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Cross-sectional Study

Factors associated with TNF-alpha levels in patients with indirect inguinal hernia: A cross-sectional study

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ABSTRACT

Introduction: Risk factors associated with inguinal hernia include a patent processus vaginalis due to an obliteration failure, defects in the transversalis fascia, increased intra-abdominal pressure, smoking, malnutrition, genetic factors, connective tissue defects and impaired collagen metabolism. Type I collagen predominates in the fascia, which plays a key role in the development of an inguinal hernia. Molecularly, the production of abnormal matrix components or increased inflammatory mediators in collagen such as TNF-α has a very important role in the occurrence of inflammation in inguinal hernias. The study aimed to determine the factors associated with TNF-alpha levels in patients with indirect inguinal hernias.

Methods: We evaluate the effect of TNF-α on the anterior rectus sheath tissue collagen in 46 patients with indirect inguinal hernia using a cross-sectional study design. The ELISA method was used to evaluate the levels of collagen TNF-α. We used ANOVA, Pearson's correlation test, and Spearman's correlation test to determine which results were statistically significant, defined by a p-value < 0.05.

Results: Body mass index (BMI) average results were 25.7 kg/m^2. Mean clinical onset was 70.13 months across 46 samples. TNF-α levels and BMI were correlated ($p = 0.009$). The TNF-α levels in the clinical-grade group ($p = 0.044$) and the clinical onset group ($p = 0.047$) varied according to ANOVA.

Conclusion: Clinical onset, BMI, clinical grade of indirect inguinal hernia, and TNF-α levels have a significant relationship.

1. Introduction

Inguinal hernias occur due to the protrusion of the abdominal viscus into the obliteration failure of the processus vaginalis. More generally, all conditions that increase pressure in the intra-abdominal cavity can contribute to hernias. The Hasselbach's triangular transversalis fascia, a triangle that connects the inguinal ligament inferiorly, the rectus abdominis muscle's lateral border medially, and the inferior epigastric vessels laterally [1], is weak, resulting in a direct inguinal hernia.

The formation of primary inguinal hernias is hypothesized to be influenced by abnormal collagen metabolism. The most prevalent connective tissue fiber is collagen, and the cross-linkage ratio between thick and thin, type I and type III collagen has a significant impact on the connective tissue's tensile strength and mechanical stability. A decrease in the ratio of type I (spindles of thin fibers) to type III collagen (spools of thick fibers) is caused by an increase in type III collagen [1,2]. The collagen fibers will become thinner as a result, which may lead to establishing a hernia or herniation. Furthermore, collagen levels in the transverse fascia and the rectus sheath have been demonstrated to decline with age. A systematic review found that inguinal hernias patients have a lower type 1:3 collagen ratio in abdominal wall tissue than controls. Although differences between hernia subtypes have been demonstrated, there is insufficient data overall. One investigation found that patients with lateral hernias had less type I collagen and significantly higher type III total collagen than controls [3,4]. In contrast to adults, children showed no change in the 1:3 ratio collagen subtype [5].

Two enzymes evaluated for their responsibility in the development of inguinal hernia are matrix metalloproteinase (MMP) (for ECM degradation) and lysyl oxidase (for collagen and elastin cross-linking). Increased MMP activity disrupts the collagen ratio in inguinal hernias,

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and decreased lysyl oxidase activity affects the mechanical strength and elasticity of the connective tissue. MMP-1, MMP-2, and MMP-9 levels were significantly elevated in the transverse fascia of inguinal hernia patients. In patients with medial hernias, the cytokine transforming growth factor-β1 (TGF-β1) raises MMP-2 levels. Increased elastase activity is also seen in medial hernias and contributes to the disruption of the elastic apparatus of the transverse fascia [5,6].

