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ORIGINAL ARTICLE

Predictive Value of Ultrasonography and Alkaline Phosphate (ALP) in Common Bile Duct (CBD) Stones.

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ABSTRACT… Objective: To assess the predictive performance of trans-abdominal US (TAUS) and serum ALP for detecting CBD stones in adults by taking MRCP as the reference standard. **Study Design:** Prospective Cross-validation study. **Setting:** Department of Gastroenterology, Kulsoom Bai Valika Hospital, Karachi, Pakistan. **Period:** Oct 2024 to Apr 2025. **Methods:** Adults (≥ 18 years) with clinical suspicion of common bile duct stones underwent TAUS (2–5 MHz convex probe) and serum ALP measurement within 6 hours of admission. All participants then received MRCP within 48 hours, interpreted by a radiologist blinded to TAUS and ALP results. In a subset proceeding to surgery (n=80), intraoperative findings and cholangiography confirmed stone presence and clearance. We calculated sensitivity, specificity, positive and negative predictive values, overall accuracy and area under the receiver-operating-characteristic curve (AUC) for TAUS, ALP ≥ 400 IU/L and their combination. **Results:** Of 210 enrolled patients (mean age 45.7 ± 12.5 years; 61.9 % female), MRCP confirmed choledocholithiasis in 122 (58.1 %). TAUS detected stones with 78.7 % sensitivity, 72.1 % specificity, 80.0 % PPV and 71.1 % NPV. ALP ≥ 400 IU/L yielded 65.6 % sensitivity, 42.0 % specificity, 61.1 % PPV and 46.8 % NPV. Among 80 surgically explored patients, 68 (85 %) had stones confirmed and 42 of 45 (93.3 %) underwent successful intraoperative cholangiographic clearance. **Conclusion:** High-resolution TAUS outperform ALP ≥ 400 IU/L for non-invasive choledocholithiasis detection and should remain the frontline diagnostic modality. MRCP or endoscopic ultrasound should be reserved for equivocal cases or intermediate-risk patients.

Key words: Alkaline Phosphatase, Choledocholithiasis, Diagnostic Accuracy, Magnetic Resonance Cholangiopancreatography, Pakistan, Ultrasonography.

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INTRODUCTION

Gallstone disease (GSD) is one of the most prevalent biliary disorders worldwide, with population-based studies estimating that up to 20 % of adults in SouthAsia harbour gallstones at some point in their lives.[1] Although the majority remain within the gallbladder, between 1 % and 15 % migrate into the common bile duct (CBD)[2], producing choledocholithiasis; an entity associated with obstructive jaundice, acute cholangitis and biliary pancreatitis if left untreated.[3] Rapid and accurate identification of CBD stones therefore underpins safe surgical planning and helps to avert the morbidity and cost of delayed or missed diagnoses.[2]

In highresource settings, magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound have become firstline, noninvasive tests because both approach the diagnostic yield of endoscopic retrograde cholangiopancreatography (ERCP) without its attendant procedurerelated risks.[4,5] Unfortunately, limited scanner availability, long waiting lists and prohibitive costs often restrict their routine use in Pakistan's public hospitals.[4] Consequently, clinicians continue to rely on two inexpensive and readily accessible surrogates: transabdominal ultrasonography (TAUS) and serum alkaline phosphatase (ALP).[4] US offers the attractive combination of low cost, bedside portability and the ability to demonstrate both intraductal echogenic foci and secondary ductal dilatation.[4,5] Yet its diagnostic accuracy is highly variable; published figures span from as low as 15% to as high as 40%, a range largely determined by stone size, anatomical location and operator skill.[4]

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Biochemical markers provide complementary pathophysiological information. ALP, a membranebound glycoprotein released from injured cholangiocytes, rises proportionally with the degree and duration of biliary obstruction.[6] A crosssectional survey from Lahore reported a positivepredictive value (PPV) of nearly 90 % for ALP concentrations ≥ 400 IU/L when intraoperative findings were taken as the gold standard.[7] In contrast, a British series demonstrated that while persistent ALP elevations (> 370 IU/L) were indeed associated with stones, the standalone sensitivity of the enzyme was only 42 %, underscoring the danger of using biochemistry in isolation.[5]

These disparate results highlight two enduring uncertainties: first, the optimal ALP cutoff point for maximising discrimination in different populations; and second, the incremental value obtained when ultrasonographic findings are interpreted in tandem with concurrent ALP levels. Existing Pakistani data are limited to retrospective or singlemodality evaluations, leaving a knowledge gap regarding how best to integrate imaging with biochemistry for frontline triage in resourceconstrained environments. The present study therefore set out to prospectively assess the predictive performance of TAUS and serum ALP for detecting CBD stones in adults presenting to a large tertiarycare hospital in Karachi by taking MRCP as the reference standard.

