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A retrospective analysis of magnetic resonance cholangiopancreatography investigating gallstones in a contemporary surgical setting

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cholangiopancreatography, choledocholithiasis, gallstones, magnetic resonance, predictive value of tests.

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Abstract

Backgrounds: The New Zealand Public Health System operates in a resource limited environment. Pre-operative investigation of choledocholithiasis (CDL) is variable. Protocol driven practice has improved patient outcomes and cost-effectiveness. The aim is to explore risk stratification for CDL and specific thresholds for accessing magnetic resonance cholangiopancreatography (MRCP) in this contemporary setting.

Methods: All adult (16+ years) acute inpatient MRCP requests for gallstone work-up between 1 Jan 2018 and 2031 Dec 2019 at Dunedin Hospital were included. Patients with characteristics not in fitting with an acute symptomatic examination were excluded. Receiver operating characteristic curves were estimated for bilirubin versus MRCP positive by the presence/absence of dilated ducts, indication and American Society of Gastrointestinal Endoscopy (ASGE) risk grouping.

Results: A 106 patients were included. Mean bilirubin at presentation and time of MRCP, 47 versus 28 μmol/L, respectively. MRCP confirmed CDL in 39 (37%) patients. 38 (97%) had biochemical changes with choledocholithiasis. 21 (40%) with CBD dilation had ductal stones versus 18 (34%) with normal ducts. ASGE risk stratification showed 36 (34%), 66 (62%) and 4 (4%) were high, intermediate and low risk, respectively. Of these groups 44%, 35% and 0% had CBD stones on MRCP, respectively. Combination thresholds involving duct size and bilirubin can yield negative predictive values >90%, substantially reducing MRCP load.

Conclusions: MRCP requests can be triaged to maximize stones detected without overly increasing the rate of missed duct stones whilst protecting the limited MRI and ERCP resources. International thresholds and risk stratification alone may not be applicable in our resource limited environment.

Introduction

In patients with gallstone disease it is important to identify the risk of common bile duct (CBD) stones to proceed with appropriate surgical management. Magnetic Resonance Cholangiopancreatography (MRCP) is accurate and internationally its preoperative use has increased due to its availability and non-invasive nature.[1] However, surgical departments within New Zealand are operating within a resource limited system that has severe limitations.[2] Using risk stratification would aid in allocating resources appropriately to improve flow of inpatient care and cost effectiveness.[3,4] Protocol driven care can achieve this.[5] The American Society of Gastrointestinal Endoscopy (ASGE) guidelines stratify CBD stone risk into high, intermediate and low categories (Table S1).[6] These are used internationally, and multiple studies have evaluated their efficacy.[7] Contentious accuracy of 62.1% (47.4% sensitivity, 73% specificity) has been reported by He *et al*., and they create a heavy burden on endoscopic and radiologic services, with up to 72% reporting negative findings despite appropriate guideline use.[3,7] Up to 35% of MRCP are unnecessary and not performed in accordance to guidelines.[3,4,8,9] Recent research has suggested sonographic and biochemical thresholds (dilated CBD and bilirubin >39 μmol/L) to assess the utility of MRCP in specific contexts.[10,11] Similarly, sonographic dilated CBD and serum bilirubin >68 μmol/L may have a

proclivity to more accurately predict choledocholithiasis (specificity 94%, PPV 85%) in an ASGE high risk population.[7] In response, the authors' radiology department attempted to restrict MRCP access using an isolated bilirubin threshold.

The objective is describe current MRCP practice in a resource limited environment, investigate the local use of international thresholds to aid in efficient and clinically indicated use of MRCP and assess if specific thresholds have a basis for use in a contemporary New Zealand surgical setting.

Methods

A retrospective search on the local radiology database for all MRCP requests between 1 Jan 2018 and 2031 Dec 2019 at Dunedin Hospital for patients having MRCP as an acute inpatient for gallstone work up. Exclusion criteria: Not under the care of a surgical team, no ultrasound (USS) within 7 days prior to MRCP, history of previous cholecystectomy and an indication other than acute gallstone work-up (Fig. S1).