TNF-α, also called 17-kDa cytokine, is produced by inflammation-activated macrophages that cause a broad range of local metabolic and cellular reactions. TNF-α′s property of pleiotropy is distinguished by numerous pathways that lead to a variety of reactions, including cell proliferation, differentiation, and cell death. TNF-α inhibits the synthesis of elastin, osteocalcin, and type I collagen, the most important structural component of connective tissue, which lowers extracellular matrix (ECM) deposition. TNF-αalso inhibits the activation of type I collagen gene expression in cell cultures by transforming growth factor-β (TGF-β). This disrupts the physical structure and strength of the abdominal wall's collagen matrix, which instigates the harm in people with this condition [7].

It is important to understand the pathogenesis of inguinal hernia, the relationship between collagen abnormalities and the occurrence of inguinal hernias, and the importance of TNF-α factors in the complex inflammatory mechanism in inguinal hernias to support a better disease outcome. Researchers are interested in conducting TNF-α analysis on collagen anterior rectus sheath tissue in inguinal hernia patients. The study aimed to determine the factors associated with TNF-α levels in patients with indirect inguinal hernias.

2. Methods

This observational analytical study uses a cross-sectional analysis to examine the profile of collagen TNF-α levels in rectus anterior sheath tissue in individuals with indirect inguinal hernia. The investigation was conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital in Makassar, Indonesia.

The Hasanuddin University Faculty of Medicine Ethics Commission approved this study (number: 0523/U.N.4.6.4.5.31/P.P.3.6/2021), and it is registered with the Research Registry (number: 7361). Our findings are provided in this report in accordance with the Strengthening the Reporting of Cohort Studies in Surgery guidelines [8].

Indirect inguinal hernia patients who had not undertaken surgery, as well as those who were willing to participate in the trial and gave their informed consent, were eligible. Patients who had previously undergone surgery for an indirect inguinal hernia (relapse), patients with prostate illness or inguinal region tumors, patients with chronic lung disease, and patients with a BMI of less than 18 kg/m^2 (undernutrition) were excluded.

2.1. Inguinal hernias

Inguinal hernias are classed as femoral, direct, and indirect based on the location of the herniation in relation to surrounding structures [9–11]. All patients treated for indirect inguinal hernia at our hospital were included in the research. This study's sample is drawn from a larger population study that fits research criteria (consecutive sampling).

2.2. Body mass index (BMI)

We used the Indonesian Ministry of Health's BMI classification [12]: underweight (<18.5 kg/m^2), normal weight (18.5 ≤ 24.9 kg/m^2), overweight (25.0 ≤ 29.9 kg/m^2), and obese (>30.0 kg/m^2).

2.3. Age groups

According to the Indonesian Ministry of Health's (2009) standards [12], we divided people into three age groups: young adults (11–19 years old), adults (20–60 years old), and elderly age (>5 years old).

2.4. Clinical onset

Clinical onset refers to the interval between when people with an indirect inguinal hernia first notice symptoms associated with the hernia diagnosis and when they receive definitive therapy (surgery).

2.5. Clinical grade

We define the clinical grade based on the severity of the hernia. Grade is determined by the patient's medical history and clinical symptoms (signs of peritonitis, degree of inflammation, mechanical blockage, cellulitis, and systemic shock) [13].

A hernia is classified as reducible when the contents of the hernia can be inserted intra-abdominally through the layers of the abdominal wall. The hernia is classified as irreducible/incarcerated if the contents are trapped and cannot be returned to the main peritoneal cavity [14,15].

2.6. Sample excision from the anterior rectus sheath

During surgery, a 0.5 × 1 cm sample was excised in the muscular tissue of the rectus femoris sheath (Fig. 1). Before homogenization, the tissue was washed in phosphate-buffered saline (PBS) solution (pH 7.4) and weighed. It was minced and homogenized by vortexing the tissue in PBS solution. The completed solution was kept at −200 °C. The sample was incubated at room temperature for 60 min. The solution was centrifuged at 2200–3100 rpm for 16–20 min before completing the test.

2.7. Sample examination

The TNF-α Sandwich ELISA (catalog no. E0082Hu) from BT-Lab (Zhejiang, China) was used to examine collagen TNF-α levels, following the manufacturer's recommendations.

