cấp 2. Học viện Quân y.* 2016:87-89.

8. Nguyễn Trung Sinh. Chấn thương chỉnh hình. *Nhà xuất bản Y học. Hà Nội.* 2013:243-245.

RESULTS OF ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION USING THE ALL-INSIDE TECHNIQUE AT PHO NOI HOSPITAL: A RETROSPECTIVE STUDY

Nguyen Van Cuong[1], Pham Anh Tuan[2], Do Van Chuc[1]*
Nguyen Duc Thang[1], Nguyen Ngoc Vinh[1]

Abstract

Objectives: To evaluate clinical and functional outcomes of anatomic anterior cruciate ligament (ACL) reconstruction using the all-inside technique. ***Methods:*** A retrospective study on 30 patients who underwent primary anatomic ACL reconstruction using the all-inside technique from January 2019 to January 2022 at Pho Noi Hospital, Hung Yen. The Lysholm score and International Knee Documentation Committee (IKDC) score were used to evaluate outcomes before surgery, at 6 months, and ≥ 12 months postoperatively. ***Results:*** Among 30 patients who underwent all-inside ACL reconstruction, the mean follow-up time was 26.5 months (13 - 50 months), the mean age was 32.43 ± 10.6, and the mean duration between the injury and surgery was 9.4 months. The mean graft diameter was 7.8 ± 0.5mm (6.5 - 9mm), the mean femoral tunnel length was 28.8 ± 1.7mm (25 - 35mm), and the mean tibial tunnel length was 30.5 ± 2.1mm (30 - 35mm). Functional outcomes: Preoperatively, the IKDC score was 55.2 ± 0.5, and the Lysholm score was 61.1 ± 4.5. At 6 months postoperatively, symptoms improved; at over 12 months postoperatively, the IKDC score was 91.5 ± 2.5. The rate of normal and nearly normal grades was 96.7% and the Lysholm score was 94.1 ± 2.5. The rate of excellent and good grades was 100%. ***Conclusion:*** The ACL reconstruction using the all-inside technique provides good functional outcomes and anteroposterior knee stability at short-term follow-up.

Keywords: Anterior cruciate ligament; Reconstruction; All-inside technique; Single bundle; Clinical outcome.

---

[1]Orthopedic Trauma and Burns Department, Pho Noi Hospital, Hung Yen

[2]Department of Mathematics and Information, Vietnam Military Medical University

[*]Corresponding author: Nguyen Van Cuong (manhcuongft23@gmail.com)

Date received: 16/01/2024

Date accepted: 18/3/2024

http://doi.org/10.56535/jmpm.v49i4.709

INTRODUCTION

Anterior cruciate ligament tear is a detrimental event for every patient, and appropriate management is important to ensure patients return to pre-injury activity and to prevent long-term complications due to the knee injury. Surgical management of the ACL tear appears to be the answer for patients who wish to restore their pre-injury activity level. The all-inside technique is one of the surgical techniques that has many advantages in ACL reconstruction. An all-inside technique of anterior cruciate ligament reconstruction is defined as creating the bone socket from the articular side of the tibia rather than conventional full-length tunneling through the knee joint and outer cortex [1] (*Figure 1*). Following the evolution of the technique, the suspensory cortical button is mainly utilized as a graft fixation method. The advantages of combining the all-inside technique and suspensory graft fixation include biomechanically higher graft durability, greater preservation of flexion strength, and less bone tunnel widening in long-term follow-up [2, 3]. The purpose of this study is: *To evaluate clinical and functional outcomes of anatomic ACL reconstruction using the all-inside technique*.

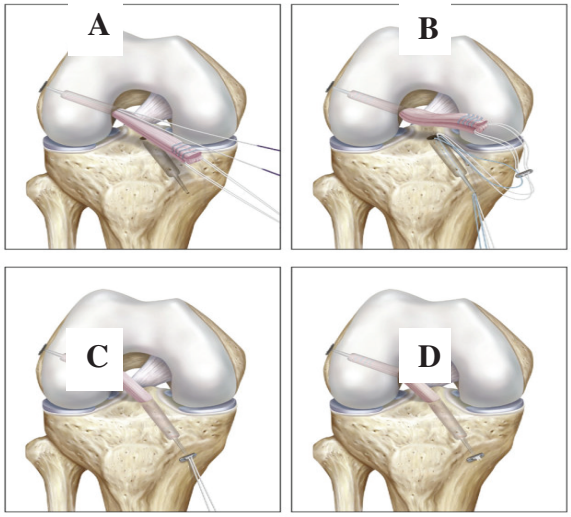


Figure 1. The all-inside technique of ACL reconstruction: In all 4 illustrations, the lateral femoral cortical suspensory button is flipped.