Information was collected from the medical records including age, wait time to MRCP from time of request, CBD dilation on ultrasound, serum bilirubin at time of ultrasound (=first bilirubin) and MRCP (=second bilirubin), abnormal serum liver function enzyme panel (LFT), risk stratification as per ASGE guidelines[6] and final diagnosis. Local department policy was to preoperatively define and treat CBD stones where suspected, prior to Laparoscopic cholecystectomy. The primary outcome was the presence of choledocholithiasis (CBD stone) on MRCP (MRCP+) or absence (MRCP−). For the same 2 year period, a retrospective search was completed for diagnosis of 'retained bile stone' on the local audit software for any of the patients included in this analysis. Similarly, readmissions within 30 days of acute cholecystectomy were also individually reviewed for retained bile stone diagnosis.

Statistical analysis

Age, wait time, first bilirubin and second bilirubin were summarized with mean and standard deviations (SD); all other variables were categorical and were summarized with frequency and percent, both overall and by whether choledocholithiasis was identified or not. *T*-tests were used to compare the bilirubin levels (first and second separately) between those with and without stones and a paired *t*-test was used to compare the change in first and second bilirubin for those people with two measures. The proportion MRCP+ was compared using a difference in proportions test for those with and without dilated ducts. For all tests the difference in mean or proportion was estimated along with the 95% confidence interval.

Receiver operating characteristic curves which plot sensitivity versus 1 minus specificity for varying thresholds were estimated for the second bilirubin measure versus the outcome of MRCP+. The area under the curve was also estimated and reported along with its 95% confidence interval. This was then estimated separately for the presence/absence of dilated ducts, by indication and by ASGE risk grouping. A test for the equality of the ROC areas was then used to test for differences between each of these subgroups. All analyses were conducted in Stata version 16.1.[12]

Results

The search identified 223 patients for inclusion. After applying the exclusion criteria there were 106 patients included in the study. Table 1 shows the characteristics of the included patients Overall, 39 (37%) were MRCP positive (MRCP+) with choledocholithiasis (CBD stone) identified. Half (50%) of the patients had dilated ducts. Of those with dilated ducts 21 (40%) were MRCP+ compared with 18, (34%) of those with non-dilated ducts (difference in proportion = −5.7%, 95%CI −24.0% to 12.7% $P = 0.546$).

For those patients where there were both mean bilirubin measures recorded there was a mean difference of 14.0 μmol/L with 95% CI (6.2–21.9 μmol/L) $P = 0.0008$ indicating that bilirubin will tend to be lower by the time of the MRCP. was a mean 8.5 μmol/L higher in the MRCP+ group compared to the MRCP− group with a 95% CI (−3.2 to 20.3) $P = 0.15$. Overall, 38 (97%) of those who were MRCP+ had abnormal LFT.

Risk stratification using international ASGE guidelines identified those at high, intermediate and low risk for choledocholithiasis. At the time of second bilirubin 36 (34%), 66 (62%) and 4 (4%) were in the high, intermediate, and low risk groups, respectively. Forty-five patients also had a first bilirubin measure collected with 23 (22%) classified as high, 22 (21%) as intermediate and 1 (1%) as low. For those who had both measures, 37 (80%) had the same classification at both time points. Of those classified as high risk at the first time point 52% were MRCP+, for intermediate 32% were MRCP+ and none of the low risk group were MRCP+. At the second time point 44% of the high risk group were MRCP+, 35% of the intermediate and 0% of the low.

Looking at diagnoses the most common diagnosis was, 30 (28%) acute pancreatitis (AP) followed by 28 (26%) Biliary colic (BC), 25 (24%) acute cholecystitis (AC) and 19 (18%) had cholangitis (CG). Of those with Cholangitis 37% were MRCP+, AC 24%, AP 23% and BC 68%. The proportion MRCP+ differed by diagnosis ($P < 0.001$).

Mean second bilirubin levels of those MRCP+ and MRCP- for each diagnosis showed CG 41 versus 51 μmol/L, respectively (difference in mean = −10, 95%CI −42 to 23, $P = 0.53$), AC 23 versus 22 (difference in mean = 1, 95%CI −20 to 22, $P = 0.93$), AP 20 versus 10 (difference in mean = 10, 95%CI 4–16, $P = 0.002$) and BC 39 versus 18 (difference in mean = 21, 95%CI −4 to 47, $P = 0.09$).

The sensitivity versus 1-specificity (ROC curve) of second bilirubin (at varying thresholds for test positivity) for MRCP± status is shown in Figure 1(a). The AUC was 0.70 (95%CI 0.61–0.80, $P = 0.0504$). This identified a second bilirubin threshold of ≤8 μmol/L yielding a sensitivity, specificity, PPV and NPV of 100%, 22%, 43% and 100%, respectively. Similarly, potentially clinically significant thresholds of ≤12 and ≤17 μmol/L yielded sensitivity, specificity, PPV and NPV of 92%, 43%, 49% and 91%, and 79%, 66%, 57% and 85%, respectively.

