

# Gallbladder and other pathologies: 7,788 cases, a cohort study in North Western India

Vesícula biliar e outras patologias: 7.788 casos, um estudo de coorte no noroeste da Índia

Bhushan Sanjay Bhalgat<sup>1</sup>, Pinakin Patel<sup>1</sup>, Suresh Singh<sup>1</sup>, Phanindra Swain<sup>1</sup>, Pravin Kumar<sup>1</sup>, Kamal Kishor Lakhera<sup>1</sup>, Bhairu Gurjar<sup>2</sup>, Raj Govind Sharma<sup>3</sup>, Ashwini Dilip Haibatpure<sup>4</sup>

## ABSTRACT

**Introduction:** Gallbladder diseases are a well-studied subset of diseases in the Gangetic belt of India. But, the prevalence of gallbladder diseases, both benign and malignant (as a whole subset) has not been studied in Eastern Rajasthan yet. This study aims to provide an epidemiological overview of all histopathologically proven gall bladder diseases from standard pathology laboratories of Jaipur. **Material and Methods:** In this chart review analysis, we scrutinized all the records of histopathologically proven diseases at four major pathology departments and labs in Jaipur, Rajasthan over five years; of which 7,788 patients had gallbladder pathologies. We harnessed this raw data of gall bladder pathologies to obtain meaningful results. **Results:** Histopathological analysis revealed the percentage of gall bladder diseases overall of all the histopathologically proven diseases, in Rajasthan as 2.59%. The malignant pathologies accounted for 2.65% of it. Cholelithiasis (41.32%) was the most common benign pathology with acute cholecystitis with cholelithiasis (29.49%), chronic cholecystitis with cholelithiasis (18.73%), acute cholecystitis (8.28%), acalculous cholecystitis (1.11%), reactive hyperplasia (0.69%), mucocele (0.09%) and xanthogranulomatous cholecystitis (0.08%) in descending order of frequency. Adenocarcinoma (83.49%) was the most common malignant pathology found, followed by undifferentiated carcinoma (5.34%), squamous cell carcinoma (4.85%) and adenosquamous carcinoma (1.94%) in that order. Gradewise, malignancies were the most commonly of grade 2. The sex ratio favoured females in both the subsets; being 1:4 for benign and 1:2 for malignant pathologies. 61 to 70 years of age is the most affected age group for gall bladder malignancies for both the sexes. **Conclusion:** This study would make the difference in the national average and contribute hugely to the national registry, since it showcases the analysed data from a large geographic location of the country. It would also benefit the clinicians of Rajasthan in better decision-making for the patients of this region.

**Keywords:** Gallbladder neoplasms; Neoplasms; India; Epidemiology.

1. SMS Medical College and Hospital, Surgical Oncology - Jaipur - Rajasthan - India.
2. SMS Medical College and Hospital, Pediatric Surgery - Jaipur - Rajasthan - India.
3. MGM Medical College and Hospital, Surgical Oncology - Jaipur - Rajasthan - India.
4. SDM Hospital,, Department of Neurology - Jaipur - Rajasthan - India.

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**Correspondence author:** Bhushan Sanjay Bhalgat.