A. The tibial side of the graft loop is shown to be linked to ACL TR-RT;

B. Tibial ACL TR-RT passing sutures and pull sutures are passed into the tibial socket;

C. Emerging from the proximal AM tibial metaphysis (bottom right) is the ACL TR-RT pull sutures (white);

D. The tibial ACL TR-RT pull sutures have been tied and cut [1].

MATERIALS AND METHODS

1. Subjects

30 patients who underwent primary anatomical ACL reconstruction using the all-inside technique from January 2019 to January 2022 at Pho Noi Hospital, Hung Yen.

* *Inclusion criteria:* Single-bundle (SB) ACL reconstruction using the all-inside technique, age 16 - 60, minimum of 6 months of clinical follow-up, full medical records, pre-operation X-ray, and MRI.

* *Exclusion criteria*: Revision cases, multiple ligament injuries.

2. Methods

* *Research design:* A retrospective study.

* *Sample size*: A convenient sample size.

* *Research methodology:* All patients had their medical histories recorded, and were given a clinical examination and laboratory tests in accordance with the guidelines. The patient variables included sex, age. The operative variables included meniscus lesion, graft diameter, femoral tunnel length, tibial tunnel length.

All categorical variables are reported as frequency and percentage.

* *Outcome assessment:* Functional outcome measures, including the Lysholm score with 4 grades (excellent: 91 - 100 points; good: 84 - 90 points; fair: 54 - 83 points; unsatisfactory: ≤ 64). The IKDC score with 4 grades (A: Normal; B: Nearly normal; C: Abnormal; D: Severely normal) according to the criteria: Knee joint effusion, passive range of motion limitation, knee joint examination (Lachman's test and Pivot shift's Test), physical examination of the compartments, knee joint degeneration, single leg hop test. All criteria were used to evaluate outcomes before surgery, at 6 months, and ≥ 12 months postoperatively [4, 5].

* *Statistical analysis:* The software Microsoft Excel and SPSS 20.0 were used.

3. Ethics

Ethical approval was obtained from the institutional review board of Pho Noi Hospital, Hung Yen, Viet Nam. Informed consent was obtained from the patients included in the study. All procedures in this study were performed following the ethical standards of the 1964 Helsinki Declaration and its later amends or comparable ethical standards. The authors declare to have no conflicts of interest.

RESULTS

For all 30 patients who underwent all-inside ACL reconstruction, we achieved follow-up on all 30 patients at a minimum of 6 months. The mean follow-up time was 26.5 months (13 - 50 months). There were 20 males (66.7%) and 10 females (33.3%) with a mean age of 32.43 ± 10.6 (19 - 52 years). In 21 of 30 (70%) patients, ACL injury occurred during sports, the mean duration between the injury and surgery was 9.4 months (2 weeks - 8 years). 14 of 30 patients (46.67%) were without additional meniscal tears. The mean graft diameter was 7.8 ± 0.5mm (6.5 - 9mm). The mean femoral tunnel length was 28.8 ± 1.7mm (25 - 35mm), and the mean tibial tunnel length was 30.5 ± 2.1mm (30 - 35mm) (*Table 1*).

Table 1. Demographic characteristics.

