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Gallbladder Ejection Fraction is Unrelated to Gallbladder Pathology in Children and Adolescents

Patrick M. Jones, M.D.[1]

Marc B. Rosenman, M.D.[2,5]

Marian D. Pfefferkorn, M.D.[1]

Frederick J. Rescorla, M.D.[4]

William E. Bennett, Jr., M.D.[1,2,3]

1. Section of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics.

2. Section of Children's Health Services Research, Department of Pediatrics.

3. Section of Pediatric and Adolescent Comparative Effectiveness Research, Department of Pediatrics.

4. Section of Pediatric Surgery, Department of Surgery

5. Regenstrief Institute.

Indiana University School of Medicine, Indianapolis, IN.

Corresponding Author:

705 Riley Hospital Drive, ROC 4210

jonespam@iu.edu

Patrick M. Jones – study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript.
Marc B. Rosenman – acquisition of data, analysis and interpretation of data
Marian D. Pfefferkorn – critical revision of the manuscript for important intellectual content
Frederick J. Rescorla – critical revision of the manuscript for important intellectual content
William E. Bennett, Jr. – study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision

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ABSTRACT

Background and Aims: Biliary dyskinesia is a common diagnosis that frequently results in cholecystectomy. In adults, most clinicians use a cutoff value for the gallbladder ejection fraction (GBEF) of <35% to define the disease. This disorder is not well characterized in children. Our aim was to determine the relationship between GBEF and gallbladder pathology using a large state-wide medical record repository.

Methods: We obtained records from all patients 21 years old and younger who underwent HIDA testing within the Indiana Network for Patient Care (INPC) from 2004 to 2013. GBEF results were obtained from radiology reports using data mining techniques. Age, gender, race, and insurance status were obtained for each patient. Any gallbladder pathology obtained subsequent to a hepatic iminodiacetic acid (HIDA) scan were also obtained and parsed for mention of cholecystitis, cholelithiasis, or cholesterolosis. We performed mixed effects logistic regression analysis to determine the influence of age, gender, race, insurance status, pathologist, and GBEF on the presence of these histologic findings.

Results: 2,841 HIDA scans on 2,558 patients were found. Of these, 310 patients had a full text gallbladder pathology report paired with the HIDA scan. GBEF did not correlate with the presence of gallbladder pathology (cholecystitis, cholelithiasis, or cholesterolosis) when controlling for age, gender, race, insurance status, and pathologist using a mixed effects model.

Conclusions: Hypokinetic gallbladders are no more likely to have gallbladder pathology than normal or hyperkinetic gallbladders in the setting of a patient with both a HIDA scan and a cholecystectomy. Care should be used when interpreting the results of HIDA scans in children and adolescents.

Keywords: biliary dyskinesia, chronic cholecystitis, hyperkinetic gallbladder, hypercontractile gallbladder

What is known about this subject?

- Biliary dyskinesia is an increasingly common diagnosis in pediatrics and indication for cholecystectomy
- It is traditionally diagnosed with gallbladder ejection fraction less than 35%
- Pathologic review of hypocontractile (<35%) gallbladders in adults often reveals evidence of chronic cholecystitis

What are the new findings?

- There were more than expected cholecystectomies for GBEF values above 35%
- Gallbladder ejection fraction did not correlate with underlying microscopic gallbladder pathology
- This should cast some doubt on the importance of GBEF when managing these difficult patients

BACKGROUND

Biliary dyskinesia refers to a hypocontractile gallbladder causing biliary-type symptoms including right upper quadrant abdominal pain, nausea and vomiting, and fatty food intolerance. It is typically diagnosed with nuclear medicine cholescintigraphy, the hepatobiliary iminodiacetic acid (HIDA) scan. During a HIDA scan, technetium (99mTc) based radiopharmaceuticals are intravenously injected. They dissociate from albumin prior to hepatocyte uptake, and then follow the same secretion/excretion pathway as bilirubin, allowing assessment of hepatobiliary function. In the case of suspected biliary dyskinesia, a cholecystagogue like the cholecystokinin (CCK) analog sincalide, is given via slow intravenous infusion and gallbladder emptying of the tracer is measured at 60 minutes.[1] Values of gallbladder ejection fraction (GBEF) less than 35% have been accepted as abnormal and diagnostic of biliary dyskinesia ever since a study in 1991 used this value as their cutoff.[2] Treatment has generally been with laparoscopic cholecystectomy, with symptom resolution ranging from 44% to 96% in adult series.[3-7]