METHODS

This prospective cross-validation study was conducted in the Department of Gastroenterology, Kulsoom Bai Valika Hospital, Karachi from Oct 2024 and Apr 2025. Ethical approval was obtained from the institutional review board (ERC No: 664), and written informed consent was secured from all participants.

Sample size of 217 to 220 patients was estimated on Open Epi sample size calculator using PPV of ALP (≥400 IU/L) as 90%[7], margin of error as 4% and 95% confidence level. Patients of age more than and equal to 18 years of either gender presenting with cholelithiasis and elevated ALP (≥400IU/L) that underwent open cholecystectomy were included. Cholelithiasis was suspected in patients with rightupperquadrant pain (VAS>4) for ≥6 weeks and was diagnosed upon US evidence of stones in the gall bladder (echoic shadow). Exclusion criteria comprised known malignancy, chronic liver disease, empyema gallbladder, acute cholecystitis, previous biliary surgery, pregnancy, hemodynamic instability precluding imaging, and refusal to consent. Non-probability consecutive sampling method was employed for sample selection.

TAUS was performed within 6 hours of admission by credentialed sonographers using a Philips Affiniti 70 (2–5 MHz convex probe). Sonographers were blinded to ALP results. CBD diameter, presence of intraductal echogenic foci with posterior acoustic shadowing and gallbladder status were recorded. CBD dilatation was defined as > 8 mm. US was considered positive if any echogenic focus was visualized or if CBD dilatation coexisted with gallstones. A venous blood sample was obtained concurrently from all of the patients. ALP was measured on a Roche Cobas 6000 (IFCCtraceable method; upper reference limit 130 IU/L). ALP ≥400IU/L was considered as a positive test. Then all 210 participants underwent MRCP within 48 hours of admission on a 1.5 T scanner, using heavily T2weighted singleshot fast spinecho sequences in axial and coronal planes. A boardcertified radiologist; who was blinded to US and ALP results interpreted each MRCP. Choledocholithiasis was confirmed by the presence of one or more discrete signalvoid filling defects within the CBD. During surgical exploration, CBD stones were visualized directly or extracted using choledochotomy or transcystic approaches. In several cases, dilated bile ducts and impacted stones were observed, correlating with preoperative imaging and biochemical markers. The nature of the stones varied from soft, pigment-rich sludge to hard, cholesterol-laden calculi. Intraoperative cholangiography was employed in selected cases to delineate ductal anatomy and confirm stone clearance, thereby supporting or contradicting preoperative ultrasound and ALP findings.

Data was analyzed using SPSS version 23. Mean and SD were computed for continuous data and frequencies and percentages were computed for categorical. Two by two was used to calculated sensitivity, specificity, PPV, negative predictive

value (NPV) and diagnostic accuracy for TAUS and ALP≥ 400 IU/L by taking MRCP as reference standard. Twotailed p < 0.05 denoted significance.

RESULTS

Of 220 eligible patients, 4 declined or were lost, leaving 216; 6 were later excluded (three incomplete imaging, 3 indeterminate MRCP), yielding 210 for analysis. Baseline characteristics are presented in Table-I. The overall mean age was 45.7 years (SD=12.5), and sex distribution showed a modest female predominance (61.9 %). Overall, median ALT, total bilirubin and ALP were found as 200 (121.75–286.25) IU/L, 3.5 (2.18–5.64) mg/dl, and 450 (299.75–632.50) IU/L respectively.

MRCP confirmed CBD stones in 122 of 210 patients (58.1 %). TAUS correctly identified 96 of these 122 cases (sensitivity 78.7%) and correctly excluded 64 of 88 stonefree patients (specificity 72.1 %), yielding a PPV of 80.0 % and a NPV of 71.1 %. The area under the ROC curve for TAUS was 0.75. Using a threshold of ALP ≥ 400 IU/L, 80 of 122 stone cases were detected (sensitivity 65.6 %), but only 37 of 88 nonstone patients were correctly classified (specificity 42.0 %), with a PPV of 61.1 % and NPV of 46.8 %. The AUC for ALP was 0.64, indicating poor overall discrimination. When either US or ALP (≥ 400 IU/L) was positive, sensitivity remained at 78.7 % but specificity fell to 68.2 %, and the combined AUC was 0.73; not a meaningful improvement over TAUS alone. (Table-II & Figure-1)

Eighty patients (38% of the cohort) underwent surgical CBD exploration. Intraoperatively, stones were directly visualized or extracted in 68 patients (85%). Stone composition was mixed: 54% were hard, cholesterolladen calculi and 46% soft, pigmentrich sludge. Intraoperative cholangiography was performed in 45 cases and confirmed complete ductal clearance in 42 (93.3%).