The ROC curves for second bilirubin versus MRCP+ were fit separately for specific sub-groups. There was no difference when comparing presence or absence of dilated CBD. AUC was 0.72 versus 0.69, respectively, (95%CI 0.59 to 0.86 versus 0.54 to 0.83, $P = 0.71$). This is shown in Figure 1(b).

Table 1 Patient characteristics overall and by whether they had a CBD stone

	CBD Stone				Total	
	Yes		No			
Characteristics	Number	Mean (SD)	Number	Mean (SD)	Number	Mean (SD)
Age (years)	39	63.1 (18.2)	67	60.9 (19.2)	106	61.7 (18.8)
Wait time (days)	39	1.6 (1.4)	67	2.1 (1.7)	106	1.9 (1.6)
first bilirubin (μmol/L)	19	45.8 (24.8)	26	47.7 (41.7)	45	46.9 (35.2)
second bilirubin (μmol/L)	39	33.7 (27.4)	67	25.2 (30.5)	106	28.3 (29.5)
Dilated duct	Number	Row percent	Number	Row percent	Number	Column percent
N	18	34	35	66	53	50
Y	21	40	32	60	53	50
ASGE Risk at first bilirubin $n = 46$ *collected in 1 year only						
High	12	52	11	48	23	50
Intermediate	7	32	15	68	22	48
Low	0	0	1	100	1	2
ASGE Risk at second bilirubin $n = 106$						
High	16	44	20	56	36	34
Intermediate	23	35	43	65	66	62
Low	0	0	4	100	4	4
Indication						
Acute cholecystitis	6	24	19	76	25	24
Acute pancreatitis	7	23	23	77	30	28
Cholangitis	7	37	12	63	19	18
Biliary Colic	19	68	9	32	28	26
Hepatitis	0	0	1	100	1	1
RUQ Pain	0	0	3	100	3	3
Abnormal LFT						
N	1	10	9	90	10	9
Y	38	40	58	60	96	91
ERCP						
N	9	90	1	10	10	28
Y	25	96	1	4	26	72
Total	39	37	67	63	106	100

