

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 Bhalgat¹, Pinakin Patel¹, Suresh Singh¹, Phanindra Swain¹, Pravin Kumar¹, Kamal Kishor Lakhera¹, Bhairu Gurjar², Raj Govind Sharma³, Ashwini Dilip Haibatpure⁴

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.

Financial support: none to declare.

Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.

Correspondence author: Bhushan Sanjay Bhalgat.

E-mail: bhalgatbs@gmail.com

Received on: August 8, 2022 | **Accepted on:** October 31, 2022 | **Published on:** December 13, 2022

DOI: <https://doi.org/10.5935/2526-8732.20220366>



This is an open-access article distributed under the terms of the Creative Commons Attribution License.

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.^{1,2} In India, gallbladder cancer is the 20th most common malignancy overall and the most common among all the biliary tract malignancies.³ The majority of gallbladder cancers occur in the developing countries.⁴ The epidemiological data suggest that Indian gallbladder cancer burden accounts for 10% of global burden.⁵ The prevalence of gall bladder diseases is higher in Northern and Eastern India compared to the southern counterpart.^{6,7} As per the ICMR report, gallbladder cancer accounts for 3.7% cases in females versus 2.2 % in males.⁸ But this prevalence is more on the Ganges basin (Uttar Pradesh, Bihar, Orissa, West Bengal) and Assam.⁹⁻¹¹ 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).

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).

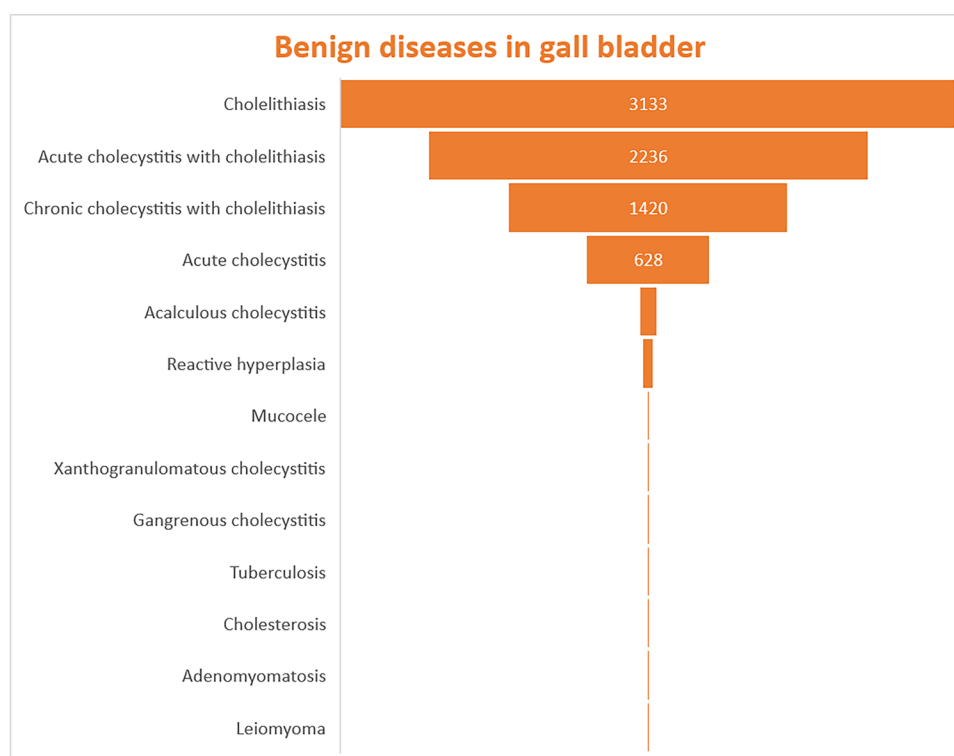


Figure 1. Chart showing the prevalence of benign gall bladder diseases in North-Western India (Numbers represent absolute values)

