INTRODUCTION

Cholelithiasis is the most common disease in the gallbladder. It is estimated that 10-15% of the population in western countries suffer from cholelithiasis.1 Eighty-five percent of these cases are cholesterol stones.2 According to Abbas et al.,3 the prevalence of cholelithiasis occurs in 17% of the Asia population and 11-36% around the world. In Indonesia, the incidence of cholelithiasis per year has not been officially published.

Types of gallbladder stones can be classified into cholesterol stones (containing cholesterol> 50%), mixed stones (containing 20-50% cholesterol), and pigment stones (containing <20% cholesterol).4 Cholesterol stones will be brownish yellow, pigment stones are amorphous, brittle, calcium carbonate stones are shaped like black granules, green grains like mud or black, and others.5

Cholelithiasis causes various histopathological changes in the gallbladder’s mucosa, such as acute and chronic inflammation, cholelithiasis, hyperplasia and carcinoma. Due to persistent irritation, trauma and, chronic inflammation.6

According to Bidaya et al.7 study Histopathological changes in the gallbladder have an important role in the process of stone formation. In contrast to the study of Kereh et al.8 stated that there was no relationship between the type of stones and changes in the gallbladder mucosa. As far as the knowledge of researchers in North Sumatra has never conducted this research. Because there are still differences of opinion, the authors are interested in knowing the histopathological relationship to the type of stones in cholelithiasis patients at USU Hospital.

METHOD

This study used a cross sectional design, which was conducted during the period 2017 to 2018 at the Universitas Sumatera Utara. Hospital. The study population was all patients with a diagnosis of cholelithiasis. The sample of this study is a population of stones in cholelithiasis patients at Universitas Sumatera Utara Hospital, Medan, Indonesia. The authors are interested in knowing the histopathological relationship to the type of stones in cholelithiasis patients at USU Hospital.
this study were cholelithiasis accompanied by cholecystitis and no gallstones were found after surgery. Data analysis in this study used SPSS version 25.0 for Windows (IBM Corporation, Armonk, USA), the chi-square test was used to assess the relationship of gallstones to the histopathological features of the gallbladder. All values are considered significant if p <0.05.

RESULT
The mean age of the sample in this study was 48.76 (± 6.46) years, consisting of 16 men (32.7%) and 33 women (67.3%). Whereas for stone types, mixed stones were the most stone types with 24 people (49.0%), followed by 16 people (32.7%), and cholesterol with 9 people (18.4%). The last characteristic assessed in this study was histopathology, where chronic inflammation was the most common type with 18 people (36.7%), followed by acute inflammation, hyperplasia, and cancer, respectively, namely 16 people (32.7%), 11 people (22.4%), and 4 people (8.2%) (Table 1).

The type of stone has a relationship to the histopathology of the gallbladder tissue. In cholesterol stones, from 9 samples, from the histopathological results it had 5 acute inflammation and 4 chronic inflammation, whereas for hyperplasia and cancer were not found. In pigment stones, there were respectively 8 acute and chronic inflammation and no hyperplasia and cancer were found. As for mixed stones, there were 3 samples with acute inflammation, 6 with chronic inflammation, 11 with hyperplasia, and 4 with cancer. There is statistically significant relationship between type of stone and the histopathology of the gallbladder tissue (p=0.001) (Table 2).

DISCUSSION
Cholelithiasis or gallstones are essentially deposits of one or more bile components (cholesterol, bilirubin, bile salts, calcium, and protein). Gallstones occur when there is an imbalance in the chemical elements of bile which results in the deposition of one or more components. There are many factors, which cause stone formation, namely impaired gallbladder function, supersaturated bile, cholesterol nucleation factors, and circulating absorption of bile acids.

It is estimated that 10-15% of the population in western countries has cholelithiasis. According to Abbas et al., the prevalence of cholelithiasis occurs in 17% of the Asian population, 10% of the population in Western countries and 11-36% of all world countries. In Indonesia, the incidence of cholelithiasis per year has not been officially published. In this study, 49 patients had cholelithiasis, with the mean age being 48.76 ± 6.46 years. The cholelithiasis frequency increases with age, increasing sharply to 4 to 10 times more often in patients over 40 years of age. In this study, it was found that the number of female patients was more than the number of male patients (16 men (32.7%) and 33 women (67.3%). Female sex is twice as likely to develop cholelithiasis during fertile/pre-menopausal periods (< 40 years) than men, related to female sex hormones (estrogen), parity, use of oral contraceptives and estrogen replacement therapy.