In an attempt to identify clinical and radiographic factors that would predict a successful outcome after surgery in children, our institution identified nausea, pain, and GBEF less than 15% as predictors of a positive response

to surgery.[3] Other researchers have found that children with symptom duration less than 12 months had better post-operative outcomes than those with longstanding symptoms of more than one year.[8] In patients who do not improve, uncovered organic etiologies or other functional disorders are possible.[9] The diagnosis is controversial, however, as some point to the strong placebo effect of a surgical intervention, as well as the finding that patients who were observed for a year or more had similar symptom improvement compared to those who had an operation.[10] Pathologic review of gallbladders from pediatric patients diagnosed with biliary dyskinesia have shown increased numbers of inflammatory cells, particularly mast cells,[11] and that these also have a high degree of activation.[12]

In contrast to hypocontractility of the gallbladder, we have also observed classic biliary-type symptoms in pediatric patients who instead have very high GBEF values (>80%) suggesting hyperkinetic or hypercontractile gallbladders. There are few studies in the literature regarding hyperkinetic gallbladders. One recent retrospective study described twelve pediatric patients who underwent cholecystectomy for GBEF values 80% or greater and found that all had cholecystitis on pathology and all had symptom resolution up to a mean follow-up period of sixteen months.[13] Prior to our current study, we performed a similar retrospective review and found a comparably high rate (88.9%) of cholecystitis in resected gallbladders of patients who had GBEF greater than 80% (unpublished work). In the present study, we have expanded our previous analysis to include a larger cohort of patients in a statewide health information exchange (HIE), the Indiana Network for Patient Care (INPC) and performed more sophisticated statistical analysis to determine the association of HIDA scan results and gallbladder pathology.

METHODS

Data Source

The INPC is a large HIE maintained by investigators at the Regenstrief Institute in Indianapolis, IN, USA. Hospitals in most large healthcare systems in Central Indiana contribute patient data to the INPC. These systems include a wide variety of hospital types, including pediatric institutions, large tertiary referral centers,

and smaller community hospitals. Institutional consent for data use record release was obtained from each hospital / healthcare system prior to data analysis. This study was approved by the Indiana University Institutional Review Board.

We first queried INPC for all patients aged 21 years and younger who received a HIDA scan during the ten-year period from January 2004 – December 2013. Demographic characteristics of these patients were obtained: age, gender, and race. We then obtained all pathology reports pertaining to these patients and the demographic data, HIDA scans, and gallbladder pathology reports were linked together by a unique subject identification number. All Protected Health Information (PHI) was stripped prior to obtaining the final data set from the INPC. The actual GBEF values were extracted from HIDA radiology reports using the following data mining strategy: First, all HIDA reports without report text indicating an ejection fraction were eliminated (1876 of 4208). Next, all text strings terminating in "%" were isolated, and leading numeric characters isolated from that. Reports containing multiple "%", or "35%" were inspected by hand (WEB and PMJ) to determine which text string was referring to the patient results. With the exception of HIDA scans without report texts or specific ejection fraction listed, our data set did not contain missing values, so imputation was unnecessary.

Statistical Analysis

Pathology reports from tissues other than gallbladder were eliminated, and the remaining reports were assessed directly by one author (PJ) and the following data were extracted: attending pathologist, presence of cholecystitis, presence of cholelithiasis, and presence of cholesterolosis. In patients who underwent multiple HIDA scans, each GBEF value was linked to the same resected gallbladder specimen and treated individually during data analysis. Logistic regression was then performed to determine relationships between the independent variables of age, gender, race, pathologist, and GBEF on the dependent variables of cholecystitis, cholelithiasis, and cholesterolosis. A mixed effects model was used for data analysis. Age was divided into 5 year increments between zero and twenty one and treated as a categorical variable. Gallbladder ejection fraction was divided into categories based on published data on hypocontractile gallbladders in children

(<15%), hypocontractile gallbladders in adults (<35%), a rough estimate of normal EF (35-80%), and our previous experience with hypercontractile gallbladders (>80%). Categorized age, gender, race, and categorized GBEF were treated as fixed variables and pathologist was treated as a random effect. We computed adjusted odds ratios for each independent variable and p-values and confidence intervals (CIs) for each. Significance was determined at a p-value < 0.05. We used the R software package (http://www.r-project.org) and the *lme4* library (http://cran.r-project.org/package=lme4/) to build a generalized linear model.

