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Risk Factors Affecting the Occurrence of Gallstones at Prof. Dr. IGNG Visits General Hospital Denpasar Bali

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ABSTRACT

Backgrounds: Gallstone disease is a common medical condition closely associated with risk factors such as diabetes mellitus, smoking habits, hypercholesterolemia, and genetic or racial characteristics. ***Objective:*** This study aims to identify the relationship between these risk factors and the occurrence of gallstones. ***Methods:*** This observational analytical study with a case-control design involved 120 patients at Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, divided into a case group with a diagnosis of gallstones (n=56) and a control group without a diagnosis of gallstones (n=64). Data were collected through medical records and analyzed using chi-square and logistic regression. ***Results:*** No significant relationship was found between diabetes mellitus (p=0.274) and smoking habits (p=0.980) with the occurrence of gallstones. However, female gender (OR=3.519; p=0.001), hypercholesterolemia (OR=3.554; p=0.008), and Balinese race (OR=0.257; p=0.004) were significantly associated with an increased risk of gallstones. Multivariate analysis showed that hypercholesterolemia was the most significant risk factor affecting the occurrence of gallstones. ***Conclusion:*** Female gender and hypercholesterolemia are significant risk factors for the occurrence of gallstones, while the Balinese race appears to be a protective factor. There is no significant relationship between diabetes mellitus and smoking habits with the occurrence of gallstones. Further research is needed to understand the mechanisms behind these relationships and the impact of lifestyle and dietary factors.

Keywords: gallstones; hypercholesterolemia; diabetes mellitus; smoking; race; gender

INTRODUCTION

Gallstones are abnormal masses that form in the bile ducts or intra-hepatic bile ducts, where the masses formed can block the ducts or move out into the intestines. This gallstone disease has been around for a long time, and it was found in the mummy of an Egyptian priestess in 1500 BC [1].

Gallstones are calcified according to the main constituent components: pure cholesterol, pure pigment, or a combination of cholesterol and pigment. According to composition, pigment stones are divided into black and brown pigment stones. Cholesterol stones and black pigment stones form in the gallbladder. Meanwhile, brown pigment stones form in blocked and infected bile ducts.

Gallstones that form in the gallbladder or primary gallstones can cause acute cholecystitis or move to the bile duct and become secondary stones[2]. 80% of gallstone cases are cholesterol stones, while the rest are mixed stones[3]. In the latest research on the pathogenesis of cholesterol stones, five main factors cause cholesterol stones to form: lithogenic genes, cholesterol hypersecretion, bile duct motility disorders, cholesterol absorption factors in the small intestine, and deposition of cholesterol crystals. These five factors are being studied to see more clearly the pathological development of cholesterol-type gallstones[3].

Symptoms of gallstones vary. There are stones in the bile duct, but no symptoms yet. Then, it continued with gallstones with mild symptoms ranging from abdominal pain to symptoms of bile duct infection, pancreatitis, and gastrointestinal obstruction [4]. Recurrence of gallstones also often occurs due to multifactorial factors, including infection, abnormal bile duct structure, inflammation, and surgery [5]. Life-threatening complications that usually arise in cases of gallstones include acute cholangitis and biliary pancreatitis[2]. The number of gallstone deaths in the United States is estimated at 3,000 each year[6].

Gallstones are a common digestive disease. The incidence of gallstones in Europe and the United States reaches 10-20% of the total population[7]. In Indonesia, the incidence of gallstones has yet to be well recorded using existing data. Gallstones are the most common disease in patients seeking treatment at European digestive surgery clinics. Gallstones also have high costs to treat because of the symptoms and complications they cause[8], so gallstone disease causes social and economic problems in a country[3]. Traditionally, the main factors causing gallstones are obesity, female gender, age over 40 years, and parity or what is usually called "4F" fat, female, forty, fertile[6]. These classic risk factors are no longer used significantly anymore. Recent research has proven that there is a change in the incidence of gallstones depending on age, gender, and others. At the age of children, it is less than that of older people. However, it was found that there was an increase in the prevalence of gallstone cases from 0.78 to 2.7 per 100,000 cases in the UK and 8.8 to 13.0 per 100,000 cases in Canada. In Asia, it reached 11.0 per 100,000 cases.

Meanwhile, in Indonesia, data regarding the prevalence of gallstones needs to be gathered from basic health research or the Ministry of Health. However, several studies have been conducted in several regional hospitals in Indonesia, one of which found 113 cases of gallstones at Prof. Dr. RD Kandou Manado Hospital from October 2015 to October 2016; the increase in prevalence throughout the world is thought to be due to changes in lifestyle such as decreased physical activity, obesity, smoking, and diabetes mellitus[8].

