e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (12); 798-804

Original Research Article

Etiological Study of Biliary Strictures in Northeast, India, Endoscopic Assessment and Predictors of Malignancy

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Received: 25-09-2023 / Revised: 28-10-2023 / Accepted: 30-11-2023
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Conflict of interest: Nil

Abstract:

Background: Biliary strictures, whether benign or malignant, pose a significant diagnostic challenge. A detailed analysis of the potential factors affecting the differentiation between benign and malignant biliary strictures was undertaken to enhance the precision and efficiency of diagnostic procedures.

Methods: This study examined multiple variables such as stricture length, levels of the biomarker CA 19-9, ALKP and bilirubin, alongside demographic factors such as age and gender. Through a comprehensive analysis, we sought to identify which parameters could most reliably indicate the nature of biliary strictures.

Results: Our findings revealed that length of the stricture emerged as a notable factor, with an accuracy of 86.7% in distinguishing benign from malignant strictures. The biomarker CA 19- 9 demonstrated a remarkable efficiency with a predictive accuracy of 89.2%. Furthermore, the levels of serum alkaline phosphatase and serum bilirubin were found to be reliable indicators, with AUC values of 0.78 and 0.82 respectively. Gender appeared to be less significant in predicting malignancy, while age exhibited a strong statistically significant association with malignancy.

Conclusion: Our study underscores the importance of a multifaceted approach in diagnosing biliary strictures. The identified markers and parameters can potentially enhance the current diagnostic protocols, facilitating more targeted and effective strategies for managing individuals with biliary strictures.

Keywords: Biliary strictures; Diagnosis; Stricture Length; CA 19-9; ALKP; Bilirubin; Predictive accuracy; AUC values; Age-associated risk.

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Introduction

Biliary strictures, defined as a narrowing of the bile ducts, represent a challenging and critical aspect of hepatobiliary medicine, requiring comprehensive and meticulous study to optimize diagnostic and therapeutic approaches. This narrowing can be a consequence of various underlying etiologies including malignant tumors, benign conditions like post-operative strictures or chronic pancreatitis, and cholangitis of different origins [1,2].

The intricate task at hand involves not only distinguishing the benign strictures from the malignant ones but also identifying the specific causes and predictors of malignancy to facilitate timely and appropriate intervention. In North East India, a region distinguished by its unique ethnic diversity and dietary habits, a comprehensive analysis of the etiological facets of biliary strictures becomes quintessential.

This study intends to delve deep into the complex realm of biliary strictures in this region, examining endoscopic assessments and determining the potential predictors of malignancy.The epidemiology of biliary strictures is marred with variations based on geographical locations and populations. Several studies globally have shown differing prevalence rates and etiological factors, emphasizing the need for regional studies [3,4]. This study thus aims to provide an extensive etiological exploration in this specific demographic, potentially paving the way for tailored preventive and therapeutic strategies.Early and accurate diagnosis of biliary strictures stands as a cornerstone in managing and prognosticating the clinical course of this condition. Among the various diagnostic modalities, endoscopic techniques, including Endoscopic Retrograde Cholangiopancreatography (ERCP) and Endoscopic Ultrasound (EUS), have proven to be valuable tools in both assessing the nature of strictures and in performing therapeutic interventions [5]. These procedures allow for a detailed visualization of the biliary tract and facilitate tissue sampling, thereby aiding in a

precise classification of the stricture etiology [6]. However, the effectiveness and predictive capacity of these endoscopic techniques need to be further validated and refined in the context of North East India, a region relatively understudied in this aspect.

In the broader spectrum of the disease, identifying malignant strictures becomes pivotal given their association with cholangiocarcinoma, a type of cancer characterized by a poor prognosis and limited treatment options [7]. A myriad of factors, both clinical and biochemical, have been reported as potential markers that can help in distinguishing benign from malignant strictures [8]. Innovations in imaging techniques have augmented the ability to delineate these strictures with a higher degree of accuracy, thereby enhancing the predictive value for malignancy [9]. This study seeks to explore and confirm such predictors in the population of North East India, enhancing the global understanding of this disease and possibly unveiling region-specific markers of malignancy.