Variables	Quantity (n)	Percentage (%)
No. of patients	30	
Follow-up	26.5 months (13 - 50 months)	
Sex		
Male	20	66.7
Female	10	33.3
Age (years)	32.43 ± 10.6	
Meniscus lesion		
Lateral	7	23.33
Medial	6	20
Lateral and medial meniscus	3	10
No meniscus injury	14	46.67
Graft diameter	7.8 ± 0.5 (6.5 - 9mm)	
Femoral tunnel length	28.8 ± 1.7mm (25 - 35mm)	
Tibial tunnel length	30.5 ± 2.1mm (30 - 35mm)	

A significant improvement of symptoms, pain, daily function, and sports activity level, assessment based on IKDC and Lysholm scores. The IKDC score

preoperatively was 55.2 ± 0.5, and the Lysholm score was 61.1 ± 4.5. At 6 months postoperatively, the symptoms improved; at over 12 months postoperatively, the IKDC score was 91.5 ± 2.5 and the Lysholm score was 94.1 ± 2.5 (*Table 2*).

Table 2. Clinical outcomes change over time.

Follow-up	IKDC	Lysholm
Preoperation	55.2 ± 0.5	61.1 ± 4.5
6 months	84.1 ± 2.1	88.1 ± 2.5
≥ 12 months	91.5 ± 2.5	94.1 ± 2.5

A B

Figure 2. 3 years postoperatively, the range of motion of the knee joint, including the knee flexion at 135° (A) and the knee extension at 0° (B).

Table 3. Lysholm score (n = 30).

Lysholm score	Pre-operation (%)	Post-operation (%)	
		6 months	≥ 12 months
Excellent	0	60	70
Good	0	36.7	30
Fair	76.7	3.3	0
Unsatisfactory	23.3	0	0

At 6 months postoperatively, the rate of excellent was 60%, at over 12 months it was 70%; good at 6 months was 36.7%, and at over 12 months was 30%.

Table 4. IKDC score (n = 30).

IKDC score	Pre-operation (%)	Post-operation (%)	
		6 months	≥ 12 months
A	0	66.7	73.3
B	0	30	23.4
C	30	3.3	3.3
D	70	0	0

According to the IKDC, there was improvement in knee function both before and after surgery. At over 12 months, the normal level was 73.3%, and nearly normal was 23.4%

DISCUSSION

The study found that primary anatomic ACL reconstruction using the all-inside technique provides good functional outcomes and anteroposterior knee stability at short-term follow-up. This study demonstrates an improvement in IKDC and Lysholm scores preoperatively compared to postoperatively (*Table 2*). The all-inside ACL reconstruction technique has been used in clinical practice for several years, and many studies have addressed the clinical outcome of this technique in the

literature. Genc (2023) [6] assessed over 20 athletes in various sports who underwent anterior cruciate ligament reconstruction using the all-inside technique. The patients were evaluated preoperatively and 6 months postoperatively. The preoperative IKDC score was 50.15 ± 8.8 and the Lysholm score was 72.5 ± 8.13. After 6 months, there was a significant improvement in the IKDC score (91.25 ± 6.23), and the Lysholm score postoperatively at 98.2 ± 2.66 with $p < 0.05$. Lubowitz (2013) [7] compared the clinical outcomes of the all-inside technique and the full tibial tunnel technique. The author found a difference in IKDC scores between baseline (47.4 ± 15) and over 12 months follow-up (86.5 ± 11.6) for the all-inside group, which is comparable with the findings of this study, with 55.2 ± 0.5 and 91.5 ± 2.5, respectively.

According to the IKDC assessment (*Table 4*), preoperatively, 9 of 30 patients (30%) were at level C, and 21 of 30 patients (70%) were at level D. After 6 months, there were 1 of 30 patients (3.3%) at level C, 8 of 30 patients (66.7%) at level A, and 9 of 30 patients (30%) at level B. According to the Lysholm scoring system (*Table 3),* preoperatively, all patients were at fair and unsatisfactory levels (76.7% and 23.3%, respectively). After 6 months post-surgery, patients reached excellent and good levels (60% and 36.7%, respectively). There was a significant improvement in knee function pre and postoperatively at 6 months, which is consistent with other studies [8]. In another study, Mohsen Hussen (2012) [9] retrospectively investigated the outcomes of anterior cruciate ligament reconstruction with the SB and double-bundle (DB) techniques; the mean Lysholm score was 93.9 ± 4.3 in the DB group and 93.5 ± 3.3 in the SB group at a mean of 30 months of follow-up, which is identical to the findings of this study 94.1 ± 2.5 at over 12 months of follow-up. The subjective IKDC score was 93.3 ± 5.9 in the DB group and 93.1 ± 5.2 in the SB group, which is found to be comparable to the results of the current study of 91.5 ± 2.5.