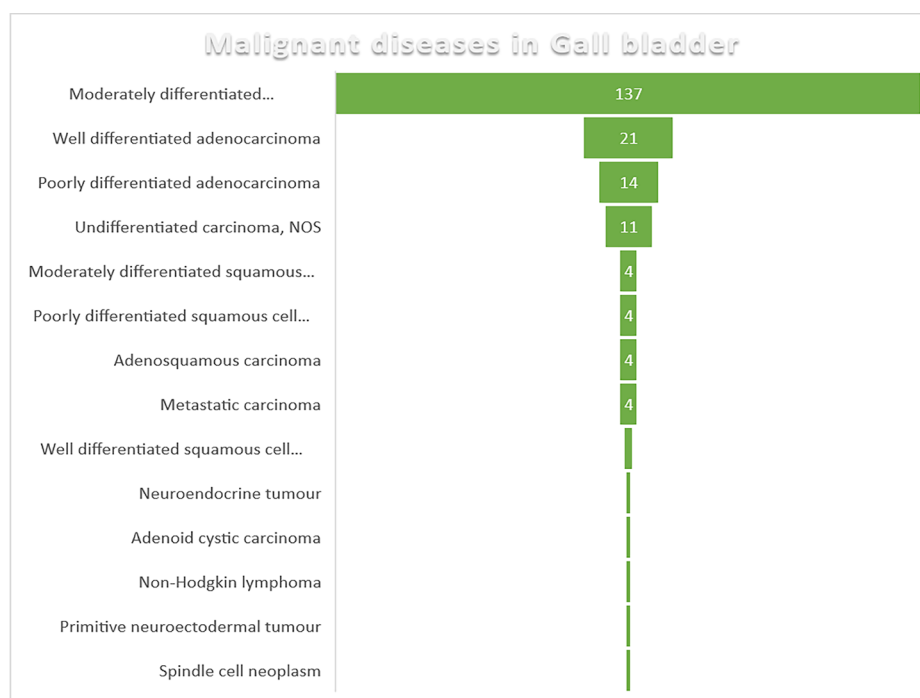


Figure 2. Chart showing the prevalence of malignant gall bladder diseases in North-Western India (Numbers represent absolute values)

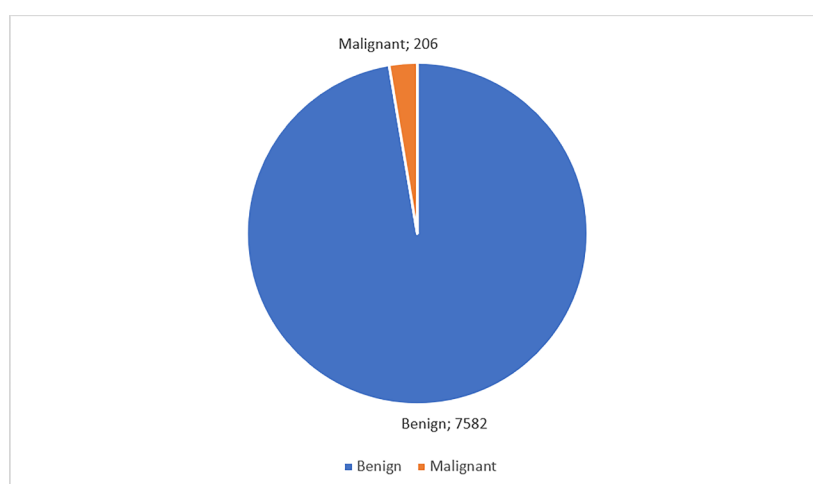


Figure 3. Chart showing the distribution of benign and malignant gall bladder diseases in North-Western India

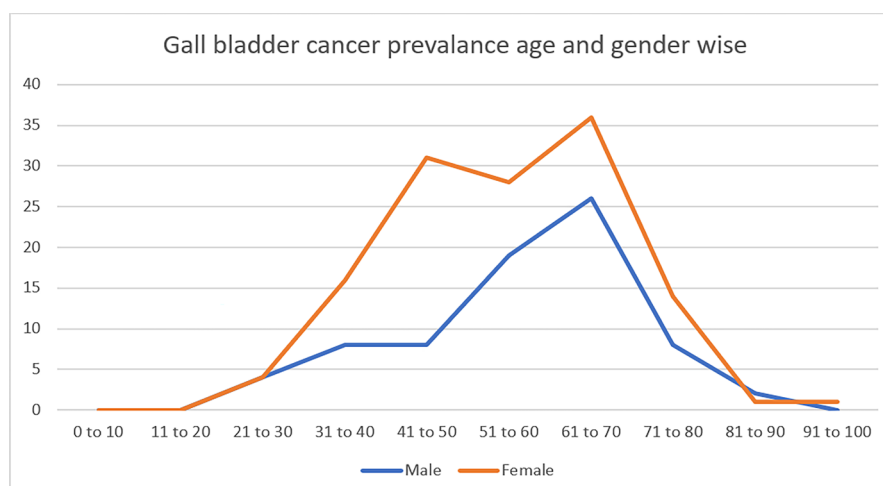


Figure 4. Prevalence of gall bladder diseases (as per age and gender)