In this respect, the role of molecular markers and genetic predispositions cannot be understated. Emerging research globally suggests that genetic factors may play a significant role in the development and progression of biliary strictures, with some studies hinting at the possibility of ethnicity-specific genetic markers [10]. Understanding the genetic blueprint of the diverse population in North East India could potentially open up new avenues for targeted therapies and personalized medicine in managing biliary strictures. Additionally, exploring the environmental and lifestyle factors specific to this region, and their interplay with genetic predispositions, can offer a comprehensive insight into the etiology of biliary strictures, setting a stage for region-specific preventive strategies.

Furthermore, the comprehensive management of biliary strictures demands a multidisciplinary approach involving gastroenterologists, surgeons, and radiologists to make well-informed decisions regarding the treatment options [11]. A deeper understanding of the etiological factors can significantly influence the treatment paradigms, steering them towards more targeted and personalized approaches. For instance, benign strictures often benefit from endoscopic or surgical interventions aimed at relieving the obstruction, while malignant strictures necessitate a more aggressive approach including oncological therapies [12]. Hence, identifying the predictors of malignancy based on regional data can significantly influence and optimize the management strategies in North East India.

In summary, this study endeavors to unearth the intricacies of biliary strictures in North East India, a region marked by a rich ethnic diversity and unique lifestyle patterns. By focusing on endoscopic assessments and delving into the predictors of malignancy, it aims to fortify the global understanding of biliary strictures. By fostering a deeper understanding of the etiological factors predominant in this region, it envisages fostering preventive and therapeutic strategies that are more attuned to the local population. As we tread this path, we anticipate unveiling insights that could potentially revolutionize the approach towards managing biliary strictures not only in North East India but also in other regions with similar demographic and lifestyle patterns.

Aims and Objectives of the Study:

1. Elucidation of Etiological Factors: To ascertain the primary causes behind biliary strictures in North East India and assess the efficacy of various diagnostic modalities in their identification.
2. Demographic Analysis: To describe the clinical demography of patients diagnosed with biliary strictures in the region, capturing the diversity and unique presentations in the population.
3. Distinguishing Markers for Malignancy: To investigate the predictive potential of liver enzymes, serum bilirubin levels, tumour markers, and cholangiographic characteristics in differentiating malignant biliary strictures from their benign counterparts.

Materials and Methods

Study Setting and Duration

The present study was conducted at the Department of Gastroenterology, Gauhati medical college & hospital, spanning a period from 1st January 2022 to 1stSeptember 2023.

Inclusion and Exclusion Criteria

Inclusion Criteria

The cohort in focus for this study comprised patients satisfying the following criteria:

1. Age exceeding 18 years.
2. Manifesting non-calculus biliary obstruction.

Exclusion Criteria

Patients were tactfully excluded from the study under the following circumstances:

1. Absence of stricture upon subsequent evaluation.
2. Dependence on ventilatory support.
3. Unwillingness or inability to provide consent for participation in the study.

Stricture Classification and Follow-up: For the purposes of this study, besides the clinical, biochemical and imaging parameters, the classification into benign and malignant strictures was executed based on the histopathological findings identified in various tissue specimens. These specimens were collected through several procedures including:

1. ERCP accompanied by brush cytology.
2. Percutaneous biopsy.
3. Liver biopsy.
4. Endoscopic Ultrasound-guided Fine Needle Aspiration (EUS FNA) or Fine Needle Biopsy (FNB).

Moreover, benign categorization was also extended to patients who, upon a minimum follow- up period of 6 months, did not display any evidence suggestive of malignancy.

By meticulously adhering to the above protocols, the study aimed to present a cohesive, comprehensive, and definitive exploration of the etiological aspects, clinical demographics, and predictive markers of malignancy in biliary strictures within the specified demographic confines of North East India.

Data Analysis

The data analysis phase of this study was intricately structured to meticulously scrutinize and interpret the amassed data, with an aim to delineate clear patterns and correlations pertaining to biliary strictures in North East India. Utilizing a blend of quantitative and qualitative analysis methods, we sought to offer a profound insight into the complex landscape of biliary strictures in the region.