E-mail: bhalgatbs@gmail.com

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## RESUMO

**Introdução:** As doenças da vesícula biliar são um subconjunto bem estudado de doenças no cinturão Gangético da Índia. Mas, a prevalência de doenças da vesícula biliar, benignas e malignas (como um subconjunto completo) ainda não foi estudada no leste do Rajastão. Este estudo tem como objetivo fornecer uma visão epidemiológica de todas as doenças da vesícula biliar comprovadas histopatologicamente dos laboratórios de patologia padrão de Jaipur. **Material e Métodos:** Nesta análise de revisão de prontuários, examinamos todos os registros de doenças comprovadas histopatologicamente em quatro grandes departamentos e laboratórios de patologia em Jaipur, Rajasthan, durante cinco anos; dos quais 7.788 pacientes apresentavam patologias da vesícula biliar. Aproveitamos esses dados brutos de patologias da vesícula biliar para obter resultados significativos. **Resultados:** A análise histopatológica revelou a porcentagem de doenças da vesícula biliar em geral de todas as doenças comprovadas histopatologicamente, em Rajasthan como 2,59%. As patologias malignas representaram 2,65% disso. A colelitíase (41,32%) foi a patologia benigna mais comum com colecistite aguda com colelitíase (29,49%), colecistite crônica com colelitíase (18,73%), colecistite aguda (8,28%), colecistite acalculosa (1,11%), hiperplasia reativa (0,69%), mucocele (0,09%) e colecistite xantogranulomatosa (0,08%) em ordem decrescente de frequência. O adenocarcinoma (83,49%) foi a patologia maligna mais encontrada, seguido do carcinoma indiferenciado (5,34%), carcinoma espinocelular (4,85%) e carcinoma adenoescamoso (1,94%), nesta ordem. Grau gradativamente, as malignidades foram as mais comumente de grau 2. A razão sexual favoreceu as mulheres em ambos os subconjuntos; sendo 1:4 para patologias benignas e 1:2 para patologias malignas. A faixa etária de 61 a 70 anos é a mais acometida pelas malignidades da vesícula biliar em ambos os sexos. **Conclusão:** Este estudo faria a diferença na média nacional e contribuiria sobremaneira para o cadastro nacional, pois mostra os dados analisados de uma grande localização geográfica do país. Também beneficiaria os médicos do Rajastão em uma melhor tomada de decisão para os pacientes desta região.

**Descritores:** Neoplasias da vesícula biliar; Neoplasias; Índia; Epidemiologia.

## INTRODUCTION

Gallbladder diseases including gall bladder malignancies are known to occur in India, Pakistan, East Asia, East Europe, and Chile.<sup>1,2</sup> In India, gallbladder cancer is the 20<sup>th</sup> most common malignancy overall and the most common among all the biliary tract malignancies.<sup>3</sup> The majority of gallbladder cancers occur in the developing countries.<sup>4</sup> The epidemiological data suggest that Indian gallbladder cancer burden accounts for 10% of global burden.<sup>5</sup> The prevalence of gall bladder diseases is higher in Northern and Eastern India compared to the southern counterpart.<sup>6,7</sup> As per the ICMR report, gallbladder cancer accounts for 3.7% cases in females versus 2.2 % in males.<sup>8</sup> But this prevalence is more on the Ganges basin (Uttar Pradesh, Bihar, Orissa, West Bengal) and Assam.<sup>9-11</sup> The climate of the state of Rajasthan is hot and dry and is different from the Gangetic basin in many ways. This geographic variation also reflects in the diseases, which the local people of this region suffer from. The current study evaluates the percentage of gall bladder diseases of all histopathologically proven diseases, both benign and malignant, as a part of a large umbrella study for all types of diseases prevalent in this region.

## MATERIAL AND METHODS

### Study design

This is a retrospective analysis, undertaken over a period of 5 years at the Surgical Oncology department of Sawai Man Singh (SMS) Medical College, Jaipur.

### Data collection

Histopathological data of three lakh patients coming to Department of Pathology of SMS Medical College, Jaipur was collected using the hospital information system; and from Santokba Durlabhji Memorial (SDM) Hospital, Jaipur; Bhagwan Mahavir Cancer Hospital, Jaipur; and Dr. Joshi Diagnostic Lab, Jaipur was collected manually. These histopathology reporting were done by accredited pathologists and the malignancies were reviewed by the expert pathologists in the field. The rare entries in the database were sorted using the sort and filter option and excluded.

### Inclusion criteria

Reports of 7,788 patients with histopathologically proven lesions in gallbladder were included in our study after ethical clearance from our institutional ethics committee. (Fig. 1)

## Exclusion criteria

Patients without any histopathologically proven diagnosis or reports with tumours of rare diagnoses or patients whose demographic data was missing were excluded from the study.

## Statistical analysis

The collected data was analyzed and results were obtained using Microsoft Excel 2019 Version 2107.

## Aim of the study

The aim of this study is to derive a baseline sorted database of histopathologically proven gallbladder diseases with respect to the epidemiological aspects of Rajasthan state.

## RESULTS

Results of our study were as follows:

Presence of gallstones in gallbladder cancer in our study was 70.87%.

