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Original article

Gamma-glutamyl transferase profile in various degrees of pruritus in cholestatic patients

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Abstract. *Introduction:* Cholestasis, a condition affecting liver function, can lead to complications like pruritus, fatigue, osteoporosis, hyperlipidemia, and steatorrhea. Pruritus is a presenting symptom in chronic cholestasis, often seen in intrahepatic disorders. It can impair life quality and be difficult to diagnose. Gamma-glutamyl transferase (GGT), a biomarker used to detect cholestasis, is linked to pruritus by inhibiting glutamine synthesis and stimulating glutamyl transferase. This study aims to determine the profile of GGT in cholestatic individuals with varying levels of pruritus. *Methods:* This cross-sectional observational study was conducted at RSUP Wahidin Sudirohusodo in Makassar and involved cholestatic patients diagnosed with chronic cholestasis. We collected demographic information, measured CGT levels in a lab prior to therapy, and used a 5D pruritus scale to measure pruritus. Data analysis was conducted using SPSS 26. *Results:* The study involved 78 participants, with a mean age of 53.8 ± 14.6 years. GGT values ranged from 15-784, and pruritus scale scores varied from 5-25. A significant negative correlation was found between GGT levels and pruritus scale scores ($r = -0.510$; $p < 0.001$). The mean GGT level was significantly lower in very severe pruritus (104.3) and greatest in moderate pruritus (356.9). *Conclusion:* This study concludes that greater levels of GGT correlate with reduced pruritus severity.

Key words: pruritus, cholestasis, gamma-glutamyl transferase, biomarkers

Introduction

Liver function is essential for human survival (1). Cholestasis involves reduced bile synthesis or flow at the hepatocyte or cholangiocyte level, limiting bile's ability to reach the duodenum due to bile duct flow issues (2). Cholestasis can be classified as extrahepatic or intrahepatic, with extrahepatic cases often caused by bile duct obstructions and gallbladder dysfunction. Chronic cholestasis can lead to liver cirrhosis, failure, and is a leading cause of pediatric liver transplants (3). Cholestasis complications include pruritus, fatigue, osteoporosis, hyperlipidemia, fat-soluble vitamin malabsorption, and steatorrhea, often with high morbidity and mortality (4,5). In patients with chronic cholestasis, pruritus is a presenting symptom, arising years before clinical signs appear (6). Pruritus may be an early sign in chronic cholestasis, commonly seen in intrahepatic disorders, such as primary biliary cirrhosis, chronic hepatitis B and C, and intrahepatic cholestasis during pregnancy, though it also occurs in extrahepatic diseases like primary sclerosing cholangitis and pancreatic head cancer (7,8). While pruritus is a mild and manageable symptom, severe cases can impair life quality, causing sleep loss, depression, and suicidal thoughts (9,10). Pruritus is challenging to diagnose and treat due to its subjective nature (8). Identification, early diagnosis, and preventative or curative therapy of pruritus can improve patients' quality of life (4). Identifying differences between cholestatic

patients with and without pruritus could reveal proteins or pathways for new treatments, making pruritus indicators critical (11). Pruritus in cholestatic patients is linked to pruritogen buildup in systemic circulation, influenced by the opioidergic and serotoninergic systems. Lysophosphatidic acid (LPA), a possible pruritus mediator, is produced by autotaxin (ATX) and associated with cholestatic itch. However, high ATX activity is also present in other liver diseases, making it a biomarker rather than a causative enzyme. Elevated serum bile acids and bilirubin in cholestasis are linked to itching due to the MRGPRX4 receptor for bile acids and bilirubin (11). Gamma-glutamyl transferase (GGT) is a biomarker used to detect cholestasis illness (12). GGT is a membrane glycoprotein that facilitates the transfer of gamma-glutamyl to other peptides, amino acids, and water. GGT is essential for the synthesis of glutathione (13). Through two processes, GGT is linked to pruritus: it decreases itching by inhibiting glutamine synthesis, and it stimulates the transfer of the glutamyl moiety of glutathione to pruritogens to inhibit their pruritogenic potential or improve water solubility to enhance renal excretion. GGT can degrade glutathione's glutamyl components, which can be converted to glutamate when it comes into contact with water (11). Research by Haijer et al. showed higher GGT levels in cholestatic patients without pruritus than those with it, with direct bilirubin levels being higher in those with pruritus. Upon adjusting for the severity of cholestasis using direct bilirubin, the negative correlation between GGT and pruritus persisted and increased (11). However, no previous research has been conducted on the relationship between GGT levels and the severity of pruritus. Therefore, this study aims to determine the profile of gamma-glutamyl transferase in cholestatic individuals with varying levels of pruritus.