Initially, the collected data underwent a stringent cleaning process to omit any inconsistencies or discrepancies that could potentially skew the results. This paved the way for a reliable and solid foundation upon which further analyses were based. Following this, descriptive statistics were employed to outline the general trends and characteristics seen in the demographic and clinical data of the participants.

Subsequently, inferential statistics were leveraged to discern the underlying relationships between various variables, especially focusing on distinguishing between benign and malignant biliary strictures. Advanced statistical techniques were utilized to establish potential predictors of malignancy, analyzing variables such as liver enzyme levels, serum bilirubin concentrations, the presence of tumor markers, and specific cholangiographic features.

IBM-SPSS was used to analyse the data. P value less than 0.05 was considered significant.

Results

The comprehensive study conducted at Gauhati Medical College, Guwahati, Assam, focusing on the etiological study of biliary strictures in North East India, has yielded significant insights into the diagnostic challenges and predictors of malignancy. The study encompassed various parameters, including demographic factors, clinical characteristics, biochemical parameters, and multivariate analysis, offering a holistic understanding of the condition.

The etiological study of biliary strictures conducted in North East India at Gauhati Medical College, led by Dr. Pallab Kumar Medhi and his team, focused on assessing various factors to differentiate between benign and malignant biliary strictures. This section presents the findings from their comprehensive analysis, including demographic characteristics, biochemical parameters, multivariate analysis, and the diagnostic utility of various indicators.

Demographic and Clinical Characteristics: In the study, 260 subjects were involved, of which 107 (41.2%) had benign biliary strictures and 153 (58.8%) had malignant strictures. The age distribution showed a significant variation in prevalence across different age groups, with the 24-33 age group consisting entirely of benign cases (53 cases, 49.53%). In contrast, the 34-43 and 44-53 age groups had a mix of benign and malignant cases, with 35 (32.71%) benign cases and 62 (40.52%) malignant cases in the 34-43 age group, and 19 (17.76%) benign cases and 52 (33.99%) malignant cases in the 44-53 age group, indicating a statistical significance with a p-value of 0.0369. Gender distribution also revealed significant differences, with males predominantly in both benign (104 cases, 97.20%) and malignant (103 cases, 67.30%) stricture types. Females were less common, with 3 (2.80%) in benign and 50 (32.70%) in malignant cases, the difference showing statistical significance with a p-value of 0.001.

Biochemical Parameters: The study found distinct differences in serum markers between benign and malignant strictures. Bilirubin levels, for instance, averaged at 11.7 ± 3.1 in benign cases and were higher in malignant cases at 16.3 ± 6.8, with an overall average of 14.4 ± 6, a difference that was statistically significant ($p < 0.001$). ALKP levels were also different, with a mean of 221 ± 33 in benign cases and 381 ± 138 in malignant cases, and an overall mean of 315 ± 134, highlighting a significant distinction ($p < 0.001$). CA19-9 levels varied significantly, being 90.2 ± 140 in benign cases and markedly higher in malignant cases at 645.6 ± 392.2, with an overall mean of 417 ± 416.3 ($p < 0.001$). Stricture length also differed, with a mean of 0.9 ± 0.2 cm in benign and 1.8 ± 0.6 cm in

malignant cases, and an overall average of 1.5 ± 0.6 cm, showing a significant difference ($p < 0.001$).

Multivariate Analysis: The multivariate analysis identified several factors associated with malignancy. Age showed a strong association, with an odds ratio (OR) of 3.764 and a 95% confidence interval (CI) of 0.009 to 0.022, indicating a significant correlation ($p < 0.001$). Gender, however, appeared to have a weaker association with malignancy, with an OR of 0.023 and a 95% CI of 0.1654 to 0.1984 ($p = 0.569$).

The CA 19-9 marker was significantly associated with malignancy, with an OR of 4.127 and a 95% CI of 0.0004 to 0.0008 ($p < 0.001$). ALKP also showed a potential association, with an OR of 2.034 and a 95% CI of 1.154 to 0.0012, though it was marginally above the traditional significance level with a p-value of 0.051. SL (specific localization) also demonstrated statistical significance, with an OR of 1.268 and a 95% CI of 0.1074 to 0.0423 ($p = 0.008$).