Surgical outcomes depend on factors such as graft diameter, femoral tunnel position, and tibial tunnel position. In the study by Do Quoc Cuong (2022) [10], it was found that graft size influenced knee joint function according to Lysholm scores. Snaebjörnsson (2017) [11] observed that increasing the graft diameter by approximately 7 - 10mm reduced the likelihood of reoperation by less than 0.86 times for

each 0.5mm increase. The positions of the femoral and tibial tunnels also impact postoperative knee function. Determining the correct tunnel positions, synonymous with accurately restoring the original position and orientation of the ligament, is crucial for successful reconstruction.

Limitations: More long-term studies are needed to assess the durability and long-term impacts of surgical intervention on patient's functional outcomes comprehensively.

CONCLUSION

The ACL reconstruction using the all-inside technique provides good functional outcomes and anteroposterior knee stability at short-term follow-up.

REFERENCES

1. Lubowitz JH, Amhad CH, Anderson K. All-inside anterior cruciate ligament graft-link technique: Second-generation, no-incision anterior cruciate ligament reconstruction. *Arthroscopy: The Journal of Arthroscopic Related Surgery*. 2011; 27(5):717-727.

2. Mayr R, Heinrichs CH, Eichinger M, Coppola C, Schmoelz W, Attal R. Biomechanical comparison of 2 anterior cruciate ligament graft preparation techniques for tibial fixation: Adjustable-length loop cortical button or interference screw. *The American Journal of Sports Medicine*. 2015; 43(6):1380-1385.

3. Monaco E, Redler A, Fabbri M, et al. Isokinetic flexion strength recovery after ACL reconstruction: A comparison between all inside graft-link technique and full tibial tunnel technique. *The Physician Sports Medicine*. 2019; 47(1):132-135.

4. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *The American journal of sports medicine*. 1982; 10(3):150-154.

5. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the international knee documentation committee subjective knee form. *The American journal of sports medicine*. 2001; 29(5):600-613.

6. Genç AS, Güzel N, Yılmaz AK, et al. Post-operative modified all-inside acl reconstruction technique's clinical outcomes and isokinetic strength assessments. *Diagnostics*. 2023; 13(17): 2787.

7. Lubowitz JH, Schwartzberg R, Smith P. Randomized controlled trial comparing all-inside anterior cruciate ligament reconstruction technique with anterior cruciate ligament reconstruction with a full tibial tunnel. *Arthroscopy: The Journal of Arthroscopic Related Surgery*. 2013; 29(7):1195-1200.

8. Trần Quốc Lâm. Nghiên cứu giải phẫu và đối chiếu trong phẫu thuật nội soi tái tạo dây chằng chéo trước khớp gối bằng kĩ thuật một bó tất cả bên trong. *Luận án tiến sĩ y học*. Đại học Y Hà Nội. 2018.

9. Hussein M, van Eck CF, Cretnik A, Dinevski D, Fu FH. Individualized anterior cruciate ligament surgery: A prospective study comparing anatomic single-and double-bundle reconstruction. *The American Journal of Sports Medicine*. 2012; 40(8):1781-1788.

10. Đỗ Quốc Cường. Kết quả điều trị nội soi tái tạo dây chằng chéo trước khớp gối bằng phương pháp tất cả bên trong tại Bệnh viện Quân y 175. *Tạp chí Y học Việt Nam*. 2022; 1(513):1-4.

11. Snaebjörnsson T, Hamrin Senorski E, Ayeni OR, et al. Graft diameter as a predictor for revision anterior cruciate ligament reconstruction and KOOS and EQ-5D values: A cohort study from the Swedish National knee ligament register based on 2240 patients. *The American Journal of Sports Medicine*. 2017; 45(9):2092-2097.