In our study, malignant cases among the overall 7788 gall bladder lesions accounted for 206 cases; leading to a malignancy index of 2.65%. (Fig. 2 and 3)

Among the benign cases, cholelithiasis was the most commonly encountered histopathology with 3133 cases (41.32%) followed by acute cholecystitis with cholelithiasis (2,236 cases; 29.49%), chronic cholecystitis with cholelithiasis (1,420 cases; 18.73%), acute cholecystitis (628 cases; 8.28%), acalculous cholecystitis (84 cases; 1.11%), reactive hyperplasia (52 cases; 0.69%), mucocele (7 cases),

xanthogranulomatous cholecystitis (6 cases), gangrenous cholecystitis (4 cases), tuberculosis (4 cases), cholesterosis (4 cases), adenomyomatosis (3 cases), and leiomyoma (1 case).

Among the malignant cases in our study, adenocarcinoma accounted for the most common histopathology with 172 cases (83.49%) followed by undifferentiated carcinoma - not otherwise specified (11 cases; 5.34%), squamous cell carcinoma (10 cases; 4.85%), adenosquamous carcinoma (4 cases), metastasis (4 cases) and neuroendocrine tumour, adenoid cystic carcinoma, non-Hodgkin lymphoma, primitive neuroectodermal tumour and spindle cell neoplasm with one case each.

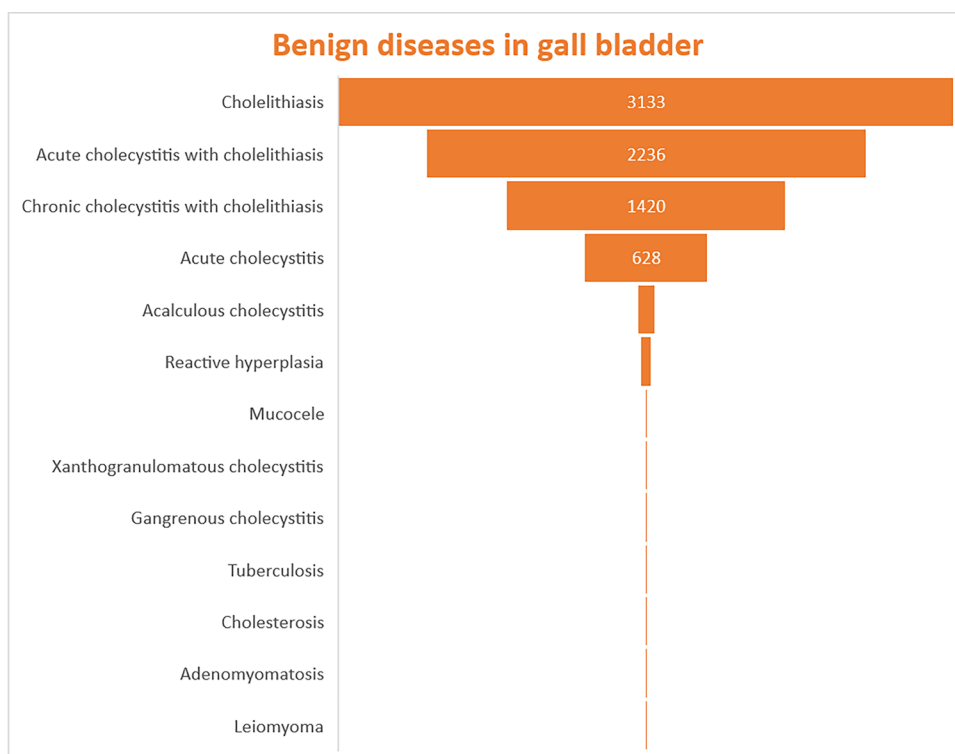
The moderately differentiated adenocarcinoma was the most common grade found with 79.65% cases of all adenocarcinomas.

Most affected age group for cholelithiasis and acute cholecystitis is 41 to 50 years each. It is 51 to 60 years for chronic cholecystitis.

The malignant counterpart affected patients of 61 to 70 age group in both genders with median age of 64 years. (Fig. 4).

Females were more commonly affected than males with a sex ratio for benign diseases of 1:4 each for cholelithiasis and acute cholecystitis, while 1:2 for chronic cholecystitis. (Fig. 5).

Malignant counterpart was less biased towards females with sex ratio of 1:2 for moderately differentiated adenocarcinoma and 1:1 for moderately and poorly differentiated adenocarcinoma and undifferentiated carcinoma each. (Fig. 6).