RESULTS

Our initial query of the database returned 2,558 patients who had a total of 2,841 HIDA scans performed during the ten-year period. Those without accompanying gallbladder pathology reports were excluded and a total of 332 patients with 385 HIDA scans remained. As seen in Figure 1, additional patients were excluded at this point for several other reasons (e.g., liver transplant patient, cholestatic infant, etc). The final data analysis was then conducted on the remaining 310 patients with 363 HIDA scans. Patient characteristics are presented in Table 1. The majority of HIDA scans were performed on teenage Caucasian females (64.5%). Upon histologic examination, microscopic cholecystitis was observed in the majority (71.6%) and cholesterolosis and cholelithiasis were present in a minority (14% and 8%, respectively) of patients.

To determine the distribution of GBEF values, histograms were generated showing all HIDA scans (Figure 2A) and only those HIDA scans accompanied by a gallbladder pathology report, and therefore a cholecystectomy (Figure 2B). In both, GBEF values are plotted along the x-axis and total number of HIDA scans with that result are plotted along the y-axis. Figure 2A displays GBEF values evenly distributed across all results, but with a relative peak in the 65-90% range, whereas Figure 2B displays a clear peak among lower GBEFs, consistent with widespread usage of the <35% cutoff to proceed with cholecystectomy.

The results of our mixed effects model are shown in Tables 2, 3, and 4. Children 5 years and younger were more likely to have cholelithiasis when compared to individuals 16-21 years of age (OR 1.45, 95% CI 1.14-1.84). For all of the dependent variables (cholecystitis, cholelithiasis, and cholesterolosis), however, GBEF value was not related to the presence or absence of any specific pathologic finding.

DISCUSSION

In the setting of classic biliary symptoms, normal laboratory studies and negative ultrasonographic evaluation of the hepatobiliary system, gallbladder scintigraphy is a frequently ordered test to assess gallbladder function. A gallbladder ejection fraction (GBEF) of less than 35% has traditionally been accepted as diagnostic of biliary dyskinesia or ineffective gallbladder contraction related to microscopic chronic cholecystitis. However, in this large retrospective review of patients who underwent HIDA testing followed by cholecystectomy, we found that GBEF was unrelated to, and therefore not predictive of, underlying gallbladder pathology, including chronic cholecystitis, cholelithiasis, or cholesterolosis. The histograms presented in Figures 2A and 2B are informative as well. In Figure 2A, one can see the natural distribution of GBEF values obtained when a HIDA scan is performed for biliary symptoms. In Figure 2B, the relative peak of values seen with lower GBEF values is an expected finding given that a GBEF <35% is a common indication for cholecystectomy, so those patients would be more likely to have a pathology report. However, it is more surprising that there were approximately 10-20 cholecystectomies performed for each 5-point GBEF range between 35 and 100 (e.g., 35-40, 40-45, 45-50, etc). Further, upon close examination of Figure 2B, one can see another smaller peak in the GBEF ranges of 80-95%, suggesting hyperkinetic gallbladder is possibly coming to be a more common indication for surgery.

One of the distinct advantages of our study is its large sample size achievable by querying a large health information database like the INPC. However, our analysis has several important limitations. First, our data are retrospective, and do not have patient-level clinical outcomes, such as the persistence of abdominal pain. Second, because we pulled information from patients statewide, in some instances occurring more than ten years ago, we had no ability to follow up with subjects to see if their pain resolved following cholecystectomy.

A third limitation is that, in patients who underwent more than one HIDA scan, we had no choice but to link each of these GBEF values to the same resected gallbladder specimen, yet treat them as individual entries during data analysis. Finally, because we only obtained data from a subset of hospitals in Central Indiana, the findings may not be generalizable to all patients. However, since our sample represents a wide variety of hospital types, we believe this form of bias to be minimal. Despite these limitations, our results should, at the very least, cast doubt on the importance placed on GBEF value when deciding whether to proceed with cholecystectomy, as we found that hypokinetic gallbladders were no more likely to have histopathology than normal or even hyperkinetic gallbladders. Future efforts should focus on performing randomized, prospective studies evaluating both operative and non-operative treatment strategies on outcomes such as persistent symptoms at various time points to further determine the importance of GBEF value in managing patients with biliary symptoms.