Risk factors such as hypercholesterolemia, diabetes, smoking, and race influence the incidence of gallstones.

Hypercholesterolemia is associated with an increased risk of gallstones, with prevalence ranging between 20-40% (Gilat et al., 2021). Patients with diabetes mellitus have a higher prevalence of gallstones, around 30-50%[9]. Smoking is also associated with an increased risk of gallstones, with a prevalence of between 15-30% [9]. Regarding race, research shows that Caucasians and Hispanics are at greater risk for gallstones compared to others [10].

Another problem that arises in cases of gallstones is ineffective screening, so many cases of gallstones are missed and not detected early [11]. This causes more severe complications and increases the burden of medical costs. Therefore, it is essential to conduct research that determines the effect of risk factors such as hypercholesterolemia, smoking, race, and diabetes in the occurrence of gallstones so that more effective and targeted screening can be carried out. This research is hoped to provide more accurate information about the risk factors for gallstones so that it can help in efforts to prevent and treat this disease.

METHODS

This research is an analytical observational study with a case-control study design. It compared 2 groups of subjects according to the categories of independent variables. The case group consists of people diagnosed with gallstones, while the control group consists of people who have not been diagnosed with gallstones. In each group, the history of risk factors, such as diabetes mellitus, hypercholesterolemia, smoking, or race type, was further traced.

The study population was patients aged 18 to 70 years seeking treatment at RSUP Prof. Dr. IGNG Ngoerah. The research population was divided into 2 groups: the case and control groups. The case group is patients aged 18 years to 70 years who came seeking treatment at RSUP Prof. IGNG Ngoerah in the period from March 2022 to December 2022 and were diagnosed with gallstones. The control group was patients aged 18 years to 70 years who came seeking treatment at RSUP Prof. Dr. IGNG Ngoerah in the period from March 2022 to December 2022 and was diagnosed with kidney stones and confirmed that he did not have gallstones. Inclusion criteria: 1) Patients aged 18 to 70 years; 2) seek treatment at RSUP Prof. Dr. IGNG Ngoerah for the period March 2022 to December 2022; 3) All gallstone and kidney stone sufferers who had laboratory examinations and abdominal ultrasound diagnostic supporting examinations were diagnosed with gallstones, whereas in kidney stone sufferers there was no evidence of gallstones from the abdominal ultrasound results. Exclusion criteria: 1) Patients with a history of systemic disease or a history of severe gastrointestinal surgery that predisposes to the formation of gallstones; 2) Patients with a history of congenital diseases that predispose to the formation of gallstones; 3) The patient is pregnant or taking contraceptive drugs; 4) The patient refuses to have interview data or laboratory data taken after providing informed consent.

Samples of patients diagnosed with gallstones were selected sequentially. Treatment preparations are done using the standard procedures for handling gallstones at RSUP Pr. Dr. IGNG Ngoerah Denpasar. Before carrying out the research, everything related to research ethics was consulted with the Research Ethics Commission, Research and Development Unit, Faculty of Medicine, Udayana University/RSUP Prof. Dr. IGNG Ngoerah to obtain a letter of ethical suitability.

Data analysis in this study consisted of descriptive statistical analysis, bivariable analysis using Chi-Square, and multivariable analysis using the logistic regression test. The risk factor assessment is statistically significant or not using the 95% CI and P value. If the P value is <0.05, then a factor is a significant risk factor for the dependent variable. If the P value is> 0.05, a factor is not a significant risk factor for the dependent variable. The entire data analysis process above uses SPSS 25 statistical software.

RESULTS

Observational analytical research with a hospital-based case-control study design took data from the patient registry in the General Surgery Department of Prof. Central General Hospital. Dr. IGNG Ngoerah, Denpasar. The extracted information includes demographic data, physical examination results, and biochemical examination results of patients taken when the patient arrived at the hospital.

This research obtained 120 patients for treatment at the Prof. Central General Hospital. Dr. IGNG Ngoerah has 56 patients diagnosed with gallstones and 64 patients diagnosed with kidney stones and not having gallstones. After obtaining this data, descriptive analysis was conducted on each research variable. Then, a correlation test is carried out to find the relationship between the independent variable, namely the risk factor, and the dependent variable, namely the patient's diagnosis. Data characteristics are presented in Table 1.

TABLE 1: Characteristics of research subjects based on cases and controls.