2.8. Statistical analysis

SPSS Statistics 26.0 (IBM Corp.) was used to examine the data collected. The Kolmogorov–Smirnov test was conducted to determine data normality. The Pearson correlation was performed if we found normal data distribution; the Spearman correlation was used if we found abnormal data distribution. A p-value of less than 0.05 was considered statistically significant. If the bivariate analysis revealed numerous statistically significant factors, a multivariate analysis was carried out using several linear tests.

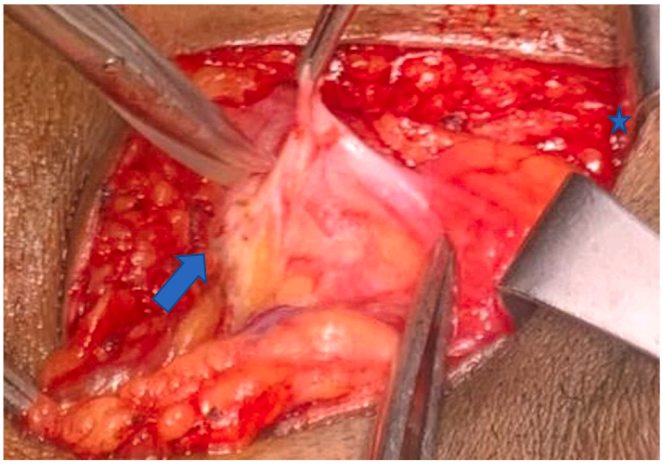

Fig. 1. Excision specimen from the anterior rectus sheath (arrow).
Note: pubic tubercle (asterisk).

3. Results

We evaluated 46 participants who met the requirements (Table 1). The shortest time between clinical onset and treatment was 2 months, and the longest time was 144 months (5 years and 10 months). Table 1 shows that most of the indirect inguinal hernia patients in this study (60.9%) were elderly; 41.3% were overweight, and 28.3% were obese. Based on the occupational category (Fig. 2), civil servants account for 19.6% (9/46) of lateral inguinal hernia patients, followed by students (21.7%, 10/46), entrepreneurs (34.8%, 16/46), and laborers (23.9%, 11/46).

The clinical grade before surgery was found to be reducible hernia in 34.8% (16/46) of the cases and irreducible hernia in 65.2% (30/46) of the cases (Fig. 3).

The ANOVA test was used in each age group to analyze the mean difference between levels of TNF-α based on age. The p-value was 0.646 ($p > 0.05$), indicating that there was a nonsignificant difference in the mean levels of TNF-α and age (Table 2).

The relationship between TNF-α levels and age group was examined using the post hoc test and the LSD method. With $p = 0.391$, the average level of TNF-α in the adult patient group did not differ statistically significantly from that of the senior group.

The ANOVA test was used to determine the significance of the mean TNF-α levels in the occupational groups and gave a p-value of 0.450 ($p > 0.05$), proving that there was no significant difference between occupations and mean TNF-α levels, even though the data in Table 2 show the lowest TNF-α mean levels in the laborer group.

The ANOVA test was used to determine the significance of the difference in mean TNF-α levels in BMI groups, yielding a p-value of 0.009 ($p < 0.05$), proving that there was a statistically significant difference between BMI and mean TNF-α, with the mean levels of TNF-α increasing as the BMI increased (Table 2).

The relationship between TNF-α levels and BMI was examined by the post hoc test using the LSD method. The obese patient group showed a significant mean TNF-α difference compared to the normal BMI group with a correlation value of $p = 0.004$. The mean TNF-α difference between the obese and the overweight groups had a correlation value of $p = 0.450$.

Spearman's test was used to determine whether there was a significant correlation between the clinical onset and TNF-α levels. The test found a p-value of 0.047 ($p < 0.05$), indicating a statistically significant correlation between the clinical onset and TNF-α levels. The correlation coefficient of 0.294 (medium significance) indicated a directly proportional correlation between longer onset and higher TNF-α levels (Table 2).

The ANOVA test was used to determine the significance of the difference in mean TNF-α levels in the clinical-grade group, yielding a p-value of 0.044 ($p < 0.05$), indicating that there was a significant mean difference between clinical grade and TNF-α levels (Table 2).