**Figure 1.** Chart showing the prevalence of benign gall bladder diseases in North-Western India (Numbers represent absolute values)

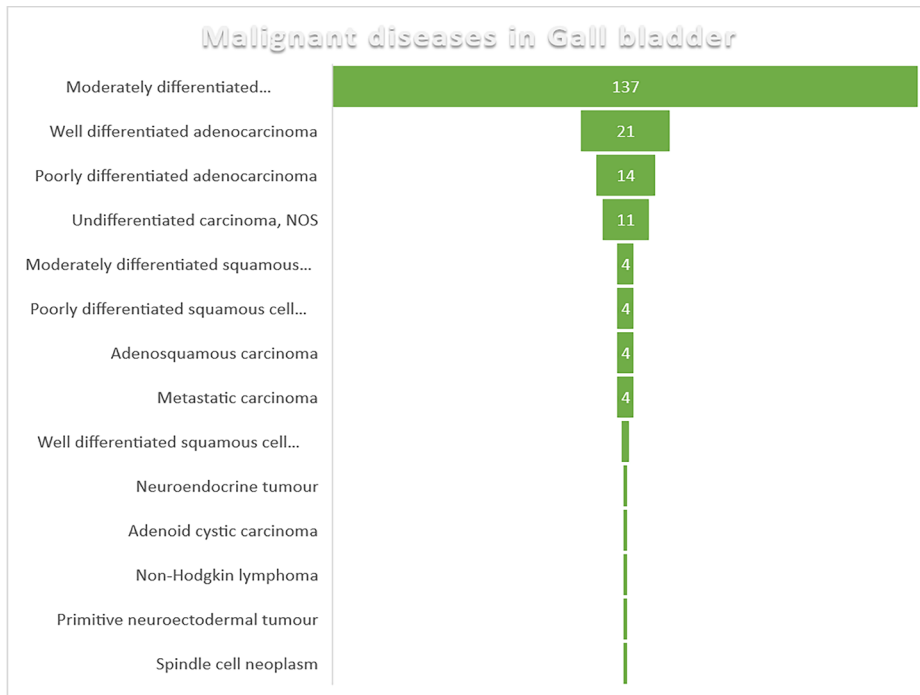


Figure 2. Chart showing the prevalence of malignant gall bladder diseases in North-Western India (Numbers represent absolute values)

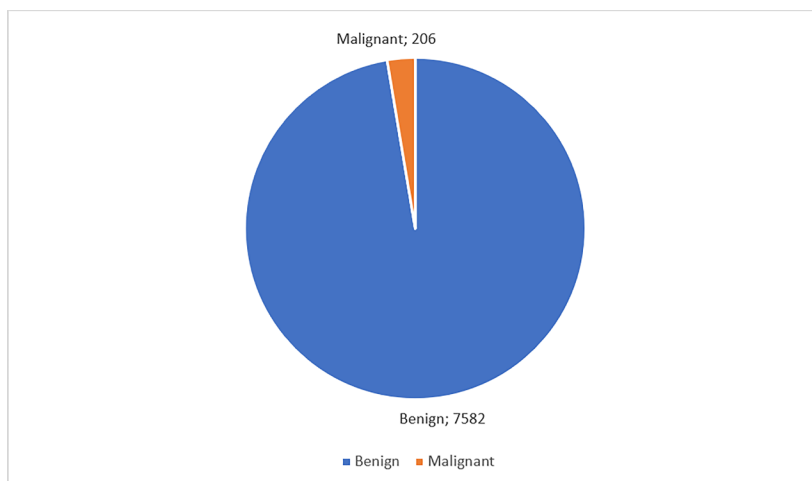


Figure 3. Chart showing the distribution of benign and malignant gall bladder diseases in North-Western India