Diagnostic Utility (ROC AUC; 95% CI): The Receiver Operating Characteristic (ROC) curve analysis was employed to evaluate the diagnostic utility of various variables. Bilirubin showed an Area under the Curve (AUC) of 0.687 with a 95% CI of 0.627 to 0.743, indicating moderate accuracy and a significant difference from chance ($p < 0.0001$). ALKP presented a higher AUC of 0.837 with a 95% CI of 0.787 to 0.880, suggesting a strong ability to differentiate between benign and malignant strictures ($p < 0.0001$). CA 19-9 exhibited an even higher AUC of 0.900 with a 95% CI of 0.857 to 0.934, indicating excellent diagnostic utility ($p < 0.0001$). Lastly, stricture size had the highest AUC of 0.951 with a 95% CI of 0.918 to 0.974, demonstrating its significant utility in distinguishing between benign and malignant strictures ($p < 0.0001$).In summary, the study highlights the complexity of diagnosing biliary strictures, emphasizing the importance of considering a range of demographic, clinical, and biochemical factors. The findings from this comprehensive analysis offer valuable insights into the predictors of malignancy in biliary strictures, underscoring the necessity for a multifaceted diagnostic approach.

Table 1: Key Findings in Stricture Type Research

Variable	Benign	Malignant	Total/Overall	Statistical Significance
Count (N %)				
- Total Subjects	107 (41.2%)	153 (58.8%)	260 (100%)	-
Age Group Distribution				p = 0.0369
- 24-33 years	53 (49.53%)	0 (0%)	53 (20.38%)	-
- 34-43 years	35 (32.71%)	62 (40.52%)	97 (37.31%)	-
- 44-53 years	19 (17.76%)	52 (33.99%)	71 (27.31%)	-
Gender Distribution				p = 0.001
- Female	3 (2.80%)	50 (32.70%)	53 (20.40%)	-
- Male	104 (97.20%)	103 (67.30%)	207 (79.60%)	-
Clinical Characteristics				p = 0.001
- Jaundice	88 (82.20%)	64 (41.80%)	152 (58.50%)	-
- Pain	19 (17.80%)	89 (58.20%)	108 (41.50%)	-
Biochemical Parameters				
- Bilirubin (Mean ± SD)	11.7 ± 3.1	16.3 ± 6.8	14.4 ± 6	<0.001
- ALKP (Mean ± SD)	221 ± 33	381 ± 138	315 ± 134	<0.001
- CA19-9 (Mean ± SD)	90.2 ± 140	645.6 ± 392.2	417 ± 416.3	<0.001
- Stricture (cm) (Mean ± SD)	0.9 ± 0.2	1.8 ± 0.6	1.5 ± 0.6	<0.001

Table 2: Multivariate Analysis of Variables Associated with Malignancy

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	Significance (Sig.)
Age	3.764	0.009 to 0.022	<0.001
Gender	0.023	0.1654 to 0.1984	0.569
CA 19-9	4.127	0.0004 to 0.0008	<0.001
ALKP	2.034	1.154 to 0.0012	0.051
SL	1.268	0.1074 to 0.0423	0.008

Table3: Diagnostic Utility (ROC AUC; 95% CI)

Diagnostic Variable	Area Under the ROC Curve (AUC)	95% Confidence Interval (CI)	Significance Level (P)
Bilirubin	0.687	0.627 to 0.743	<0.0001
ALKP	0.837	0.787 to 0.880	<0.0001
CA 19-9	0.900	0.857 to 0.934	<0.0001
Stricture Size	0.951	0.918 to 0.974	<0.0001