Multiple linear regression tests were used to evaluate the association of all significant variables with TNF-α levels. The first B value of 0.058 is held by the BMI group variable, the second is hernia onset with a B value of 0.001, and the last is clinical grade with a B value of −0.062, as determined by the order of importance of the factors to TNF-levels. The constant value is 0.855 when Sig is set to 0.000 (see Table 3).

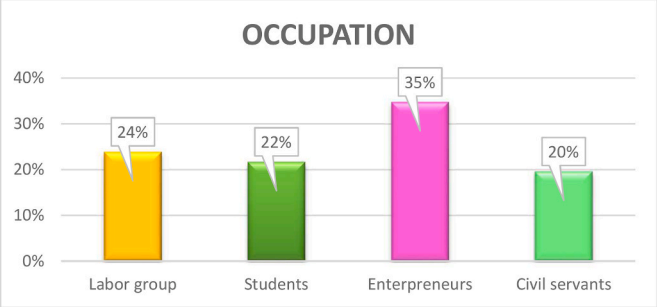

Fig. 2. Characteristics of hernia patients by occupation.

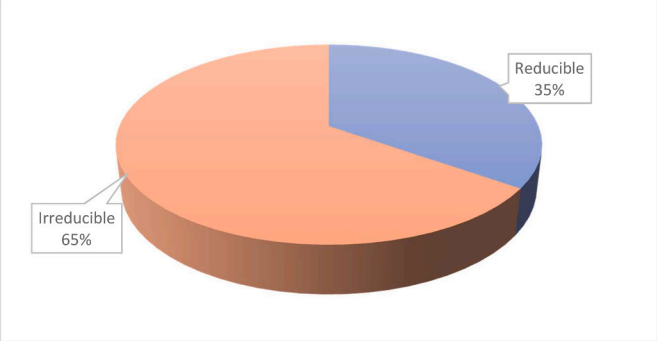

Fig. 3. Clinical grade of hernias.

4. Discussion

Hernia is a complex disease influenced by external and endogenous sources [16]. Collagen composition changes, linked to accelerated collagen degradation, play a role in hernia formation [16,17]. Changes in fascial and systemic tissues appear to be influenced by collagen composition. Type I collagen predominates in the fascia, which has a main role in the development of inguinal hernias. According to a systematic review, researchers discovered that patients with inguinal hernias have a lower 1:3 collagen ratio in the abdominal wall tissue, and this imbalance is related to fascial tissue weakening or aponeurosis [18,19]. TNF-α is one of the pro-inflammatory cytokines that play a major role in the breakdown of the ECM and also cause collagen alterations [20,21].

ECM degradation is involved in tissue remodeling, organogenesis, morphogenesis, wound healing and tissue repair [22]. TNF-α induces collagenase synthesis, which promotes ECM breakdown. TNF-α inhibits the synthesis of structural components, which lowers ECM deposition.

Table 1
Patient characteristics.

	Mean	Std. Deviation	Minimum	Maximum	Amount	Percent (%)
Age (years)	42.4783	20.7693	15	69		
11–19					4	8.7
20–60					14	30.4
>60					28	60.9
BMI (kg/m^2)	25.7391	3.69044	19	30		
Normal (≥18.5 ≤ 24.9)					14	30.4
Overweight (≥25.0 ≤ 27)					19	41.3
Obesity (≥27.0)					13	28.3
Clinical onset (months)	70.1304	43.81913	2.00	144.00		
TNF-α (ng/mL)	0.8687	0.1250439	0.4184	1.1013		

Table 2
Distribution in mean levels of TNF-α by age, occupational group, BMI, clinical grade and onset.