A CASE REPORT: MULTIPLE SCHWANNOMAS OF THE SPINE

Nguyen Xuan Phuong[1] *, Nguyen Thanh Bac*[1*]

Abstract

Neurinoma is the most common benign nerve sheath tumor originating from Schwann cells. Most benign neurinomas are single. Patients with multiple tumors can be seen in conditions such as neurofibromatosis (NF) type 2, whose typical sign is bilateral vestibular schwannomas. Some authors have described it as a form of schwannoma, which presents multiple schwannomas without associating with NF factors. Studies have recognized this condition as the third major form of NF [1, 2, 3]. We describe a case of multiple schwannomas in the spine associated with schwannomas by imaging and surgical features to clarify the characteristics of this disease.

Keywords: Multiple schwannomas; Microsurgery.

INTRODUCTION

Neurinoma, originating from Schwan cells and occurring in the spine, has an incidence of 0.3 - 0.5/100,000 people contracting annually. The disease incidence in men and women is the same. Schwannomas are usually detected at 40 - 50 years of age, and the most common location is in the lumbar region and cauda equina of the spinal cord. Tumors are usually benign and round in shape with clear boundaries [1, 2]. Clinical manifestations are discreet; magnetic resonance imaging enables the detection of the disease and the making of appropriate treatment plans.

CASE REPORT

A 66-year-old female patient with a history of dull, vague back, and leg pain for 3 months was treated as an outpatient and admitted to the hospital with pain that gradually worsened over the past 1 month, especially when in a supine position and having intermittent claudication. The pain gradually increases,

[1]**Department of Neurosurgery, Military Hospital 103**

[*]**Corresponding author: Nguyen Thanh Bac (bacnt103@gmail.com)**

Date received: 10/01/2024

Date accepted: 18/3/2024

http://doi.org/10.56535/jmpm.v49i4.684

making it impossible for the patient to sleep. It can be relieved when in a sitting position, and the patient sometimes falls due to sudden leg weakness.

Clinical examination showed normal muscle tone and strength in all muscle groups of both legs. Patellar and Achilles tendon reflexes reduced symmetrically. There were no abnormalities in pain or sensation of depth. There was a positive Lasegue sign at 60 degrees on both sides. There was no sphincter disorder. The patient did not have any lumps under the skin.

Magnetic resonance imaging of the lumbar spine showed multiple intradural lesions of varying sizes, hypointensity on T2 and T1 at the D12 - L3 level, and relatively homogeneous and hyperintensity after injecting contrast agent. The lesions were arranged in a series along the spinal canal and caused compression of the conus and cauda equina to the right, with the most significant compression of the roots at the L1 level (*Figure 1*). MRI scans of the brain, cervical spine, and thoracic spine did not detect any abnormal mass.

The patient was not diagnosed with NF type 1 or 2 and had no relevant family or medical history.

The tumors were removed by hemilaminectomy and microsurgical excision of the tumor. Schwannomas hid anterior to the conus and cauda equina nerve roots (*Figure 1*). During surgery, tumors were dissected and removed with the help of micro-neurosurgery instruments to preserve the function of the nerve roots. Five tumors that pressed the cone and adhered to the cauda equina roots were completely removed *(Figure 3*).

The postoperative progress was stable. Symptoms of back pain and leg pain were completely resolved. Tendon and bone reflexes returned to normal in a short time. The patient only had a slight decrease in pain sensation in the distribution area of the left L1 root.

Histopathology (*Figure 2*) demonstrated focal cellular tumors and showed well-circumscribed discrete nodules with compact (A) and loosely textured (B) infiltrative areas, minor focal lymphocytic inflammation, and hyalinized blood vessels. The lesions were surrounded by a thin fibrous capsule, showed markedly increased mitotic activity (1 M F/10 HPF) without significant nuclear size change, nuclear hyperchromia, or necrosis, and were classified as schwannoma. Immunoassay was positive for the S100 marker (cytoplasmic and nuclear staining) and negative for EMA and PR.