FIGURE-1

ROC curve for the US and ALP≥ 400 IU/L

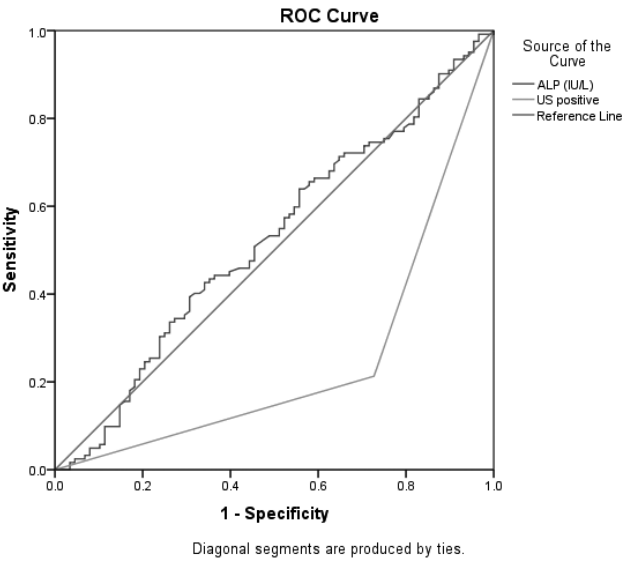

TABLE-I

Baseline demographics and laboratory parameters (n = 210)

Variable	Total Sample (n=210)	CBD Stones Present (n = 122)	CBD Stones Absent (n = 88)
Age, years (mean ± SD)	45.66 ± 12.48	45.71 ± 12.91	45.60 ± 11.94
Female sex, n (%)	130 (61.9)	61 (69.3)	69 (56.6)
ALT, IU/L (median [IQR])	200 [121.75–286.25]	239 [167.50–326.25]	150 [94–229]
Bilirubin total, mg/dL (median [IQR])	3.5 [2.18–5.64]	5.19 [3.53–6.51]	2.02 [1.27–2.99]
ALP, IU/L (median [IQR])	450 [299.75–632.50]	463.5 [301–637]	446 [300.50–603]

TABLE-II

Test accuracy of TAUS and ALP by taking MRCP as gold standard (n = 210)

Parameter	Sensitivity % (95 % CI)	Specificity % (95 % CI)	PPV % (95 % CI)	NPV % (95 % CI)	Accuracy (95 % CI)
TAUS	78.69 (70.35–85.58)	72.73 (62.19–81.68)	80 (73.75-85.07)	71.11 (63.10-77.99)	76.19 (69.84-81.78)
ALP ≥ 400 IU/L	65.57 (56.43-73	42.05 (31.60-53.05)	61.07 (55.74-66.14)	46.84 (38.38-55.47)	55.71 (48.72-62.55)

DISCUSSION

Our study confirms that choledocholithiasis in Pakistan disproportionately affects middleaged women, with 61.9 % of our overall cohort and 69.3 % of patients with MRCPconfirmed stones being female. This mirrors community surveys in Karachi showing gallstone prevalence of approximately 10.2 % and a clear female predominance.[8] The mean age of 45.7 years in our cohort similarly aligns with regional data indicating earlier onset of symptomatic disease compared with Western populations.[9] Intraoperative cholangiography in 80 surgically explored patients confirmed ductal clearance in 93.3 %, underscoring the value of operative imaging when preoperative diagnostics are equivocal.[10]

Transabdominal US delivered robust diagnostic accuracy, correctly identifying 78.7 % of MRCPconfirmed stones and excluding 72.1 % of nonstone cases. A recent systematic review and metaanalysis of 15 studies encompassing over 2000 patients reported pooled US sensitivity of 73 % and specificity of 91 % for choledocholithiasis, corroborating our findings in a Pakistani tertiarycare setting.[11] US's robust performance in our study also aligns with prior Pakistani data demonstrating sensitivity of 96% and specificity of 80.2% for CBD stone detection in tertiarycare settings.[12] While, in another Pakistani study US showed the lesser sensitivity of 29%, however, specificity was 85%.[7] Early study also demonstrated ultrasonographic sensitivity of 77% and specificity of 98% in obstructive jaundice, foreshadowing the gains achieved with today's highresolution machines.[13]