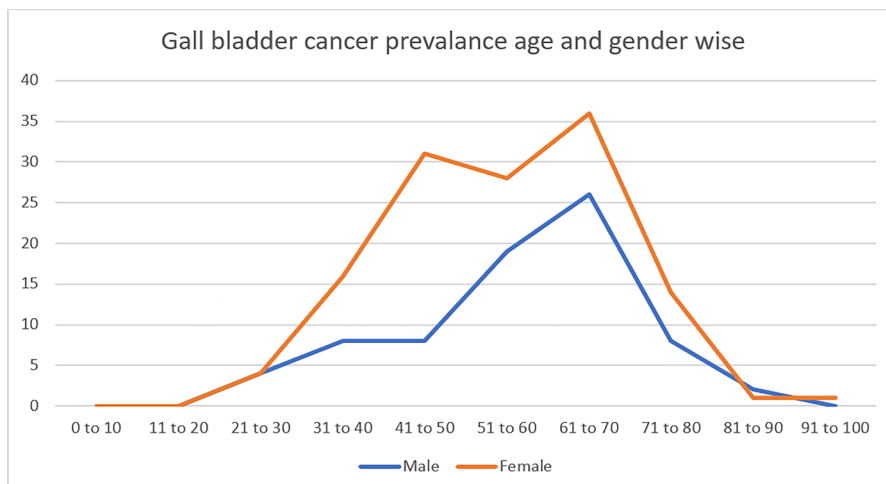
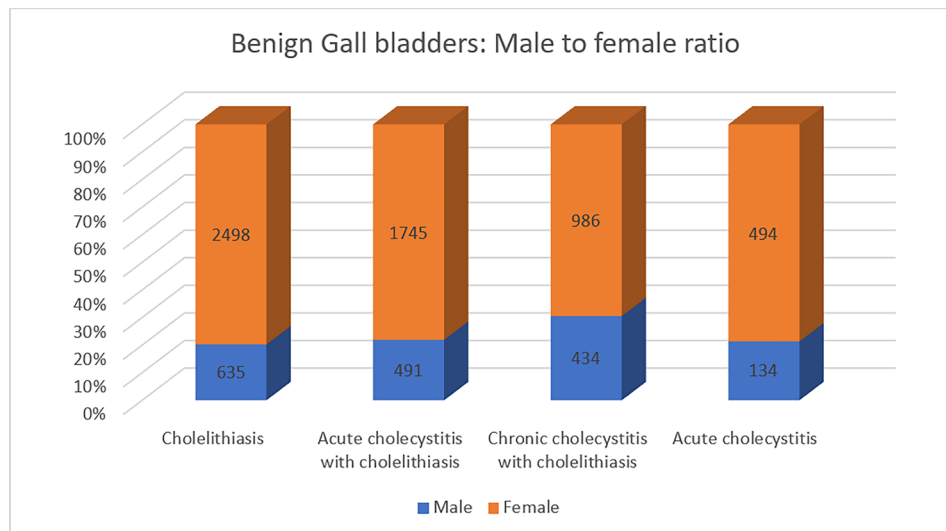
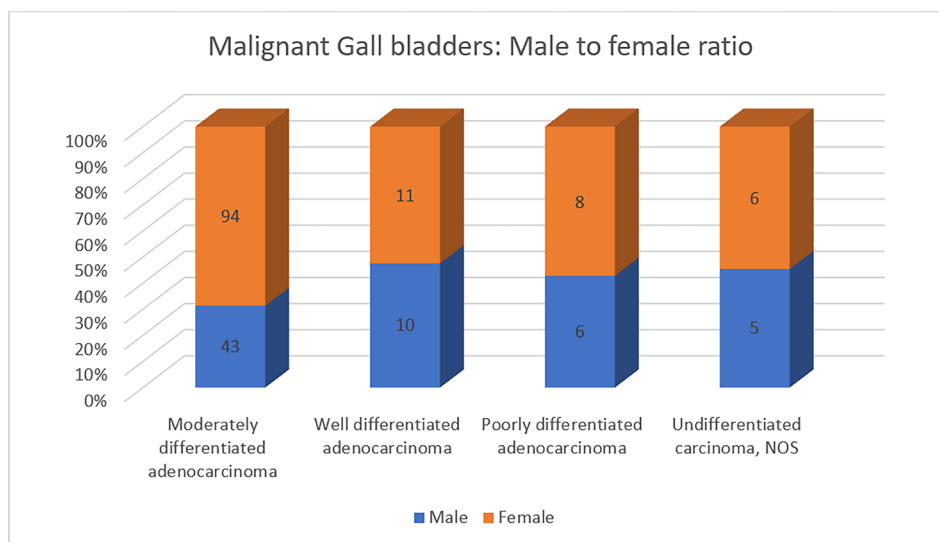