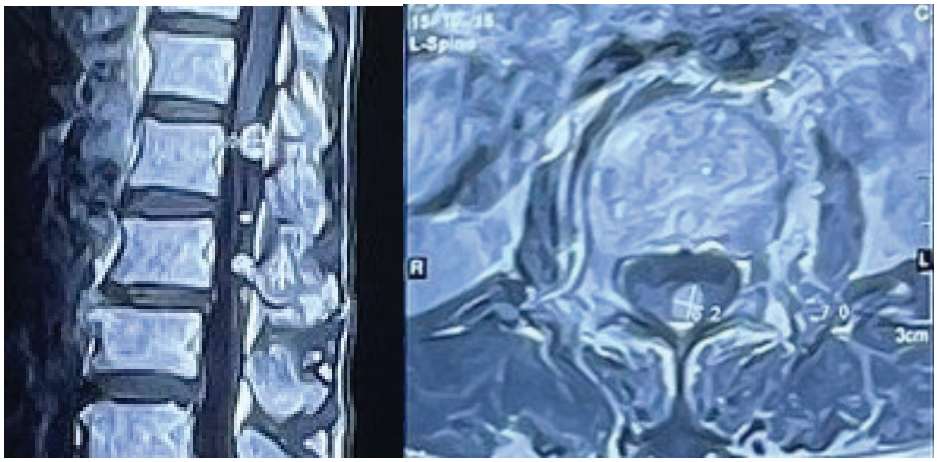


Figure 1. Tumors on magnetic resonance imaging.

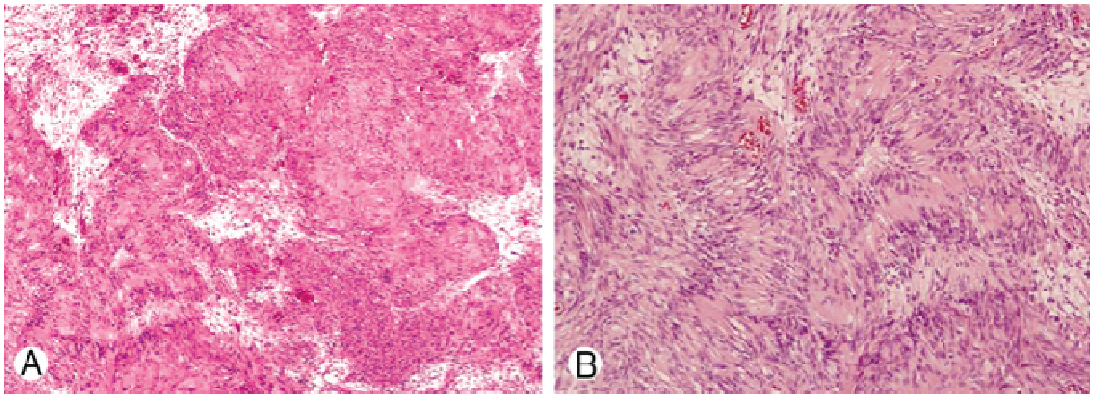


Figure 2. Histopathology of schwannom, ×100, stained Hematoxilin & Eosin (H&E) (A). Typical Verocay type ×400, H&E stain (B).

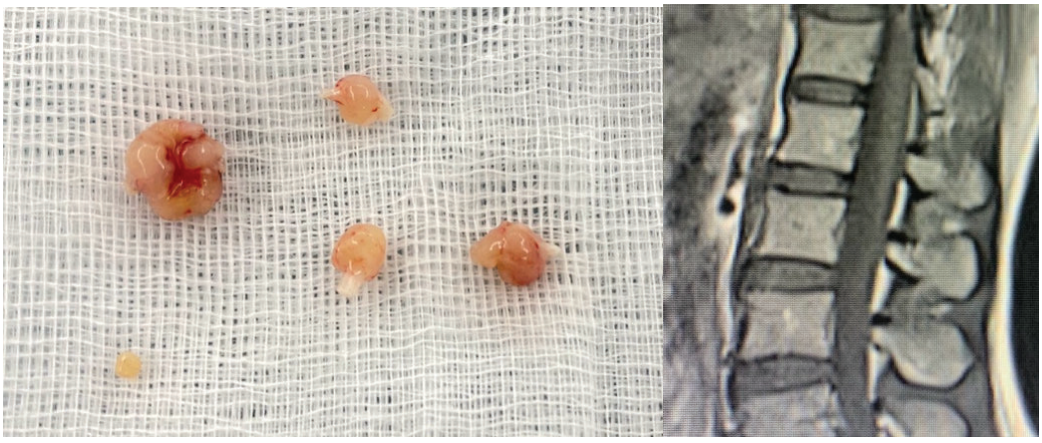


Figure 3. Five tumors were removed and a postoperative MRI of the spine.