Parameter	Gallstones (n=56)	Non-Gallstones (n=64)	Total Sample (n=120)
Age			
≥ 40 Years	43 (76.8%)	54 (84.4%)	97 (80.3%)
< 40 Years	13 (23.2%)	10 (15.6%)	23 (19.7%)
Gender (n,%)			
Woman	38 (67.9%)	24 (37.5%)	62 (51.7%)
Man	18 (32.1%)	40 (62.5%)	58 (48.3%)
BMI (n,%)			
Underweight	2 (3.6%)	1 (1.6%)	3 (2.5%)
Normal	37 (66.1%)	41 (64.1%)	78 (65%)
Overweight	12 (21.4%)	18 (28.1%)	30 (25%)
Obese	5 (8.9%)	4 (6.3%)	9 (7.5%)
Diabetes Mellitus (n,%)			
Yes	9 (16.1%)	6 (9.4%)	15(12.5%)
No	47 (83.9%)	58 (90.6%)	105 (87.5%)
Smoking (n,%)			
Yes	22 (39.3%)	25 (39.1%)	47 (39.2%)
No	34 (60.7%)	39 (60.9%)	73 (60.8%)
Cholesterol (n,%)			
Yes	21 (37.5%)	10 (15.6%)	31 (25.8%)
No	35 (62.5%)	54 (84.4%)	89 (74.2%)
Race (n,%)			
Bali	36 (64.3%)	56 (87.5%)	92 (76.7%)
Non-Balinese	20 (35.7%)	8 (12.5%)	28 (23.3%)

Based on Table 5.1, the median patient age was 54.5, with a minimum age of 24, and the oldest patient was 76. At 51.7%, patients were dominated by females, and 65% had a normal BMI. 87.5% of patients did not have diabetes mellitus, 60.8% did not smoke, 74.2% had no history of cholesterol, 76.7% were Balinese, and 35.7% were diagnosed with gallstones.

TABLE 2: Comparison of variables for the two groups.

Parameter	Gallstones (n=56)	Non-Gallstones (n=64)	OR	CI 95%	P value
Age					
≥ 40 Years	43 (76.8%)	54 (84.4%)	0.613	0.245 – 1.532	0.675
< 40 Years	13 (23.2%)	10 (15.6%)			
Gender (n,%)					
Woman	38 (67.9%)	24 (37.5%)	3,519	1,653 – 7,489	0.001*
Man	18 (32.1%)	40 (62.5%)			
BMI (n,%)					
BMI ≥ 25	17 (30.4%)	22 (34.4%)	0.832	0.386 – 1.795	0.707
BMI < 25	39 (69.6%)	42 (65.6%)			
Diabetes Mellitus (n,%)					
Yes	9 (16.1%)	6 (9.4%)	1,851	0.615 – 5.574	0.274
No	47 (83.9%)	58 (90.6%)			
Smoking (n,%)					
Yes	22 (39.3%)	25 (39.1%)	1,009	0.484 – 2.104	0.980
No	34 (60.7%)	39 (60.9%)			
Hypercholesterolemia (n,%)					
Yes	21 (37.5%)	10 (15.6%)	3,702	1,364 – 7,694	0.008*
No	35 (62.5%)	54 (84.4%)			
Race (n,%)					
Bali	36 (64.3%)	56 (87.5%)	0.257	0.102 – 0.646	0.004*
Non-Balinese	20 (35.7%)	8 (12.5%)			

*Statistically significant.

Correlation test with chi-square and difference test with Mann Whitney on the age variable with p = 0.675, OR 0.613, CI 0.245 – 1.532. The gender of patients with gallstones was more female, namely 67.9%, p-value = 0.001, OR 3.519, CI 01.653 – 7.489. The BMI of patients in both groups was dominated by BMI < 25; in the gallstone group, it was 67.5%, p-value = 0.707. Both groups of patients were likelier to have no history of diabetes mellitus, amounting to 90.6% in patients with non-gallstones, p-value = 0.274. Non-smoking patients had higher rates in both groups, amounting to 60.9% in the non-gallstone group, p-value = 0.980. There were more patients with cholesterol in the gallstone group, namely 21 patients, p-value = 0.008, OR 3.240, CI 1.364 – 7.694. Both groups were dominated by patients of the Balinese race, as many as 87.5% in the non-gallstone group, p-value = 0.004, OR 0.257, CI 0.102 – 0.646 (Table 2).

TABLE 3: Multivariate analysis.

		aOR	CI 95%	p
Step 1a	Female gender	2,873	1,259 – 6,553	0.012
	Hypercholesterolemia	3,554	1,402 – 9,006	0.008
	Balinese race	0.351	0.129 – 0.957	0.041
	Constant	0.095		0.073

aOR: adjusted Odds Ratio.
CI: Confident Interval.