Methods

This cross-sectional observational study was conducted at RSUP Wahidin Sudirohusodo in Makassar, starting from September 2024. The population consisted of all cholestatic patients at RSUP Wahidin Sudirohusodo in Makassar. The sample was obtained through consecutive sampling, with a minimum of 31 participants per group, resulting in a total sample size of 62 individuals. The sample size was determined using the comparison test formula for the means of two groups.The inclusion criteria for this study were: (1) age ≥ 18 years; (2) individuals diagnosed with chronic cholestasis; (3) individuals demonstrating cholestasis characterized by elevated alkaline phosphatase (ALP) levels (>120 U/L), increased recombinant bilirubin (>6 μmol/L), and elevated gamma-glutamyl transferase (GGT) levels (>50 U/L); and (4) individuals who provided consent to participate in the research and signed informed consent forms. Individuals with active primary dermatological diseases associated with pruritus were excluded. All procedures were conducted with the informed consent of the patient or their family. This study was approved by the Ethical Committee for Biomedical Research on Humans, Faculty of Medicine, Universitas Hasanuddin.

We collected demographic information, measured CGT levels in a lab prior to therapy, and used a 5D pruritus scale to measure pruritus. Degrees of pruritus were grouped into (14):

1. Quarter 1 score = 5 (no pruritus),
2. Quarter 2 score = 6-10 (mild pruritus),
3. Quarter 3 score = 11-15 (moderate pruritus)
4. Quarter score 4 = 16-20 (severe pruritus)
5. Quarter score 5= 21-25 (very severe pruritus)

The GGT test quantifies GGT enzymatic activity by combining a blood sample with a designated substrate, resulting in a quantifiable product analyzed via spectrophotometry. Increased GGT levels may indicate hepatic dysfunction, especially resulting from alcohol use or biliary obstruction. The ALP test additionally involves the assessment of enzymatic activity. To assess the GGT levels, patient's blood samples are mixed with a substrate that reacts with the GGT enzymes in the blood that undergoes a color change upon conversion by the ALP enzyme, and this color alteration is quantified using spectrophotometry. Elevated ALP levels may indicate liver problems, bone issues, or other conditions, including pregnancy. Bilirubin screening use photometry or colorimetry to quantify bilirubin concentrations in the blood, emphasizing

both total and direct (conjugated) bilirubin levels upon processing the sample, chemicals generate colored complexes, facilitating spectrophotometric analysis. Elevated bilirubin levels may signify hepatic dysfunction or hemolysis, the degradation of erythrocytes (15). The GGT, ALT, and bilirubin levels are assessed by the hospital's central laboratories independently from the author and this research. The results are then given to the author to be analyzed.

The acquired data were analyzed using SPSS 26. Mean ± SD is used to represent numerical variables, median (min-max) is used to represent numerical variables that are not normally distributed, and presence or absence is used to represent categorical variables. If the data is normally distributed, the independent sample t-test will be performed to determine the difference between two groups using numerical data distribution. If not, the Mann-Whitney U test will be employed. If the data is normally distributed, the ANOVA test will be performed to determine the difference between more than two groups using numerical data distribution. If not, the Kruskal Wallis test will be employed. The Saphiro-Wilk test was used to test for data normality. The chi-square test was used to check for differences between variables in all categorical data (if there isn't an anticipated count value <5), and the Fisher-exact test will be used if one of the cells has an expected count value <5).

Table 1. Study characteristics.

Variable	Category	n (78)	%
Gender	Male	41	52,6
	Female	37	47,4
Age	<60 years	53	67,9
	>60 years	25	32,1
Gamma GT	Normal	3	3,8
	Increased	75	96,2
Pruritus	No	25	32,1
	Yes	53	67,9
Severity of Pruritus	Mild	10	18,9
	Moderate	15	28,3
	Severe	13	24,5
	Very severe	15	28,3

Results

The study involved 78 participants, consisting of 41 males (52.6%) and 37 females (47.4%). Among them, 53 participants (67.9%) were younger than 60 years of age, while 25 participants (32.1%) were older than 60 years, with a mean age of 53.8 ± 14.6 years. GGT values ranged from 15-784, with a median of 224.0 and a mean of 284.3 ± 201.0. Pruritus scale scores varied from 5-25, with a median of 11.0 and a mean of 12.4±6.9. According to the pruritus degree classification, the majority were classified as moderate and severe, each comprising 28.3% (Table 1).

This study also analyzed the correlation between serum GGT levels and the severity of pruritus. A significant negative correlation was identified between GGT levels and pruritus scale scores ($r = -0.510$; $p < 0.001$) (Figure 1), indicating that greater GGT levels correspond to lower pruritus scale scores. The correlation between GGT levels and pruritus scale values is classified as strong (R>0.500) according to the R value (Table 2). The average GGT levels were significantly lower in those with pruritus (141.4) compared to those without pruritus (375.2) ($p<0.05$) (Table 3). The mean GGT level was significantly lower in cases of very severe pruritus (104.3) and greatest in moderate pruritus (356.9) ($p<0.001$) (Table 3).