In this study, mixed stones were the most common type of stone, found in 24 people (49.0%), followed by pigment stones (16 people (32.7%), and cholesterol with 9 people (18.4%). Similar findings by Chandran et al. study stated that in 200 gallstones studied in Haryana, India, 76 of them were mixed stones (38%). Research conducted in Belagavi, India also showed that mixed types of stones as many as 81.12% cases. However, study in Pakistan by Atamanalp et al. was found that the most common stone type was cholesterol stones (58.7%), where high serum cholesterol and LDL levels were associated with a high incidence of cholesterol stones.

### Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (±SD)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.76 (±6.46)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Stone type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>9 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Pigmented</td>
<td>16 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>24 (49.0)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>16 (32.7)</td>
<td></td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>18 (36.7)</td>
<td></td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>11 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (8.2)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Relationship between stone types and histology of gallbladder

<table>
<thead>
<tr>
<th>Stone type</th>
<th>Acute inflammation</th>
<th>Chronic inflammation</th>
<th>Hyperplasia</th>
<th>Cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Pigmented</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Chronic cholecystitis is the most common inflammation of the gallbladder. In this study, the histopathological results showed that chronic inflammation was the most common type (18 people (36.7%), followed by acute inflammation, hyperplasia, and cancer, respectively, namely 16 (32.7%), 11 people (22.4%), and 4 people (8.2%). This is in accordance with the results of a study conducted by Unisa et al. which showed that mononuclear infiltrates’ inflammation was found in all studied cases (100 cases). In this study gallbladder malignancy was seen in 4 cases, with 1 case of mild dysplasia and 3 severe dysplasia cases. The study of Barcia et al. also showed that the incidence of mild inflammation was present in 26% of cases, moderate in 62% of cases, and severe in 12% of cases. Our study shows that the type of stone has a relationship with the histopathology of the gallbladder tissue. In cholesterol stones, from 9 samples, from the histopathological results it had 5 acute inflammation and 4 chronic inflammation, whereas for hyperplasia and cancer were not found. In pigment stones, there were respectively 8 acute and chronic inflammation and no hyperplasia and cancer were found. As for mixed stones, there were 3 samples with acute inflammation, 6 with chronic inflammation, 11 with hyperplasia, and 4 with cancer. The p-value of 0.001 indicates that there is a statistically significant relationship between the type of stones and the histopathology of the gallbladder tissue. This is consistent with the results of a study conducted by Sunder et al. which stated that metaplastic changes were common in patients with multiple mixed stones, where there was a significant relationship between changes in the histology of gallbladder tissue and the incidence of malignancy. There is a strong correlation between the duration of the symptoms and the severity of the disease, where the prolonged duration of the symptoms significantly influences the severity of the histopathological changes. In patients with chronic inflammation, patients with a duration of symptoms of less than 4 months, the severity of histopathological changes were mild. Histopathologic changes increased over a duration lasting more than one year. Similar developmental patterns were seen in fibrosis and dysplasia. As with Sunder’s study, patients with mixed stones developed hyperplasia, metaplasia, and gallbladder carcinoma.

**CONCLUSION**

Mixed stones type still dominated (49%) and histopathological results showed 18 samples (36.7%) were chronic inflammation, and there was a significant relationship between stone type and histopathology appearance in cholelithiasis patients.

**CONFLICT OF INTEREST**

The author declares there is no conflict of interest regarding publication of this article.

**FUNDING**

This study doesn’t receive any specific grant from the government or any private sectors.

**ETHICAL CONSIDERATION**

This study has been approved by the Ethical Committee Faculty of Medicine Universitas Sumatera Utara/Haji Adam Malik Hospital, Medan, Indonesia. All study procedures in accordance to the Helsinki Declaration of human rights.

**AUTHOR CONTRIBUTION**

Adi Muradi Muhar responsible for data gathering, project administration, supervision, and writing the original draft. Denny Rifsal Siregar and Doddy Prabisma responsible for statistical analysis, and writing the original draft. All authors had reviewed the final version of the manuscript.

**REFERENCES**