In Table 3, a multivariate test with logistic regression was carried out on variables with statistically significant values (p<0.05), namely gender, cholesterol, and race. Based on the results of logistic regression, it was found that the three variables significantly influenced the incidence of gallstones. The cholesterol variable is the most influential, with a p-value = 0.008, OR 3.554, CI 1.402 – 9.006. They were followed by the race variable with a value of p=0.041, OR 0.351, CI 0.129 – 0.957, and the gender variable with a value of p=0.012, OR 2.873, CI 1.259 – 6.553.

DISCUSSION

This study looked for the influence of risk factors such as diabetes mellitus, smoking, cholesterol, and race on the incidence of gallstones.

Confounding variables were also analyzed: the patient's age, gender, and BMI. The results showed that the patient's age did not significantly influence the incidence of gallstones. This contrasts the literature, which suggests that the frequency of gallstones increases with age, increasing sharply after age 40 to 4 and 10 times more likely in older individuals [12].

The type of stone also changes with age: initially, it consists mainly of cholesterol (corresponding to increased inward secretion of cholesterol and bile saturation), but in old age, it tends to become black pigment stones. Furthermore, symptoms and complications increase with age, leading to more frequent cholecystectomies [13].

Serban et al. (2016)in his research stated that laparotomy cholecystectomy is more often performed in the elderly population (> 60 years), and Coelho et al. (2018), where laparoscopic cholecystectomy is more commonly performed in younger populations (<60 years) [14,15]. The literature suggests that older age is riskier due to exposure to other risks, such as chronic diseases that last longer and are accompanied by the aging process [16].

Gender is one of the variables that significantly influences gallstones in this study. Women are more common in patients with gallstones. This is in line with the literature, which suggests that gender is one of the most prominent risk factors for gallstone disease. At all ages, women are generally at higher risk of developing cholelithiasis than men due to women's naturally higher estrogen levels, multiparity, or consumption of estrogen-based oral contraceptives [17]. Research also shows that women are more prone to undergoing cholecystectomy procedures than men of all ages [18].

The female gender has the most exciting association with gallstone disease, especially during the childbearing years. Women are almost twice as likely as men to form stones; the gap narrows after menopause once men catch up. The underlying mechanism is female sex hormones; Parity, use of oral contraceptives, and estrogen replacement therapy are risk factors for the formation of cholesterol gallstones [19]. Female sex hormones adversely affect liver bile secretion and gallbladder function. Estrogens increase cholesterol secretion and reduce bile salt secretion, while progestins act by reducing bile salt secretion and impair gallbladder emptying, leading to stasis.

The new fourth-generation progestin, drospirenone, used in some oral contraceptives, may further increase the risk of gallstone disease and cholecystectomy; however, the increased risk is modest and unlikely to be clinically significant [20]. Cholelithiasis is quite common and can be found in approximately 6% of men and 9% of women. The highest prevalence of cholelithiasis occurs in Native American populations. Gallstones are rare in Africa or Asia. The obesity epidemic may have increased the incidence of gallstones [21].

Obesity, positively correlated with body mass index (BMI), is also a well-known gallstone risk factor [22]. This is different from the results of this study, which found that BMI did not significantly affect the incidence of gallstones. Prospective cohort studies reporting a positive association between gallstone formation and central adiposity, relative to upper and lower extremity adiposity, and regional fat distribution may thus further exacerbate the risk of gallstones. A large cohort study of 77,679 patients confirmed a close association (in both sexes, but especially pronounced in women) between an increase in BMI and an increased risk of symptomatic gallstone disease [22].

Findings from the Nurses' Health Survey show a direct relationship between the frequency of symptomatic gallstones and BMI [23].

Compared with lean women (BMI < 24 kg/m2), obese women (BMI ≥ 30 kg/m2) showed a twofold increased risk, and morbidly obese women (BMI ≥ 45 kg/m2) had a sevenfold increased risk of having gallstones symptomatic. According to research, high BMI (BMI ≥ 25 kg/m2) appears to be a risk factor for gallbladder disease in women more than in men. This is different from the results of this study because the sample size is different, and the average BMI category of the research subjects is expected so that the results may be biased.

Diabetes mellitus is not a significant risk factor influencing gallstone incidence. The literature suggests that metabolic syndrome, dyslipidemia, diabetes, and insulin resistance/hyperinsulinemia often occur together in gallstone disease [24]. Ruhl and Everhart (2000)reported a two- to threefold higher prevalence of gallstone disease in insulin-resistant subjects with type 2 diabetes [11]. Additionally, increased hepatic cholesterol secretion, bile supersaturation, and gallbladder dysmotility exacerbate the metabolic syndrome, providing an ideal setting for the development of gallstones [25].