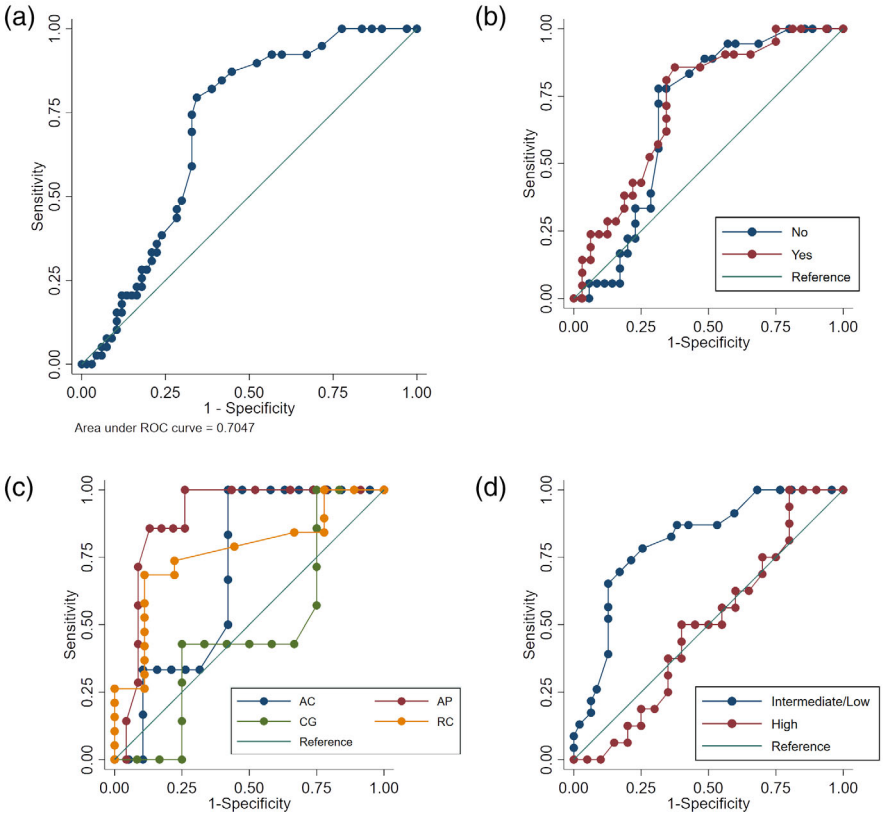

Fig. 1. (a) ROC curve showing sensitivity as a function of specificity for second bilirubin at varying thresholds for test positivity where the gold standard is MRCP± status. (b) ROC curve showing sensitivity as a function of specificity for second bilirubin at varying thresholds for test positivity where the gold standard is MRCP± status separately by presence of CBD dilation. (c) ROC curve showing sensitivity as a function of specificity for second bilirubin at varying thresholds for test positivity where the gold standard is MRCP± status separately by indication where AC is acute cholecystitis, AP is acute pancreatitis, CG is cholangitis and BC is biliary colic. (d) ROC curve showing sensitivity as a function of specificity for second bilirubin at varying thresholds for test positivity where the gold standard is MRCP± status separately by ASGE risk grouping.

There was a difference between the ROC curves by indication ($P = 0.035$). Figure 1(c) shows the ROC curve demonstrating the second bilirubin's discriminative ability for CBD stone by each diagnosis. AUC for AC, AP, CG and BC is 0.69 (95%CI 0.48–0.91), 0.89 (95%CI 0.78–1.00), 0.47 (95%CI 0.18–0.76) and 0.77 (95%CI 0.58–0.96), respectively, $P = 0.035$.

The ROC curves were different by ASGE intermediate/low versus high risk ($P = 0.005$). Second bilirubin for those who are ASGE Intermediate/low risk group can accurately predict CBD stone, AUC 0.81 (95%CI 0.70–0.92). However, in the high-risk group bilirubin was not able to discriminate at all, AUC 0.49 (95% CI 0.30–0.69) (Fig. 1(d)). The intermediate/low risk group with bilirubin thresholds of ≤12 and ≤17 yields sensitivity, specificity, PPV and NPV of 87%, 62%, 53% and 91% and 65%, 87%, 71% and 84%, respectively, this represented 30% of our sample. Utilizing these thresholds, the number avoiding MRI is 33 (31%) and 50 (47%), respectively, in this sample over 2 years (16 and 25 MRCP/year).

Of 614 cholecystectomy operations, four patients returned with retained CBD stone (0.65%) in this period. This was confirmed on ERCP at the time of re-admission. At the index admission; all were in the intermediate-risk group, two had AC and underwent laparoscopic cholecystectomy (LC) and intraoperative cholangiogram with no stone identified, and two had LC for biliary colic with no additional radiological imaging.

Discussion

This study investigated the use of MRCP in a resource limited environment to identify acute presentations with CBD stones. Recent studies have suggested sonographic features and bilirubin thresholds to access further biliary imaging.[10,11] In this study, there is a significant reduction in serum bilirubin values between presentation and the time of MRCP. The higher first value is what would be used in the clinical decision to request further imaging, however this shows that given time the value will naturally reduce after the acute phase. This study showed 80% remained in their risk group by the second bilirubin time point and MRCP+ rates within groups was similar. Comparable trends have been reported.[13] Although MRCP+ had higher bilirubin, this was not a significant difference, in comparison to Chen *et al*. who reported bilirubin 68 versus 33 μmol/L in MRCP+ versus MRCP−, respectively.

The ASGE risk stratification had similar accuracy when compared to other studies. Adams *et al*. showed high versus intermediate/low risk classification of 36% versus 65%, respectively. Compared to this study, high, intermediate, low risk of 34%, 62% and 4%, respectively. The MRCP+ result by risk stratification was therefore similar with 44%, 35% and 0% compared to 55% and 35% reported by Adams *et al*. The ASGE guidelines would suggest that all high-risk patients proceed straight to ERCP.[6] It has been shown that this can lead to a high rate of normal ERCP procedures.[13,14] In a resource limited centre this is not an option with extensive pressure on ERCP and radiological services. For example, at the authors tertiary level care institution the acute ERCP waitlist is >7 days, there is limited trained personnel and access to equipment. Therefore, it would not be feasible for every high-risk patient as well as a significant proportion of intermediate-risk patients to undergo ERCP in similar resourced centres in New Zealand.