DISCUSSION

Neurinoma is a common condition, often associated with NF1 or NF2, whereas multiple Swchanomas are rarer and may not be associated with these factors. [1, 2, 4, 5]. Symptoms of the disease often manifest as dull lumbar spine pain and vague pain, gradually increasing over time, and despite aggressive multimodal medical treatment, most patients do not have pain relief. There are 62% of patients who do not have pain relief after intensive medical treatment [6]. Depending on the location of the injury and the degree of nerve root compression, sensory disorders appear in the corresponding dominant area. Symptoms of sensory disorders often occur first due to tumors growing from sensory roots.

According to the classification of Ibrahim S (2017), neurinomas are divided into 4 types based on the location of the tumor with the dura mater and spinal canal. The tumors in our study are type I which are localized exclusively intradurally. This is the most common type, accounting for 51%. Symptoms do not improve much after surgery for type I and IV patients. However, in our case, the patient's pain symptoms were almost completely relieved [7, 8].

Neurinomas are removed by posterior hemisection and microsurgery. In cases of spinal anesthesia, neuromuscular electrical monitoring can be performed during surgery to avoid damage to functional roots and nerves. The 30-degree endoscope can be used in combination to visually explore the spinal canal, avoiding missed lesions [9]. In our patient, the largest tumor was near the foramen, so we used an endoscope during surgery to observe the foramen to remove the tumor thoroughly and avoid missing it.

Neurinomas are usually benign and can recur. According to author Gerganov, the recurrence rate of neurofibromas is generally about 0.5 - 5%, and long-term postoperative monitoring with imaging diagnostics is necessary to detect tumor recurrence [10]. Our patient was examined with magnetic resonance imaging 6 months after surgery, and no tumor recurrence was detected.

CONCLUSION

Multiple neurinomas develop along the nerve roots. Therefore, the spinal cord must be examined with an MRI before surgery. Radical tumor removal surgery preserves nerve function and brings good long-term results to the patient. As the tumor has the ability to recur, long-term monitoring and examination are required after surgery.

Acknowledgments: We would like to thank Military Hospital 103 for its professional support. We claim our research is conducted in an absolutely objective manner and have no conflicts of interest.

REFERENCES

1. Chen SL, Liu C, Liu B, et al. Schwannomatosis: A new member of neurofibromatosis family. *Chin Med J (Engl)*. 2013; 126(14):2656-2660.

2. Seppälä MT, Sainio MA, Haltia MJ, et al. Multiple schwannomas: schwannomatosis or neurofibromatosis type 2? *J Neurosurg*. 1998; 89(1):36-41.

3. Gonzalvo A, Fowler A, Cook RJ, et al. Schwannomatosis, sporadic schwannomatosis, and familial schwannomatosis: A surgical series with long-term follow-up. *Clinical article. J Neurosurg*. Mar 2011; 114(3):756-62.

4. Koontz NA, Wiens AL, Agarwal A, et al. Schwannomatosis: The overlooked neurofibromatosis? *AJR Am J Roentgenol*. 2013; 200(6):646-653.

5. Qin S, Yang C, Ren H. Cerebral hernia caused by a thoracic surgery for multiple schwannomas in a patient with Neurofibromatosis type 2. *Turk Neurosurg*. 2013; 23(2):245-248.

6. Merker VL, Esparza S, Smith MJ, et al. Clinical features of schwannomatosis: A retrospective analysis of 87 patients. *Oncologist*. 2012; 17(10): 1317-1322.

7. Ioannidis P, Mamouli D, Foroglou N. Expanding schwannomatosis phenotype. *J Neurooncol*. 2015; 122(3):607-609.

8. Sun I, Pamir MN. Non-Syndromic Spinal Schwannomas: A novel classification. *Front Neurol*. 2017; 8:318.

9. Fedaravičius A, Michaeli A, Diomin V, et al. Single root multiple spinal schwannomas: Case report, treatment strategy and review of literature. *Int J Surg Case Rep*. 2020; 74:113-116.