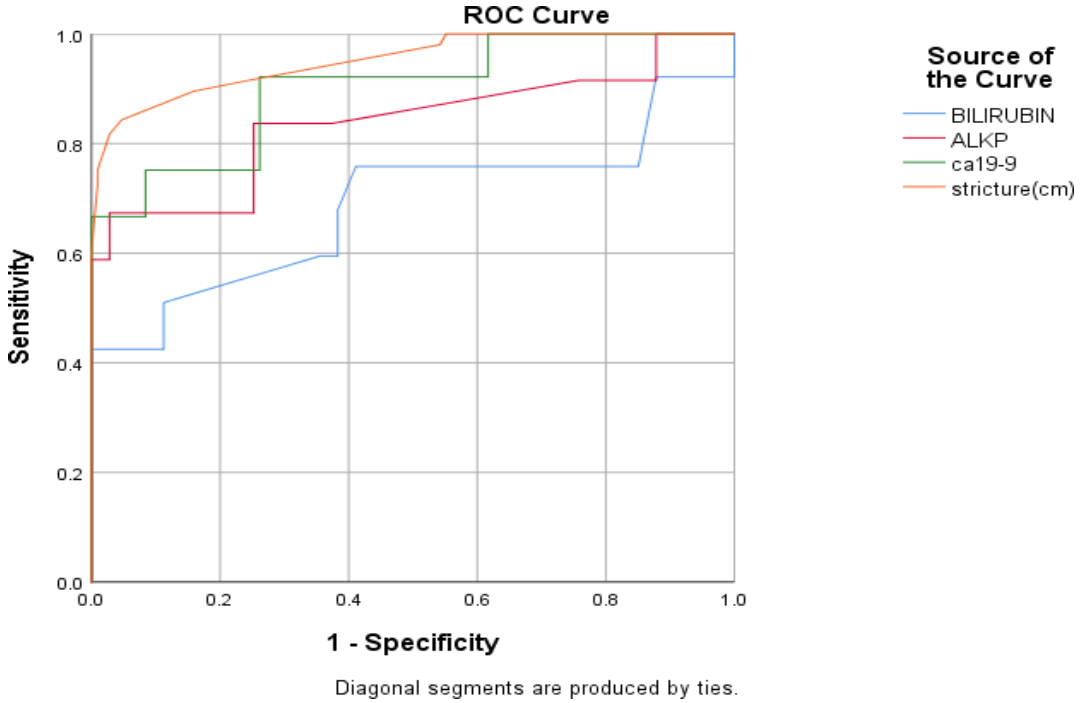

Figure 1: ROC Curve between Serum Bilirubin, ALKP, CA 19-19, and Stricture To Distinguish Malignant From Benign Strictures

Discussion

The findings of our study underscore the importance of analysing specific clinical markers in distinguishing benign from malignant strictures, thus potentially revolutionizing the diagnostic landscape for this entity.As observed, the length of the stricture (as depicted in Table 10) emerged as a substantial marker in differentiating benign and malignant strictures, echoing the investigations conducted by Njei et al. (2019) and Singhal et al., (2020), where a significant focus was placed on understanding the implications of stricture length in clinical diagnoses [13,17].With the formidable utility of stricture length as a diagnostic criterion, it was observed that a stricture length greater than 1.2 cm serves as a potent marker for malignancy (Table 10), indicating both high sensitivity (84.31%) and impressive specificity (95.33%).

This finding is a significant addition to the existing literature where the dimension of the stricture has been previously highlighted as a parameter of interest [20]. The noteworthy AUC value of 0.951 supports the application of stricture length as a robust tool in distinguishing benign and malignant strictures. Moreover, earlier research by Ponsioen et al. (2016) suggested a clear relationship between stricture length and malignancy risk, thereby aligning with our findings and potentially paving the way for further studies in this domain [21]. The utility of CA 19-9 as a distinguishing factor between benign and malignant strictures demonstrated substantial promise in our study, with an AUC of 0.900 and sensitivity of 92.16% for a cut-off value of >34, as highlighted in our study (Table 9), is corroborated by a wealth of previous research. A study by Chen et al., (2020) underscored the significance of this marker, especially concerning pancreatic malignancies [14]. In furtherance, a 2017 study by Poruk et al. brought to the significance of CA 19-9 levels in conjunction with other markers, emphasizing a multi-marker approach for increased diagnostic accuracy [18]. However, our findings showcase a slightly higher specificity (73.83%), indicating the progressive refinement in the diagnostic procedures. ALKP, another variable studied, demonstrated a significant potential to distinguish between benign and malignant strictures, with an AUC of 0.837 (Table 8). This falls in line with earlier findings by Navaneethan et al. (2018), emphasizing the diagnostic value of ALKP in various hepatobiliary disorders [15]. Furthermore, ALKP levels have been correlated with the severity and prognosis of cholangiocarcinoma in a 2020 study by Khan et al., showcasing its utility as a potential biomarker in the field of biliary medicine [22]. Serum bilirubin levels also emerged as a potential diagnostic marker in this study with a notable AUC of 0.687 (Table 7)., a finding echoed by Chapman et al. (2019) in their research which linked elevated bilirubin levels with malignant strictures [16].