Figure 4. Prevalence of gall bladder diseases (as per age and gender)



**Figure 5.** Male to female ratio for benign gall bladder diseases



**Figure 6.** Male to female ratio for malignant gall bladder diseases

## DISCUSSION

Three lakh histopathology reports from four well-known laboratories in Jaipur were reviewed in the umbrella study to furnish 7,788 cases of gall bladder lesions, owing to a 2.59% histologically proven gallbladder cases among the overall burden. A previous study from our institute in 2008 showed that gall bladder cancer to be the third most common gastrointestinal malignancy in Eastern Rajasthan.<sup>12</sup> A recent study from Western Rajasthan showed that gall bladder cancer contributes to 3.8% cases of total cancer cases registered at RCC, Bikaner.<sup>13</sup> Unisa et al. (2011)<sup>1</sup> revealed a prevalence of 6.20%. Presence of gallstones in gallbladder cancer in our study was 70.87%. It has been shown to be the most important risk factor in causation of gallbladder carcinoma (relative risk - 3.0 to 23.8) with presence in 80% of patients of gall bladder carcinoma in India.<sup>5,14,15</sup> In contrast, it was only 25% in Jokhi et al. study (2019).<sup>16</sup>

The incidences of gallbladder carcinoma in the world are 21.5 per lakh in Delhi, 13.8 per lakh in Karachi and 12.9 per lakh in Quito.<sup>17</sup> It accounts for 80 to 90 percent of biliary tract malignancies in the world.<sup>18</sup> Majority of patients are asymptomatic and are diagnosed incidentally on histopathology; but some patients with advanced disease may present with vague abdominal symptoms and carry a dismal prognosis.<sup>5,19</sup> In our study, malignant cases among the overall 7,788 gallbladder lesions accounted for 206 cases; leading to a malignancy index of 2.65%. Only those malignancies which were neither operated nor biopsied are not included in the malignancy index. A previous study from our institute in 2008 showed a malignancy index of 3.3%.<sup>12</sup> Malignancy index was 0.55%, 0.86%, 2.4%, 1.14%, 3%, 3.29%, 4%, 5%, 5.6%, and 6% in Almuslamani et al. (2011),<sup>20</sup> Sharma et al. (2015),<sup>21</sup> Terada et al. (2013),<sup>22</sup> Talreja et al. (2016),<sup>23</sup> Jokhi et al. (2019),<sup>16</sup> Shrestha et al. (2010),<sup>24</sup> Ojed et al. (1985),<sup>25</sup> Asuquo et al. (2008),<sup>26</sup> Damor et al. (2013),<sup>15</sup> and Khanna et al. (2006)<sup>27</sup> studies, respectively.

Among the benign cases, cholelithiasis was the most commonly encountered histopathology with 3,133 cases (41.32%) followed by acute cholecystitis with cholelithiasis (2236 cases; 29.49%), chronic cholecystitis with cholelithiasis (1,420 cases; 18.73%), acute cholecystitis (628 cases; 8.28%), acalculous cholecystitis (84 cases; 1.11%), reactive hyperplasia (52 cases; 0.69%), mucocele (7 cases), xanthogranulomatous cholecystitis (6 cases), gangrenous cholecystitis (4 cases), tuberculosis (4 cases), cholesterosis (4 cases), adenomyomatosis (3 cases), and leiomyoma (1 case). Jokhi et al. (2019)<sup>16</sup> had chronic cholecystitis as the most common benign entity with 112 of 130 cases (86.3%) followed by acute cholecystitis in 12 cases (9.2%). Acute cholecystitis remains the second most common cause of gall bladder pathology after its chronic counterpart.<sup>15,16</sup> Dix et al. (2003)<sup>28</sup> showed 95.5% cases of chronic cholecystitis with only 0.4% cases of acute cholecystitis. Sharma et al. (2015)<sup>21</sup> showed that the relative proportion of gallbladder diseases were chronic cholecystitis in 51.2% (442/863), chronic active cholecystitis in 40.4% (349/863), acute cholecystitis in 4.6% (40/863), neoplastic in 2.7% (23/863) and xanthogranulomatous cholecystitis in 1.04% (9/863) of patients.<sup>29</sup> Chronic cholecystitis formed 78.42% (756 cases) of all histopathologies in Taleja et al. (2016)<sup>23</sup> study too followed by cholesterosis (12.13%), acute cholecystitis (6.32%), xanthogranulomatous cholecystitis (1.24%), and adenoma in 0.73%. In Terada et al. (2013)<sup>22</sup> study, 508 (94.1%) were chronic cholecystitis, eight (1.5%) were acute cholecystitis, and 11 (2.0%) were normal gall bladders. Almuslamani et al. (2011)<sup>20</sup> study also had chronic cholecystitis (1,551 cases; 78%) as the most common benign gall bladder entity followed by acute cholecystitis (304 cases; 15%).