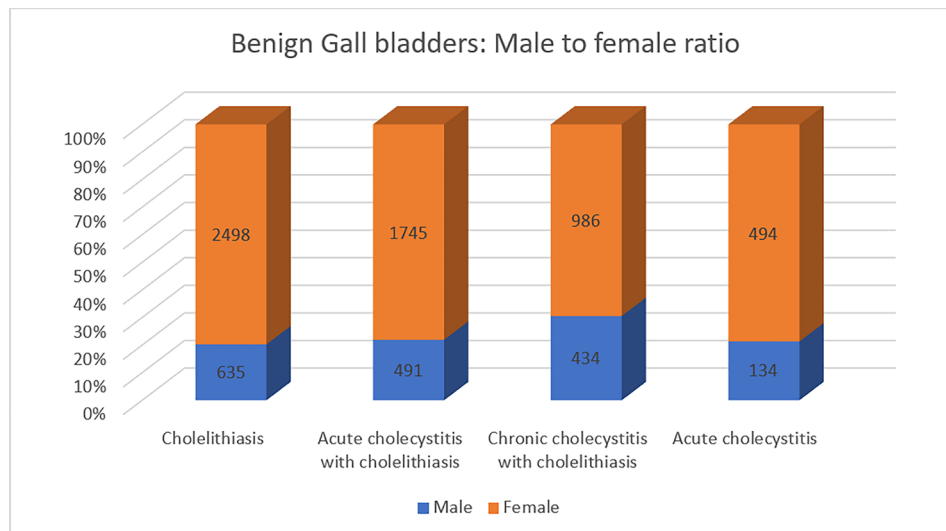


Figure 5. Male to female ratio for benign gall bladder diseases

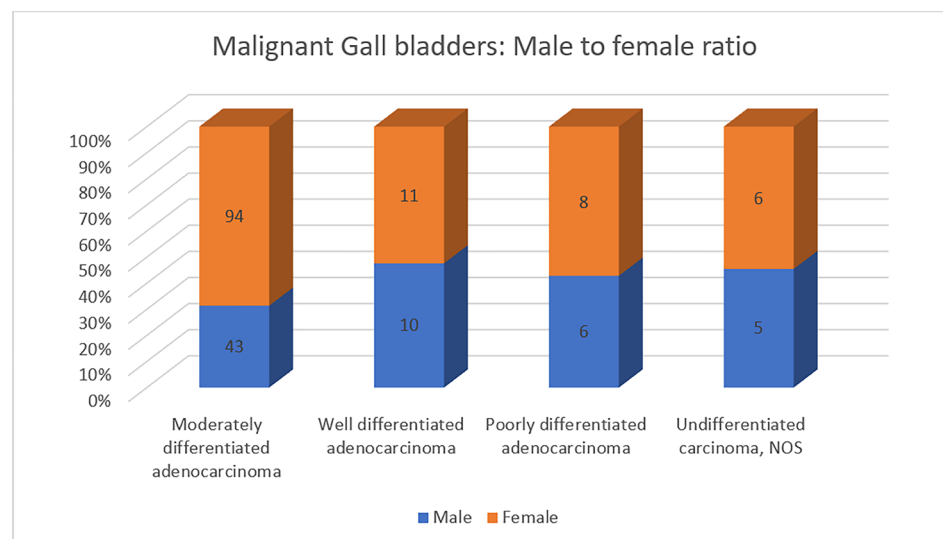


Figure 6. Male to female ratio for malignant gall bladder diseases

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.¹² A recent study from Western Rajasthan showed that gall bladder cancer contributes to 3.8% cases of total cancer cases registered at RCC, Bikaner.¹³ Unisa et al. (2011)¹ 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.^{5,14,15} In contrast, it was only 25% in Jokhi et al. study (2019).¹⁶