	TNF-α Rate						
Variable		n	Mean (ng/mL)	SD	Minimum	Maximum	p
Age	Teenager	4	0.8466	0.0229	0.8206	0.8700	0.646
	Adult	14	0.8469	0.1501	0.4350	1.0071	
	Seniors	28	0.8828	0.1209	0.4184	1.1013	
	Total	46	0.8687	0.1250	0.4184	1.1013	
Occupational group	Civil servant	9	0.8638	0.0488	0.7895	0.9186	0.450
	College student	10	0.8466	0.0824	0.7251	0.9906	
	Laborer	11	0.0914	0.0914	0.7348	1.1013	
	Entrepreneur	16	0.8489	0.1820	0.4184	1.0623	
	Total	46	0.8678	0.0184	0.4184	1.1013	
BMI	Normal	14	0.7884	0.16555	0.41	0.92	0.009
	Overweight	19	0.8911	0.06736	0.78	0.99	
	Obesity	13	0.9226	0.10337	0.73	1.10	
	Total	46	0.8687	0.12504	0.41	1.10	
Clinical grade	Irreducible	30	0.9016	0.08524	0.7251	1.1013	0.044
	Reducible	16	0.8072	0.16330	0.4184	0.9502	
	Total	46	0.4687	0.1250	0.4184	1.1013	
Onset[a]	TNF-α rate	46					0.047

[a]) Spearman's Test; Correlation Coeff (r) = 0.294.

Table 3
Multivariate analysis between all significant variables with levels of TNF-α

Model	Variable	Standard coefficient		Sig
		B	Std. error	
I	Constant	0.786	0.082	0.000
	BMI	0.058	0.021	0.010
	Onset	0.001	0.000	0.101
	Clinical grade	−0.062	0.035	0.087
II	Constant	0855	0.072	0.000
	Clinical grade	−0.074	0.035	0.040
	BMI	0.058	0.022	0.012

The basic structural components of connective tissue are elastin, osteocalcin, and type I collagen. In cell culture, TNF-α inhibits the activation of type I collagen gene expression by TGF-β [7].

The study subjects were all male. The youngest subject with a lateral inguinal hernia was 15 years old, and the oldest was 69. The average age of inguinal hernia patients in the research sample was 42.4 years. Worldwide, approximately 20 million inguinal hernia operations are performed annually. Inguinal hernias account for 75% of all abdominal wall hernias. Men account for roughly 90% of all inguinal hernias, and women account for approximately 10%. The prevalence of inguinal hernias is high in two age groups, those younger than 5 years and those older than 74 [23]. Inguinal hernia affects 5% of men aged 25–34 years, rising to 10% for those aged 35–44 years, 18% for those aged 45–54 years, 24% for those aged 55–64 years, and 31% for those aged 65–74 years. Nearly half of men over 75 (45%) will experience an inguinal hernia [11].

The lowest BMI among the participants was 19 kg/m^2, and the highest was 30 kg/m^2. The average BMI of participants was 25.7 kg/m^2. According to Rekha et al.'s [24] findings, a normal BMI was related to a high incidence of inguinal hernia in both men and women. Men with a normal BMI are more likely to have an inguinal hernia than those with a low BMI. Fat is hypothesized to be responsible for an increase in the frequency of inguinal hernias because obesity can produce an increase in abdominal pressure. In most studies, however, the risk of inguinal hernia was lower in overweight or obese people. According to Rosemar et al. [24], a one-unit rise in BMI (from 3 to 4 kg/m^2) reduces the incidence of inguinal hernia by 4% in male patients between 47 and 55 years old. However, the biological effects of collagen levels and determinants of sex and age are still being discussed, according to Sorensen et al. although clinical evidence indicates that the incidence of inguinal hernia is highest in males and the risk increases with age [16,17]. This is in line with Agustina's findings, which found that obesity is linked to the occurrence of inguinal hernia in people under the age of 25 [25].

The difference in the incidence of hernias by sex, especially in men, is related to differences in embryological characteristics in men and women. Biochemically it can be explained that abnormalities in collagen levels and TNF-α affect abnormalities of the internal annulus and stretching of the transversalis fascia, which in turn affect abnormalities of the muscular support function of the abdominal wall. Both age and gender factors play a significant role in the incidence of recurrent hernia [16].