Among the malignant cases in our study, adenocarcinoma accounted for the most common histopathology with 172 cases (83.49%) followed by undifferentiated carcinoma - not otherwise specified (11 cases; 5.34%), squamous cell carcinoma (10 cases; 4.85%), adenosquamous carcinoma (4 cases), metastasis (4 cases) and neuroendocrine tumour, adenoid cystic carcinoma, non-Hodgkin lymphoma, primitive neuroectodermal tumour and spindle cell neoplasm with one case each. This was similar to a previous study from our department, which showed that 90% of the cases were of adenocarcinomas.<sup>12</sup> Duffy et al. (2008)<sup>30</sup> showed maximum prevalence of adenocarcinoma (391 cases; 90%) followed by squamous/adenosquamous (18 cases; 4%), neuroendocrine tumour (13 cases; 3%), sarcoma/adenosarcoma (7 cases; 1.6%), unspecified (5 cases; 1.1%), and melanoma (1 case; 1%).<sup>30</sup> Adenocarcinoma accounted for all malignant cases in Jokhi et al. (2019),<sup>16</sup> and Almuslamani et al. (2011)<sup>20</sup> studies.<sup>16</sup> Pandey et al. (2001)<sup>31</sup> study showed 73.9% cases of adenocarcinoma followed by 17.4% cases of mucinous carcinoma and 8.7% cases of papillary adenocarcinoma.

The distribution of malignant gall bladders in Sharma et al. (2015)<sup>21</sup> study was well differentiated adenocarcinoma in 79% (11/14) followed by mucinous carcinoma in 7% (1/14), adenosquamous carcinoma in 7% (1/14), and poorly differentiated carcinoma in 7% (1/14) patients.<sup>29</sup> Goetze et al. (2010)<sup>32</sup> study showed 95% cases of adenocarcinoma while only 5% of squamous cell carcinoma.

The moderately differentiated adenocarcinoma was the most common grade found with 79.65% cases of all adenocarcinomas. Poorly differentiated adenocarcinomas were the most common grade with 41.8% cases followed by moderately (35.29%) and well-differentiated adenocarcinomas (23.53%) in Dubey et al. (2018)<sup>11</sup> study. Lau et al. (2017)<sup>19</sup> showed maximum prevalence of poorly differentiated tumours (42.5%) followed by moderately (38.2%) and well differentiated (15.3%) cancers. Jokhi et al. (2019)<sup>16</sup> showed otherwise the prevalence of 50% of moderately differentiated carcinoma as against 25% of poorly differentiated carcinomas like in our study.

Most affected age group for cholelithiasis and acute cholecystitis is 41 to 50 years each. It is 51 to 60 years for chronic cholecystitis. Damor et al. (2013)<sup>15</sup> sowed the most common age group for benign gallbladder diseases is 4<sup>th</sup> and 5<sup>th</sup> decades with 25% and 26% cases, respectively. Khoo et al. (2008),<sup>33</sup> Damor et al. (2013),<sup>15</sup> Khanna et al. (2006),<sup>27</sup> and Samad et al. (2005)<sup>34</sup> reported that benign gallbladder lesions occurred in 3<sup>rd</sup> to 5<sup>th</sup> decades. Sharma et al. (2014),<sup>29</sup> Sharma et al. (2015)<sup>21</sup> and Selvi et al. (2011)<sup>35</sup> study reported the maximum incidence in 4<sup>th</sup> to 6<sup>th</sup> decades.