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.¹⁷ It accounts for 80 to 90 percent of biliary tract malignancies in the world.¹⁸ 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.^{5,19} 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%.¹² 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),²⁰ Sharma et al. (2015),²¹ Terada et al. (2013),²² Talreja et al. (2016),²³ Jokhi et al. (2019),¹⁶ Shrestha et al. (2010),²⁴ Ojed et al. (1985),²⁵ Asuquo et al. (2008),²⁶ Damor et al. (2013),¹⁵ and Khanna et al. (2006)²⁷ 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)¹⁶ 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.^{15,16} Dix et al. (2003)²⁸ showed 95.5% cases of chronic cholecystitis with only 0.4% cases of acute cholecystitis. Sharma et al. (2015)²¹ 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.²⁹ Chronic cholecystitis formed 78.42% (756 cases) of all histopathologies in Talreja et al. (2016)²³ 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)²² 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)²⁰ 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.¹² Duffy et al. (2008)³⁰ 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%).³⁰ Adenocarcinoma accounted for all malignant cases in Jokhi et al. (2019),¹⁶ and Almuslamani et al. (2011)²⁰ studies.¹⁶ Pandey et al. (2001)³¹ 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)²¹ 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.²⁹ Goetze et al. (2010)³² 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)¹¹ study. Lau et al. (2017)¹⁹ showed maximum prevalence of poorly differentiated tumours (42.5%) followed by moderately (38.2%) and well differentiated (15.3%) cancers. Jokhi et al. (2019)¹⁶ 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)¹⁵ sowed the most common age group for benign gallbladder diseases is 4th and 5th decades with 25% and 26% cases, respectively. Khoo et al. (2008),³³ Damor et al. (2013),¹⁵ Khanna et al. (2006),²⁷ and Samad et al. (2005)³⁴ reported that benign gallbladder lesions occurred in 3rd to 5th decades. Sharma et al. (2014),²⁹ Sharma et al. (2015)²¹ and Selvi et al. (2011)³⁵ study reported the maximum incidence in 4th to 6th decades.

Gallbladder cancer is a disease of the geriatric population.¹⁵ The malignant counterpart affected patients of 61 to 70 age group in both genders with median age of 64 years. Kumar et al. (2006)³⁶ showed that gall bladder carcinomas belonged predominantly to the 4th and 5th decade. Dubey et al. (2018)¹¹ 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)¹⁹ study, Duffy et al. (2008),³⁰ and Everhart et al. (2002)³⁷ study was 71.2, 67 and 65 years, respectively. In contrast, gallbladder carcinoma in Indian study of Dutta et al. (2019)⁵ affected younger females in 5th and 6th 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%).²⁹ Study from our institute in the previous decade showed a similar age incidence with peak after 4th decade.¹² A recent study from Western Rajasthan showed peak incidence in 5th to 7th decades with median age of 60 years.¹³ Also, study from Delhi by Malhotra et al. (2017)³⁸ 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)¹ study was 1,703. Selvi et al. (2011),³⁵ Everhart et al. (2002),³⁷ Damor et al. (2013),¹⁵ Sharma et al. (2015),²¹ Khanna et al. (2006),²⁷ Asuquo et al. (2008),²⁶ Zoysa et al. (2010),³⁹ Tania et al. (2009),⁴⁰ and John et al. (1992)⁴¹ 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.^{10,17,19} A study from our institute previously showed a sex ratio of 1:2.33.¹² Study from Western Rajasthan showed 1:2.6 sex ratio for gallbladder cancer.¹³ Kumar et al. (2006)³⁶ 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),²⁰ Lau et al. (2017),¹⁹ Damor et al. (2013),¹⁵ Talreja et al. (2016)²³ and Duffy et al. (2008)³⁰ 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.^{5,14}

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.⁴²⁻⁴⁵ 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

ACKNOWLEDGEMENT

We are thankful to the Department of Pathology, S.M.S. Medical College & Hospital, Jaipur; Late Dr B.C. Sangal, Department of Pathology S.D.M. Hospital Jaipur; Bhagwan Mahavir Cancer Hospital Jaipur and Dr K C Joshi Diagnostic Lab Jaipur for their valuable contributions.