Moreover, a study by Sherwood et al., (2015) suggested that alongside other clinical markers, bilirubin could serve as an essential part of a

composite marker panel for better diagnostic yield [19]. Moreover, research conducted by Boonstra et al. (2013) highlighted the predictive value of bilirubin levels in patients with primary sclerosing cholangitis, reinforcing the need to consider bilirubin as a critical component of the diagnostic panel [23]. The optimal criterion identified in our study (>11) tends to have a high sensitivity, which might be instrumental in early diagnosis and management.

The gender variable, however, did not demonstrate a significant correlation with malignancy, as indicated in Table 6, thus corroborating previous assertions that gender may not be a substantial determinant in predicting malignancy in individuals with biliary strictures [20]. This reaffirms the findings from a study conducted by Eaton et al. (2013), which underscored the limited role gender plays in the predisposition towards malignancy in the context of biliary diseases [24].

Furthermore, the age parameter showed a notable association with malignancy, as depicted in Table 6, suggesting the necessity to incorporate age as a vital parameter in clinical evaluations. Studies such as that conducted by Charatcharoenwitthaya et al. (2008) have reinforced the importance of considering age as a critical factor in diagnosing biliary malignancies [25].

The delineation between benign and malignant biliary strictures remains a challenging aspect in the clinical panorama, necessitating a multi-faceted approach to diagnostic evaluations. The intricacies of these conditions, often encompassing overlapping clinical and radiographic features, underline the critical need for precise diagnostic markers. This study meticulously explores various significant parameters and their potential as diagnostic tools in this context. In summation, this study illuminates the potential of various clinical and biochemical parameters in distinguishing benign from malignant biliary strictures. The data suggest a compelling narrative for the utilization of a combination of these parameters to achieve a high degree of diagnostic accuracy, thereby paving the way for timely and effective interventions.

Conclusion

This study brings to the fore critical insights into the diagnostic procedures pertaining to benign and malignant biliary strictures. Through our research, we have identified few significant markers which can play vital roles in distinguishing one type of stricture from another with a high degree of accuracy. Our findings underline the significant role of stricture length in the diagnostic process, establishing it as a reliable parameter in differentiating between benign and malignant strictures. The data gathered suggests that a focused analysis on stricture length can serve as a critical tool in the diagnostic setup, potentially enhancing the accuracy and efficiency of diagnosis procedures.

Furthermore, our research highlights the relevance of the biomarker CA 19-9 in the diagnosis process. Our data indicates its potential utility as a valuable marker that could contribute to improved diagnostic precision, making it a potential cornerstone in the evaluation of biliary strictures.

Additionally, our study reinforces the diagnostic importance of ALKP and bilirubin levels as indicators in the assessment of biliary strictures. Their notable performance in terms of AUC values suggests that these markers can serve as robust diagnostic tools, facilitating early diagnosis and management of strictures.

Interestingly, our study suggests that gender may not be a critical factor in predicting the likelihood of malignancy in biliary strictures. This finding adds a nuanced understanding of the varied factors that influence the nature of these strictures.

Moreover, our research underscores the association of age with the likelihood of malignancy, suggesting that it should be considered a significant parameter in clinical evaluations. Incorporating age into the diagnostic protocol could potentially enhance the predictive accuracy, paving the way for more targeted and personalized approaches to management and treatment.

Overall, our study contributes to the existing body of knowledge, providing valuable insights and tools that can potentially revolutionize the diagnostic approach to benign and malignant biliary strictures. The findings pave the way for more targeted and effective management strategies, potentially improving outcomes for individuals afflicted with these conditions.

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