Discussion

Pruritus is a common manifestation in hepatic disorders, particularly cholestatic conditions (16). Also a common symptom in 80% to 100% of individuals with cholestatic liver disease, encompassing primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and intrahepatic cholestasis of pregnancy (17). According to the pruritus degree classification, the majority fell between the moderate and extremely severe categories, each consisting of 28.3% participants. Table 2 demonstrates a significant negative correlation between serum GGT levels and the severity of pruritus, indicating that elevated serum GGT levels correspond to a reduced degree of pruritus. Despite the fact that serum GGT levels are one

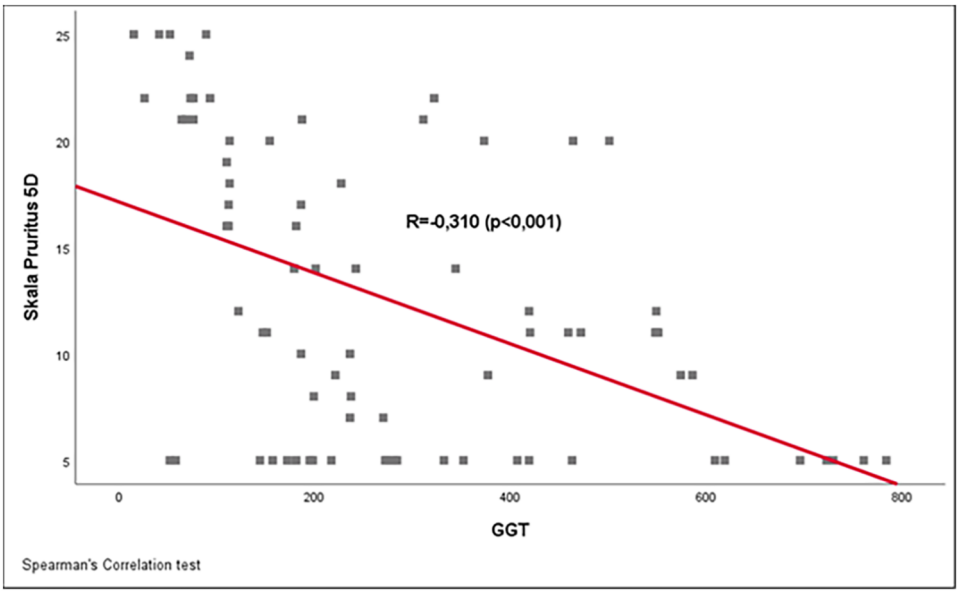

Figure 1. Correlation between GGT levels and the degree of pruritus.

Table 2. Correlation between GGT levels and the degree of pruritus.

	Severity of Pruritus (n=78)							
	Normal	Mild	Moderate	Severe	Very severe			
Gamma GT	n (%)	n (%)	n (%)	n (%)	n (%)	Total	p	r
Normal	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)	3	<0.001	-0,510
Increased	25 (33.3)	10 (13.3)	15 (20)	13 (17.3)	12 (16)	75		

Spearman's Correlation test; R=Correlation Coefficient

Table 3. Correlation between mean GGT levels and the degree of pruritus.

	Gamma GT			
Variable	n	Mean	SD	p
Pruritus				
No Pruritus	25	375,2	233,2	0,013*
Pruritus	53	241,4	169,9	
Severity of Pruritus				
Mild	10	312,2	150,5	<0,001+
Moderate	15	356,9	167,0	
Severe	13	212,0	141,0	
Very Severe	15	104,3	94,4	

*Mann-Whitney test
+ Kruskal-Walli's test

of the examinations used to diagnose cholestatic disease, there is still a lack of research on the correlation between serum GGT levels and cholestatic pruritus. Various research indicates that elevated GGT levels correlate negatively with the severity of pruritus (11). The method by which GGT inhibits the pruritus response involves glutathione, the primary antioxidant in human cells. Healthy individuals also exhibit low quantities of glutathione in their blood plasma. GGT promotes the transfer of glutamyl glutathione groups to pruritogens, hence mitigating their pruritogenic potency (11). In a previous study, Haijer et al. examined the association between GGT and cholestatic pruritus in 235 chronic cholestatic patients. They discovered a strong negative correlation between the degree of pruritus and GGT levels. The mean blood GGT level was 967 IU/L in patients without pruritus, considerably elevated compared to 561 IU/L in patients with pruritus ($p<0.001$) (11). Koofy et al. reported a significant negative correlation between GGT levels and the severity of pruritus ($r = -0.55$, $p < 0.01$). The 5-D pruritus scale correlated with blood GGT levels, revealing a higher score in individuals with normal serum GGT levels compared to those with elevated serum GGT levels (17.86 ± 6.3 vs 11.57 ± 5.2; $p = 0.01$) (18). Fujino et al., in their study on pruritus in individuals with chronic liver disease, measured pruritus using the numerical rating scale (NRS) and identified GGT as a major factor linked with pruritus (19).

Conclusion

This study concludes that greater levels of gamma-glutamyl transferase correlate with reduced pruritus severity.

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