By contrast, serum ALP at a threshold of 400 IU/L underperformed, yielding only 65.6 % sensitivity and 42.0 % specificity. This confirms that a universal cutoff of 400 IU/L misses one in three true stones and falsely flags more than half of nonstone patients. This mirrors findings from a prospective analysis in which an ALP cutoff of 78 IU/L achieved 97.6 % sensitivity but only 72.6 % specificity, illustrating the sensitivityspecificity tradeoff inherent to biochemical markers.[14] Conversely, ALP's PPV in a study conducted at Lahore reached 90 % at thresholds ≥ 400 IU/L, but sensitivity remained low (42 %), limiting its utility as a standalone screen.[7] Biochemical markers alone cannot substitute for imaging, especially given the overlap of ALP elevations in gallbladder inflammation and other hepatobiliary conditions.

MRCP remains the noninvasive diagnostic gold standard, with pooled sensitivities and specificities exceeding 85 % and 90 %, respectively.[15] However, MRCP access in Pakistan is severely limited. According to the World Health Organization's Global Health Observatory, Pakistan had just 0.22 MRI units per million population as of 2013, a figure that has seen only marginal improvement in the ensuing decade.[16] A 2011 RADAID International report documented merely 19 MRI systems serving some 170 million Pakistanis, equivalent to 0.11 units per million and concentrated in private urban hospitals, leaving entire provinces without any MRI access.[17] The cost of MRCP (PKR 15 000–25 000; ~USD 85–140) places it beyond the reach of many publicsector patients, resulting in delayed or foregone definitive imaging.

Endoscopic ultrasound (EUS) has demonstrated superior sensitivity (96-100%) and specificity (92-100%) for choledocholithiasis compared to MRCP in previous studies.[4,18] When combined with samesession ERCP, EUS-directed interventions reduce patient burden and overall costs associated with repeat procedures.[19] Adoption of EUS in Pakistan is limited by equipment scarcity and a shortage of trained endosonographers, but initial experiences at tertiary centres have been encouraging, suggesting that broader EUS integration could alleviate MRCP shortages.[4]

Clinical practice guidelines increasingly advocate riskstratified approaches. The American Society for Gastrointestinal Endoscopy (ASGE) classifies verystrong predictors (e.g., CBD stones on US, bilirubin > 4 mg/dL) and recommends MRCP or EUS for intermediaterisk patients.[2] European associations similarly endorse selective imaging, balancing diagnostic yield against cost and resource utilization.[19] In Pakistan, adapting these algorithms with locally validated biochemical thresholds and transabdominal US criteria could optimize resource utilization.

Costeffectiveness analyses from comparable low and middleincome countries indicate that a tiered approach; initial transabdominal US, followed by MRCP only for those at intermediate risk can reduce unnecessary MRCP by up to 70% and save significant healthcare expenditure.[20] Similarly, laparoscopic common bile duct exploration, available in several Karachi surgical units, achieves stone clearance rates above 80% and may be more costeffective than repeated imaging or ERCP in selected cases.[21]

Our study's foremost strength lies in its prospective design with rigorous blinding and use of MRCP as a uniform reference standard for all participants, which minimizes spectrum and verification biases and reflects realworld practice in a busy tertiarycare hospital. Nevertheless, our singlecentre setting and reliance on examinations performed by highly trained sonographers may limit the generalizability of these findings to less expert environments. Only 38 % of patients underwent surgical confirmation, introducing potential verification bias, and we did not assess alternative biomarkers such as gammaglutamyl transferase or capture patientcentred outcomes like quality of life and downstream healthcare utilization. Looking ahead, multicentre validation across Pakistan's diverse healthcare facilities will be critical, as will costeffectiveness analyses tailored to local resource constraints, broader training programs to standardize ultrasound proficiency, and exploration of integrative predictive models including clinical scores and machinelearning approaches to optimize noninvasive diagnosis and guide resource allocation in settings where advanced imaging remains scarce.

CONCLUSION

Highresolution TAUS outperforms ALP ≥ 400 IU/L for noninvasive choledocholithiasis detection and should remain the frontline diagnostic modality. MRCP or endoscopic ultrasound should be reserved for equivocal cases or intermediaterisk patients. Future work should refine locally appropriate ALP thresholds, validate combined risk scores and expand access to advanced endoscopic imaging.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Ramsha Waseem:** Concept of study,
2	**Iram Dayo:** Data analysis, manuscript writing.
3	**Nimra Aslam:** Data analysis.
4	**Muhammad Ghayasuddin:** Final review.
5	**Rakshanda Najam Siddiqi:** Manuscript preparation.
6	**Muhammad Ali:** Literature review.