However, the contribution of hyperglycemia to the development of gallstones is still debated. The literature reports that no difference was found in glycemic control (HbA1c) between T2DM with and without gallstones, and no association between T1DM and gallstones was found even though most T2DM had poor glycemic control [26]. This could be the underlying reason why, in this study, diabetes mellitus was not significantly correlated with the incidence of gallstones.

Studies examining the relationship between smoking habits and gallstone formation are also controversial. The literature finds that heavy smoking (more than 35 cigarettes per day) is a substantial risk factor among women for gallstones. A large population-based study also confirmed that smoking is a significant risk factor for developing symptomatic gallstones. However, some studies have found no association between smoking and the development of gallstones [27]. This is in line with the results of this study, which did not find any significant influence of smoking habits on the incidence of gallstones.

High cholesterol was the risk factor that significantly influenced the incidence of gallstones in this study (p=0.008, OR 3.554, CI 1.402 – 9.006). In Western countries, gallstones consist mainly of cholesterol in 75-80% of cases and are often associated with systemic disorders (Portincasa et al., 2016). Primary prevention strategies in the general population and at-risk study participants are conceivable when studying metabolic pathways [15,28]

The literature suggests that the risk of gallstone disease also depends on specific dietary components: fast food consumption, at least once a week, and meat consumption, which have been identified as additional risk factors for symptomatic gallstones [22]. Additionally, a high intake of sugar and sweet foods may be a risk factor for gallstone disease in both sexes. This mechanism involves increased insulin levels, increased hepatic cholesterol synthesis, and hypersecretion of cholesterol into the bile, leading to increased bile cholesterol saturation. Important factors contributing to cholesterol gallstone formation are impaired gallbladder motility, hypersecretion and accumulation of mucin gel in the gallbladder lumen with ongoing local immune-mediated inflammation, rapid cholesterol phase transition from saturated hepatic bile, and deposition of crystals. solid cholesterol [15,28,29]

Additional features include gene polymorphisms, increased hepatic cholesterol secretion, increased biliary and dietary cholesterol absorption, sluggish intestinal motility, and qualitative, quantitative, or topographic changes in the intestinal microbiota [15,28,29]. The complex and variable interactions of these pathogenic factors contributing to cholesterol cholelithiasis require comprehensive discussion to address disease management adequately.

Race is one of the variables that significantly influences the incidence of gallstones. The basis for the occurrence of gallstones is multifactorial, including infection, genetic susceptibility, and modifiable lifestyle factors. Of particular note are the significant differences in rates of gallstone occurrence by ethnicity/race and geography. The prevalence is highest among Hispanic populations in Central and South America and individuals with Native American ancestry. In the US, the prevalence of gallstones is also much higher in Hispanics compared with other ethnic/racial groups. Genetic factors partially explain some of the observed racial differences in incidence; Large population-based studies estimate that genetic effects account for 25% (95% CI = 9-40%) [30].

Other factors may explain a more significant fraction of the risk of causing gallstones, including lifestyle factors related to obesity and diet. In this study, the Balinese ethnic group had a dominant number in both gallstone and non-gallstone groups and was a protective risk factor that had a possible influence. The Balinese ethnic group had genetic variations that protected gallstone formation, including differences in cholesterol metabolism or bile excretion. Additionally, a typical dietary pattern rich in fiber, low in saturated fat, and oriented towards consuming fruits, vegetables, and whole grains common in the traditional Balinese diet may contribute to a lower risk. A more active lifestyle and less exposure to environmental factors contributing to obesity may also be protective factors. Most likely, the protection afforded by the Balinese breed against gallstones results from a combination of genetic, dietary, and lifestyle factors, which create an environment less conducive to gallstone formation.

Gender, cholesterol, and race are risk factors that significantly influence the incidence of gallstones. However, age, BMI, diabetes mellitus, and smoking habits did not significantly influence the incidence of gallstones in this study.

Several shortcomings were due to research limitations in carrying out this research, including 1) A single researcher conducted this research, so there is the possibility of bias in data collection and analysis; 2) Many medical records cannot be found, so some patient data cannot be obtained. The research was only carried out on one site, so it may be different if used on other sites.

CONCLUSION

Based on the results of the research that has been carried out, the conclusions of this research are:

1. There was no significant relationship between risk factors for diabetes mellitus and the incidence of gallstones.
2. Female gender is a significant risk factor for gallstones.
3. Hypercholesterolemia is a significant risk factor for gallstones.
4. There was no significant relationship between the risk factor of smoking and the incidence of gallstones.
5. Balinese race type is a protective risk factor for the incidence of gallstones.

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Declarations

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