To restrict appropriate MRCP access, radiology departments have been known to place bilirubin thresholds. However, not all gallstone pathology can be treated the same with significantly differing pathophysiology especially concerning biliary pancreatitis.[13] These results suggest that the likelihood of CBD stone does differ by diagnosis and that a one size fits all bilirubin threshold may not be appropriate. MRCP+ acute pancreatitis appears to have twice the bilirubin level as MRCP- pancreatitis. While biliary colic also had a markedly raised bilirubin level in MRCP+ patients, although this was not significant. No difference in bilirubin was noted between MRCP+ versus MRCP- in the cholangitis and cholecystitis patients. This is a direct contrast to the findings of Chen *et al*. in their cohort of cholecystitis patients. The ROC analysis appears to support this with AP and BC having higher AUC. However, this contrasts with prior studies that have shown biliary pancreatitis as a negative independent predictor of CBD stones.[7,14]

The management of acute gallstones can require MRCP, endoscopic ultrasound (EUS), ERCP or cholecystectomy with cholangiogram.[15] In the authors institution the risk stratification alone is unlikely to dictate the management due to the availability of each resource. This can be variable worldwide. In the UK, the NHS instituted a management of straight to operative management for nearly all presentations.[16] This protocol driven approach prioritizing surgery first reduces unnecessary preoperative testing, length of stay and is cost efficient with no difference in complications.[5,17,18] Unfortunately for smaller centres and a growing rate of general surgeons who do not perform laparoscopic complete bile duct exploration,[16] this may not be appropriate. Equally, MRCP and ERCP systems have similar pressures with staffing, schedules, time and cost.

Implications for clinical practice

This study shows that risk stratification could be used in combination with bilirubin thresholds. This is not dissimilar to He *et al*. who showed improved CBD stone identification at ERCP with bilirubin >68 μmol/L in ASGE high risk group.[7] A second bilirubin level in low/intermediate group patients accurately predicted CBD stone with AUC 0.81. Clinically significant thresholds that were identified was 12mmo/L and 17mmo/L this achieves NPV of 91% and 84%, respectively. For this centre the thresholds would allow, 31% and 47%, respectively, of patients to potentially avoid MRI imaging and proceed to surgery. This would reduce the burden on MRCP services and potentially reduce length of stay for gallstone admissions. A standardized rate of retained gallstone after cholecystectomy is 0.5–2.3%.[19] Reviewing current practice in a resource limited environment, our rate was comparable at 0.65%. Therefore using MRCP request restrictions, this can triage those patients most unlikely to have CBD stones and proceed straight to the operating theatre without a higher rate of missed stones.

Limitations

The limitations of this study are inherent in its retrospective nature. First bilirubin levels were only collected for 1 year and were from

the day of admission, whereas second bilirubin levels were collected for 2 years of data analysis and were on the day of MRCP except for several cases where it was within 48 h of the MRCP. Defined time bilirubin levels were inconsistent given the retrospective design, instead levels correspond to a snapshot in time of the imaging modality. This creates uniformity within the sample. Diagnoses were recorded from discharge summaries that were from a consultant surgeon ward round and corroborated with radiologic evidence where available. However the former relies on subjective clinician judgement. There are no hepatobiliary specific radiologists at this centre, MRCP were single read, this could lead to variability in reporting. Management decisions for patients will have been influenced by individual skill and availability of surgical staff, radiology and ERCP services. Local protocol for our institution dictated preoperative investigation of choledocholithiasis (CDL) risk. Alternative policies exist in other centres and management can be variable depending on resource availability (e.g., post-operative or intra-operative ERCP). Therefore results may not be applicable to other centres. However, our hospital is similarly resourced to other New Zealand tertiary centres and will be affected by similar pressures on patient care.

Conclusion

MRCP requests can be triaged to maximize stones detected without overly increasing the rate of missed duct stones whilst protecting the limited MRI and ERCP resources. International thresholds and risk stratification guidelines alone may not be applicable in the current resource limited environment. However, if combined with bilirubin thresholds, patients may be able to avoid further investigations and proceed earlier to definitive surgery. A multicentre audit or surveillance of utilization of restricted access may be required to ensure rates of missed stones is not increasing if a restrictive protocol was used.

Author contributions

Christian Robinson: Conceptualization; data curation; investigation; methodology; project administration; resources; writing – original draft; writing – review and editing. **Robin Turner:** Formal analysis; software; supervision; writing – review and editing. **Jon Potter:** Conceptualization; methodology; supervision; writing – review and editing.

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Conflict of interest

None declared.

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Ethical approval

Not applicable. Institutional approval was given for the interrogation of the database for bile stone admissions between January 2018 and December 2019 at Dunedin Public Hospital for the purposes of audit.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Supporting Information