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Figure 1 – Flowchart of cohort creation from INPC administrative data, HIDA scan reports, and pathology reports

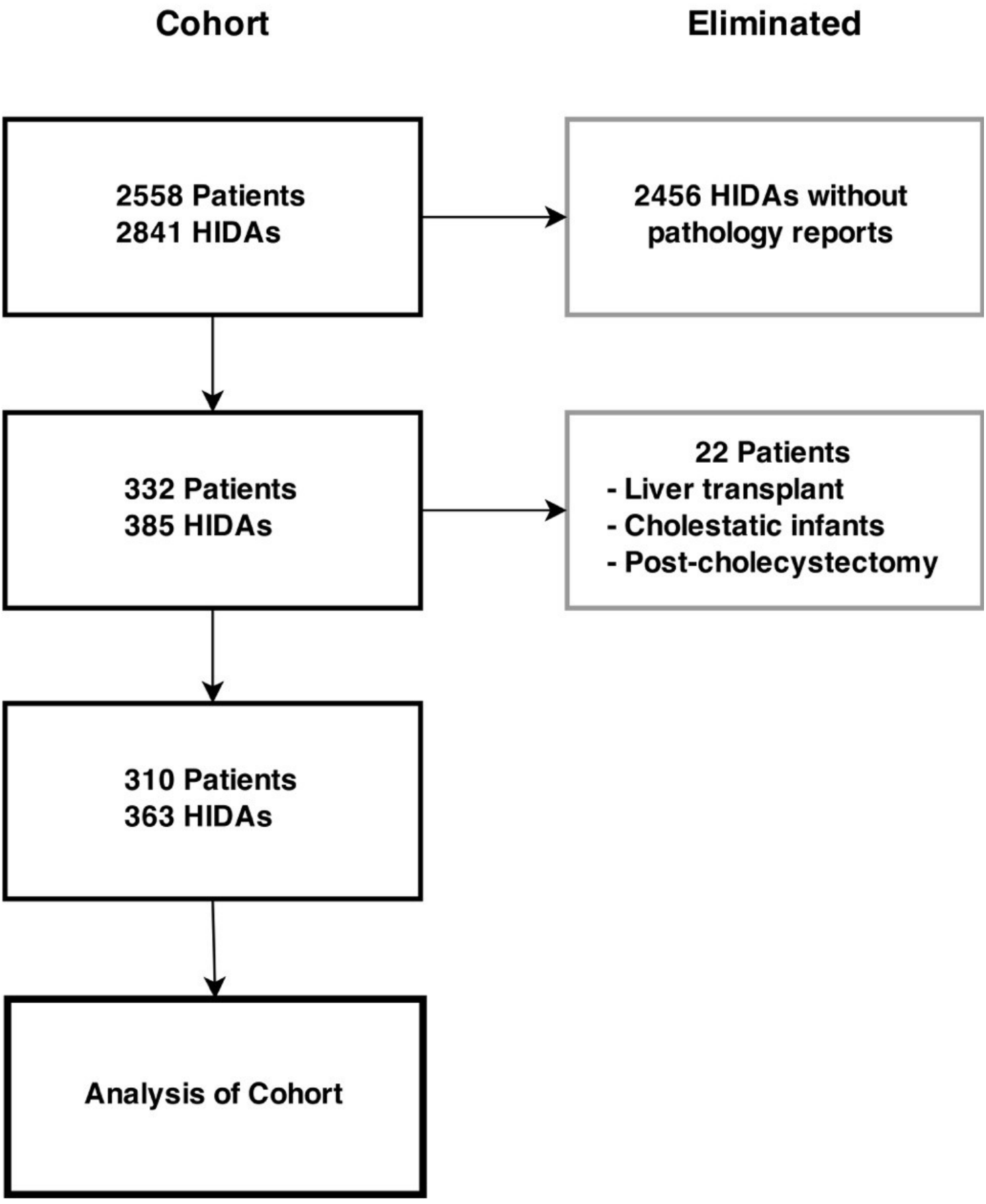

Figure 2 – (A) Histogram of GBEF for all HIDA scans performed (2841 scans, 2558 patients). **(B)** Histogram of GBEF for all HIDA scans with a paired gallbladder pathology report (363 scans, 310 patients).