Gallbladder cancer is a disease of the geriatric population.<sup>15</sup> The malignant counterpart affected patients of 61 to 70 age group in both genders with median age of 64 years. Kumar et al. (2006)<sup>36</sup> showed that gall bladder carcinomas belonged predominantly to the 4<sup>th</sup> and 5<sup>th</sup> decade. Dubey et al. (2018)<sup>11</sup> study showed age range from 27 to 76 years with median age of 51.8 years and peak age group of 41 to 50 years. Average age of diagnosis in Western study of Lau et al. (2017)<sup>19</sup> study, Duffy et al. (2008),<sup>30</sup> and Everhart et al. (2002)<sup>37</sup> study was 71.2, 67 and 65 years, respectively. In contrast, gallbladder carcinoma in Indian study of Dutta et al. (2019)<sup>5</sup> affected younger females in 5<sup>th</sup> and 6<sup>th</sup> decade. Age range for neoplastic gallbladder diseases was from 28 to 78 years with the peak age group at 41 to 60 years of age (78%).<sup>29</sup> Study from our institute in the previous decade showed a similar age incidence with peak after 4<sup>th</sup> decade.<sup>12</sup> A recent study from Western Rajasthan showed peak incidence in 5<sup>th</sup> to 7<sup>th</sup> decades with median age of 60 years.<sup>13</sup> Also, study from Delhi by Malhotra et al. (2017)<sup>38</sup> showed similar age incidences.

Females were more commonly affected than males with a sex ratio for benign diseases of 1:4 each for cholelithiasis and acute cholecystitis, while 1:2 for chronic cholecystitis. Odds ratio of females to males in Unisa et al. (2011)<sup>1</sup> study was 1,703. Selvi et al. (2011),<sup>35</sup> Everhart et al. (2002),<sup>37</sup> Damor et al. (2013),<sup>15</sup> Sharma et al. (2015),<sup>21</sup> Khanna et al. (2006),<sup>27</sup> Asuquo et al. (2008),<sup>26</sup> Zoysa et al. (2010),<sup>39</sup> Tantia et al. (2009),<sup>40</sup> and John et al. (1992)<sup>41</sup> showed a sex ratio of 1:2, 1:2, 1:2.3, 1:2.8, 1:4.8, 1:5, 1:3, 1:2.8, and 1:4, respectively.

Malignant counterpart was less biased towards females with sex ratio of 1:2 for moderately differentiated adenocarcinoma and 1:1 for moderately and poorly differentiated adenocarcinoma and undifferentiated carcinoma each. It is also more common in the females worldwide with two to six times the males.<sup>10,17,19</sup> A study from our institute previously showed a sex ratio of 1:2.33.<sup>12</sup> Study from Western Rajasthan showed 1:2.6 sex ratio for gallbladder cancer.<sup>13</sup> Kumar et al. (2006)<sup>36</sup> also had female predominance in gallbladder carcinomas with only 75 cases in males and 253 cases in females with a sex ratio of 1:3.37. Another study by Almuslamani et al. (2011),<sup>20</sup> Lau et al. (2017),<sup>19</sup> Damor et al. (2013),<sup>15</sup> Talreja et al. (2016)<sup>23</sup> and Duffy et al. (2008)<sup>30</sup> showed a sex ratio of 1:1, 1:2.41, 1:5, 1:2, and 1:2, respectively. The cause could be the higher estrogen and progesterone hormones in females which causes gall bladder stasis and in turn stone formation.<sup>5,14</sup>

There is a limitation to the study that it does not give an idea about the correlation of etiological factors to the pathologies found in the region. A study will be required in the future to correlate the same. There could be an information bias due to the lack of a few records from other laboratories; but that would not make a significant difference in the data owing to the coverage of major laboratories of the region.

## CONCLUSION

The prevalence of gall bladder disorders as a whole has been scarcely studied across the state.<sup>42-45</sup> The percentage occurrence of each disorder, the malignancy index, the most affected age groups and the sex predilection in Eastern Rajasthan has been well analysed in this study. Moderately differentiated adenocarcinoma of gallbladder remains the most common malignant pathology while choledocholithiasis is the most common benign pathology in gall bladder. The limitation of the study in terms of finding out the etiology of the quantitative variables should be taken into account during further research.

## ETHICAL COMMITTEE APPROVAL

ECSMS/210/22

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