REFERENCES

1. Unisa S, Jagannath P, Dhir V, Khandelwal C, Sarangi L, Roy TK. Population-based study to estimate prevalence and determine risk factors of gallbladder diseases in the rural Gangetic basin of North India. *HPB (Oxford)*. 2011 Feb;13(2):117-25. DOI: <https://doi.org/10.1111/j.1477-2574.2010.00255.x>
2. Indian Council of Medical Research (ICMR). National Cancer Registry Programme [Internet]. Bangalore: ICMR; 2002; [access in 2022 Nov]. Available from: https://www.ncdirindia.org/All_Reports/PBCR_1997_98/PBCR1997_1998.pdf
3. International Agency for Research on Cancer (IARC). World Health Organization (WHO). India – Globocan 2020 [Internet]. Geneva: IARC/WHO; 2020; [access in 2021 Mar]. Available from: <https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf>
4. Shukla HS, Sirohi B, Behari A, Sharma A, Majumdar J, Ganguly M, et al. Indian Council of Medical Research consensus document for the management of gall bladder cancer. *Indian J Med Paediatr Oncol*. 2015 Apr/Jun;36(2):79-84.
5. Dutta U, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Chin Clin Oncol*. 2019 Aug;8(4):33. DOI: <https://doi.org/10.21037/ccco.2019.08.03>
6. Sikora SS, Kapoor R, Pradeep R, Kapoor VK, Saxena R, Kaushik SP. Palliative surgical treatment of malignant obstructive jaundice. *Eur J Surg Oncol*. 1994 Oct;20(5):580-4.
7. Diehl AK. Epidemiology of gallbladder cancer: a synthesis of recent data. *J Natl Cancer Inst*. 1980 Dec;65(6):1209-14.
8. Indian Council of Medical Research (ICMR). Article [Internet]. Bangalore: ICMR; 2021; [access in 2021 Sep]. Available from: https://ncdirindia.org/All_Reports/HBCR_2021/
9. Nandakumar A, Gupta PC, Gangadharan P, Visweswara RN, Parkin DM. Geographic pathology revisited: development of an atlas of cancer in India. *Int J Cancer*. 2005;116(5):740-54. DOI: <https://doi.org/10.1002/ijc.21109>
10. Dhir V, Mohandas KM. Epidemiology of digestive tract cancers in India IV. Gall bladder and pancreas. *Indian J Gastroenterol*. 1999 Jan/Mar;18(1):24-8.
11. Dubey AP, Rawat K, Pathi N, Viswanath S, Rathore A, Kapoor R, et al. Carcinoma of gall bladder: demographic and clinicopathological profile in Indian patients. *Oncol J Indian*. 2018;2:3-6.