According to Taniguchi et al. age did not find a significant impact on collagen structure and levels [26]. In general, the amount of collagen will decrease with age. Children are made up of 80% type I collagen and 15% type III collagen [27]. Type I collagen continues to increase until age 35, after which it will decrease with age. The relationship between age and the amount of collagen is not yet clear, but the amount of collagen in humans older than 60 is significantly less than in younger adults [28]. There was no statistically significant association between age and TNF-α levels in this study, with the ANOVA average test yielding a value of $p = 0.646$ ($p > 0.05$), indicating that the difference in mean TNF-α levels at different ages is not statistically significant.

There was no statistically significant relationship between work and level of TNF-α with a p-value = 0.450 ($p > 0.05$). However, careful observation reveals that the average level of TNF-α tends to be lower in the laborer group than in other professions. Hernias generally occur as a result of structural failure and are often reported to be triggered by risk factors such as heavy lifting, chronic obstructive pulmonary disease, advanced age, and smoking. It is generally believed that work requiring heavy lifting, such as laborer occupations, is associated with the development of hernias. Several studies have linked hernias and working conditions because heavy lifting can increase intra-abdominal pressure [29]. Ruhl et al. [30] concluded that the risk factors that could trigger the occurrence of hernias, apart from degenerative changes in collagen, were prostatism, constipation, cough, and physical activity in the form of lifting habits (heavy load). The physical activity of lifting heavy weights in is identical to the work of the laborors [30,31].

Flich et al. found a relation between the nature of labor and the appearance of hernia [32]. According to a study, there is no clinical evidence to support the theory that a hernia can arise as a result of a single traumatic or strenuous event [33]. Wantz concludes that heavy lifting can cause hernia development only if a deficiency exists previously [34,35]. Balamaddaiah [36] conducted a study in India that revealed that most (52.4%) inguinal hernia patients had heavy work or physical activities such as lifting heavy weights, followed by digestive

disorders and smoking. Although hernia is a condition of chronically increased intra-abdominal pressure, comorbidities such as chronic cough, constipation, cirrhosis, pregnancy, loss of turgor from the Hasselbach area, and peripheral collagenolysis caused by smoking can increase the risk factors for hernias and a history of abdominal surgery.

The ANOVA mean test between BMI and TNF-α levels shows a p-value = 0.009, which revealed a significant direct correlation between BMI and TNF-α levels in a linear relationship. Guevara et al. investigated the amino acid profile of overweight and obese patients, categorizing the population as normal weight ($18.5 \leq 24.9$ kg/m^2), overweight ($25 <$ 29.9 kg/m^2), and obese (>30 kg/m^2) based on BMI. Young individuals who were overweight or obese had a reduced hernia rate compared to those who were normal weight. In 2007, Sorensen et al. reported that dietary factors were not correlated to collagen levels and TNF-α levels in obese samples. Obesity, on the other hand, was shown to be a predictor of recurrent hernia in clinical studies [37]. TNF-α′s effect on obesity has been linked to insulin resistance, increased free fatty acid production by adipocytes, decreased adiponectin synthesis, and poor insulin signaling [38,39]. TNF-α promotes serine phosphorylation of insulin receptor-substrate-1 (IRS-1) in cultured adipocytes and hepatocytes, but TNF-α suppresses the tyrosine phosphorylation and receptor activity of insulin IRS-1. This is the molecular mechanism responsible for insulin's reduced involvement, especially in obese people. If the BMI value is overweight or obese, the TNF-α level is above normal due to increased TNF-α secretion by adipose tissue. Adipose tissue is a dynamic endocrine organ that secretes adipokines, including TNF-α, that contribute to systemic and vascular inflammation [21].

The current study revealed a significant association between the clinical onset of inguinal hernia and the level of TNF-α with a correlation coefficient of 0.153 (medium significance strength). The longer the clinical onset of the hernia, the higher the level of TNF-α. Changes in the tissue structure of adult hernia patients are related to the secondary pathophysiology of collagen metabolism, which ultimately impacts collagen levels and TNF-α levels, according to a study published by Taniguchi et al. [26] that examined the TNF-α in the inguinal sheath's supporting tissues. Collagen metabolism is linked to hernias, and the principal pathophysiology is related to the patency of the processus vaginalis, which causes the occurrence of indirect inguinal hernia [26].