10. Gerganov V, Petrov M, Sakelarova T. Schwannomas of Brain and Spinal Cord. *Adv Exp Med Biol*. 2023; 1405:331-362.

THỂ LỆ GỬI BÀI ĐĂNG TRONG TẠP CHÍ Y - DƯỢC HỌC QUÂN SỰ

Tạp chí Y - Dược học quân sự xuất bản 9 số/năm, đăng tải các công trình nghiên cứu, các bài tổng quan về y dược học quân sự, y sinh học và y xã hội học, những thông tin Y - Dược học trong nước và quốc tế, thông tin về nghiên cứu và đào tạo.

I. Một số yêu cầu về bài đăng công trình nghiên cứu khoa hoc.

1. Bài gửi đăng công trình nghiên cứu khoa học chưa đăng ở bất kỳ tạp chí quốc gia nào.

2. Các thuật ngữ thống nhất theo từ điển Bách khoa Việt Nam.

3. Bài gửi đăng đánh máy bằng tiếng Việt, rõ ràng, cách dòng, một bài không dài quá 7 trang khổ A4, kể cả bảng biểu và tài liệu tham khảo. Các danh từ tiếng Việt nếu dịch từ tiếng nước ngoài viết kèm theo tiếng nước ngoài. Các chữ viết tắt phải có chú thích các từ gốc của các chữ viết tắt.

4. Trình tự các mục trong bài:

a) Đầu đề.

b) Họ và tên tác giả: Không ghi học hàm, học vị, chức danh. Có ghi chú đơn vị công tác của từng tác giả ở cuối trang thứ nhất bài báo.

c) Nội dung:

Tóm tắt tiếng Việt và tiếng Anh, bao gồm mục tiêu, đối tượng và phương pháp nghiên cứu, kết quả và kết luận (khoảng 250 từ). Ghi từ khóa tiếng Việt và tiếng Anh.

Đặt vấn đề: bao gồm cả phần mục tiêu nghiên cứu.

Đối tượng và phương pháp nghiên cứu.

Kết quả nghiên cứu và bàn luận.

Kết luận.

Tài liệu tham khảo.

Chỉ sử dụng những bảng, biểu, hình ảnh cần thiết và phải có chú thích rõ. Mỗi bài viết không quá 5 hình. Cuối bài phải nêu rõ xuất xứ của công trình, làm tại đâu, thời gian.

Tài liệu tham khảo (không quá 10 tài liệu và phải mang tính cập nhật) sắp xếp theo thứ tự xuất hiện trong bài báo. Tài liệu tham khảo ghi theo thứ tự sau: Họ tên tác giả, tên cuốn sách (bài báo), tên tạp chí, năm xuất bản, tập, số và trang tài liệu tham khảo
Dùng font Unicode.

5. Mỗi tác giả đứng tên đầu của bài báo chỉ được đăng tối đa một bài trong một số.

6. Bài gửi đăng không trả lại bản thảo.

7. Cuối mỗi bài báo, tác giả ghi số điện thoại cá nhân và địa chỉ email của người chịu trách nhiệm chính.

II. Đối với các bài tổng quan, thông tin, bài dịch.

- Đối với các bài tổng quan cần có đầy đủ các tài liệu tham khảo và nguồn số liệu đã được trích dẫn trong bài. Tác giả bài tổng quan ghi rõ chức danh, học hàm, học vị, chuyên ngành, cơ quan và hội chuyên khoa ở phần ghi chú cuối trang đầu tiên của bài tổng quan. Bài tổng quan cũng được đánh máy trên khổ A4 và không dài quá 7 trang kể cả biểu bảng và tài liệu tham khảo.

- Các thông tin, bài dịch cần ghi rõ xuất xứ của nguồn dữ liệu. Đối với bài dịch cần chụp toàn văn bài báo tiếng nước ngoài gửi kèm theo bản dịch.

*** BÀI VIẾT XIN GỬI VỀ TẠP CHÍ Y DƯỢC HỌC QUÂN SỰ - HỌC VIỆN QUÂN Y**
SỐ 160 ĐƯỜNG PHÙNG HƯNG, HÀ ĐÔNG - HÀ NỘI
ĐIỆN THOẠI: 069. 566. 250 HẶC GỬI THEO ĐỊA CHỈ EMAIL: tcydhqs@vmmu.edu.vn