12. Sharma RG, Ratnawat SS, Kumar R, Mehta JM. Clinico-pathological and epidemiological study of gallbladder cancer with special reference to gastrointestinal malignancies in Eastern Rajasthan Region. *J Clin Oncol*. 2008;26(15 Suppl 1):S15662.
13. Maheshwari G, Arora V, Dhanawat A, Jakhar SL, Sharma N, Kumar HS. Retrospective analysis of incidence of gallbladder cancer in North-Western India over 5 years. *J Radiat Cancer Res*. 2020;11(2):52-5.
14. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. *Clin Epidemiol*. 2014 Mar;6(1):99-109.
15. Damor NT, Chauhan HM, Hr J. Histological study of human gallbladder. *Int J Biomed Adv Res*. 2013;4(9):597-601.
16. Jokhi CD, Kanetkar SR, Vohra NV. Study of histopathological findings in gallbladder diseases. *Indian J Pathol Oncol* 2019;6(4):627-35.
17. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int J Cancer*. 2006;118(7):1591-602. DOI: <https://doi.org/10.1002/ijc.21683>
18. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 2001;51(6):349-64.
19. Lau CS, Zywtot A, Mahendraraj K, Chamberlain RS. Gallbladder carcinoma in the United States: a population based clinical outcomes study involving 22,343 patients from the surveillance, epidemiology, and end result database (1973-2013). *HPB Surg* 2017;2017:1532835.
20. Almuslamani AJ, Alsoude M. Histopathological examination on suspicious gallbladder specimens at Royal Medical Services Hospitals. *Rawal Med J*. 2011;36(2):1-7.
21. Sharma I, Chaudhari D. Histopathological patterns of gallbladder disease with special reference to incidental cases: a hospital based study. *Int J Res Med Sci*. 2015;3(12):3553-7.
22. Terada T. Histopathologic features and frequency of gall bladder lesions in consecutive 540 cholecystectomies. *Int J Clin Exp Pathol*. 2013;6(1):91-6.
23. Talreja V, Ali A, Khawaja R, Rani K, Samnani SS, Farid FN. Surgically resected gall bladder: is histopathology needed for all. *Surg Res Pract*. 2016;2016:1-4.
24. Shrestha R, Tiwari M, Ranabhat SK, Aryal G, Rauniyar SK, Shrestha HG. Incidental gallbladder carcinoma: value of routine histological examination of cholecystectomy specimens. *Nepal Med Coll J*. 2010 Jun;12(2):90-4.
25. Ojed VJ, Shilkin KB, Walters MN. Premalignant epithelial lesions of the gallbladder: a prospective study of 120 cholecystectomy specimens. *Pathology*. 1985 Jul;17(3):451-4.
26. Asuquo MS, Umoh V, Nwabgbara A, Inyang CA. Cholecystectomy: indication at University Of Calabar Teaching Hospital, Calabar, Nigeria. *Ann Afr Med*. 2008 Mar;7(1):35-7.
27. Khanna R, Rashmi C, Mohan K, Shukla H. Histological changes in gallbladder due to stone disease. *Indian J Surg*. 2006;68:201-4.
28. Dix FP, Bruce IA, Krypczyk A, Ravi S. A selective approach to histopathology of the gallbladder is justifiable. *Surg J R Coll Surg Edin Irel*. 2003 Aug;1(4):233-5.
29. Sharma JD, Kalita I, Das T, Goswami P, Krishnatreya M. A retrospective study of post-operative gall bladder pathology with special reference to incidental carcinoma of the gall bladder. *Int J Res Med Sci*. 2014 Aug;2(3):1050-3.
30. Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol*. 2008 Dec;98(7):485-9.
31. Manoj P, Pathak AK, Gautam A, Aryya NC, Shukla VK. Carcinoma of the gallbladder: a retrospective review of 99 cases. *Dig Dis Sci*. 2001 Jun;46(6):1145-51.
32. Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. *Surg Endosc*. 2010 Sep;24(9):2156-64.
33. Khoo JJ, Misron NA. A clinicopathological study of nine cases of gallbladder carcinoma in 1122 cholecystectomies in Johor, Malaysia. *Malaysian J Pathol*. 2008 Jun;30(1):21-6.
34. Samad A. Gall bladder carcinoma in patients undergoing cholecystectomy for cholelithiasis. *J Pak Med Assoc*. 2005 Nov;55(11):497-9.
35. Selvi RT, Sinha P, Subramaniam PM, Konapur PG, Prabha CV. A clinicopathological study of cholecystitis with special reference to analysis of cholelithiasis. *Int J Basic Med Sci*. 2011;2(3):68-72.
36. Kumar JR, Tewari M, Rai A, Sinha R, Mohapatra SC, Shukla HS. An objective assessment of demography of gallbladder cancer. *J Surg Oncol*. 2006 May;93(8):610-4. DOI: <https://doi.org/10.1002/jso.20526>
37. Everhart JE, Yeh F, Lee ET, Hill MC, Fabsitz R, Howard BV, et al. Prevalence of gallbladder disease in American Indian populations: findings from the Strong Heart Study. *Hepatology*. 2002;35(6):1507-12. DOI: <https://doi.org/10.1053/jhep.2002.33336>
38. Malhotra RK, Manoharan N, Shukla NK, Rath GK. Gallbladder cancer incidence in Delhi urban: a 25-year trend analysis. *Indian J Cancer*. 2017 Oct/Dec;54(4):673-7.
39. Zoysa SK, Silva LA, Illeperuma A. Is routine histological examination of gallbladder specimen. *Ceylon Med J*. 2010 Mar;55(1):13-5.
40. Tantia O, Jain M, Khanna S, Sen B. Incidental carcinoma gallbladder during laparoscopic cholecystectomy for symptomatic gallstone disease. *Surg Endosc*. 2009 Sep;23(9):2041-6.
41. Paraskevopoulos JA, Ross B, Dennison AR, Johnson AG. Primary carcinoma of gallbladder: a 10- year experience. *Ann Royal Coll Surg Engl*. 1992 May;74(3):222-4.

42. Bang BA, Sharma RG, Kapoor R. Abstract distribution of malignant neoplasms in the eastern Rajasthan region of India. *J Clin Oncol*. 2014;30(15 Suppl 1):e12014. DOI: https://doi.org/10.1200/jco.2012.30.15_suppl.e12014
43. Sharma RG, Kumar R, Jain S, Jhahria S, Gupta N, Gupta SK, et al. Distribution of malignant neoplasms reported at different pathology Centres and Hospitals in Jaipur, Rajasthan. *Indian J Cancer*. 2009 Oct/Dec;46(4):323-30.
44. Sharma RG, Ajmera R, Saxena O. Cancer profile in Eastern Rajasthan. *Indian J Cancer*. 1994 Sep;31(3):160-73.
45. Sharma RG, Maheshwari MS, Lodha SC. Cancer profile in Western Rajasthan. *Indian J Cancer*. 1992 Sep;29(3):126-32.