The current study discovered that clinical grades and TNF-α levels had a statistically significant connection. Wagh et al. discovered that the anterior rectus sheath above the defect was thinner than typical in individuals with direct inguinal hernia, which was attributable to a decrease in collagen. The fibroblast cultures collected from the anterior rectus sheath indicate this could be related to decreased fibroblast proliferation [10].

Compared to patients with indirect inguinal hernias and controls, the anterior rectus sheath of patients with direct inguinal hernias was thinner, had significantly lower collagen and elastin content, and had a lower hydroxyproline-to-proline ratio. These data imply that patients with direct inguinal hernia have a thinner rectus sheath with less collagen and a transverse fascia with greater levels of immature collagen, resulting in fascial resistance reduction [2].

A study of five patients with a direct inguinal hernia found that the anterior rectus sheath over the defect was thinner than usual due to a decrease in collagen, especially hydroxyproline levels. This may be due to decreased fibroblast proliferation, as demonstrated by fibroblast culture taken from the anterior rectus sheath [40,41].

In 2016, Ivanov [42] showed that the pathophysiology of hernia is caused by a lack of collagen production and an amino acid deficiency. A protein produced by leukocytes can trigger and activate the immune system against inflammatory responses such as hernias. Under normal circumstances, pathogens in the immune system trigger non-specific and specific immunity. Although collagen is formed by amino acids closely related to TNF-α, TNF-α itself is a component that affects collagen quality, particularly in the breakdown of the ECM, resulting in a drop in the ratio of type I to type III collagen when TNF-α levels rise.

Multivariate analysis revealed that BMI has the most significant correlation with the levels of TNF-α in patients with lateral inguinal hernia, followed by variable onset and clinical grade. The onset variable was found to be significant in the bivariate analysis but not significant in the multivariate analysis. Therefore, the onset of events has a small effect on the level of TNF-α. This finding corresponds with the Guevara et al. study, which discovered that patients with a BMI in the obese group have a more complex amino acid profile than those with a BMI in the underweight group [17,24].

TNF-α levels are detected above normal values at overweight or obese BMI ranges, according to Laurence et al. due to increased TNF-α secretion by adipose tissue, which plays a role in collagen deterioration [21]. According to Asserin et al. both the aging process and a bad diet might impair the body's collagen content, affecting not only the amount of collagen in skin but also the quality of the collagen network. During skin aging, the fragmentation of the dermal collagen network by MMPs has been described to have major consequences for both the skin's structure and the microenvironment of the dermal fibroblasts [43].

Our study used a limited sample size, and the research mainly focused on TNF-α levels. The co-occurrence of other characteristics such as comorbidities, lifestyle, and smoking are confounding factors that could not be controlled by convenience sampling. We suggest a larger-scale study to explore different ELISA levels in the collagen of rectus sheath tissue and control confounding factors that can create bias in the research.

5. Conclusion

Clinical onset, BMI, clinical grade of indirect inguinal hernia, and TNF-α levels have a significant relationship. However, there is no correlation between TNF-α levels and age or occupation in patients with indirect inguinal hernia.

Ethical approval

All procedure for human experiment has been approved by Ethics Commission Faculty of Medicine, Hasanuddin University Number: 0523/U.N.4.6.4.5.31/P.P.3.6/2021.

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None.

Author contribution

Warsinggih, Devby Ulfandi, and Amir Fajar wrote the manuscript and participated in the study design. Warsinggih, Devby Ulfandi, Amir Fajar, and Muhammad Faruk drafted and revised the manuscript. Warsinggih, Devby Ulfandi, Amir Fajar, and Muhammad Faruk performed treatment and surgery. Warsinggih, and Devby Ulfandi performed bioinformatics analyses and revised the manuscript. All authors read and approved the final manuscript.

Registration of research studies

This study is registered with the Research Registry and the unique identifying number is: researchregistry7361.

Guarantor

Warsinggih.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Consent

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients have given their written informed consent on admission to use their prospective data base and files for research work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.103858.

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