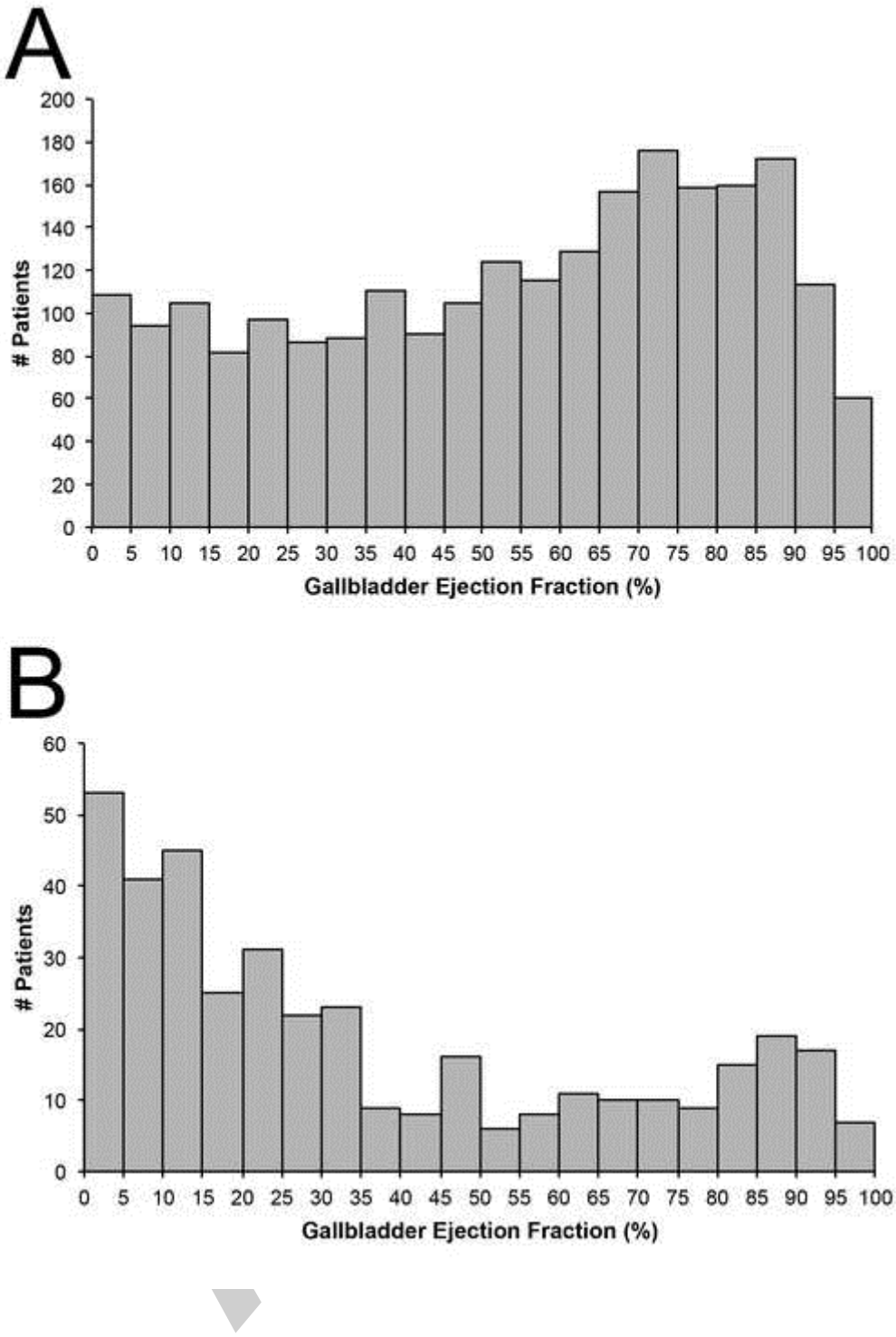

Table 1 – Demographic and clinical information for final cohort.

N	363	
Age		
0-5	5	1.4%
6-10	20	5.5%
11-15	115	31.7%
16-21	223	61.4%
Gender		
Female	284	78.2%
Male	79	21.8%
Race / Ethnicity		
White	325	89.5%
Black	22	6.1%
Hispanic	5	1.4%
Other	10	3.0%
HIDA Ejection Fraction		
0-15% (Very low)	133	36.6%
16-34% (Low)	97	26.7%
35-80% (Normal)	77	21.2%
80-100% (Hyperkinetic)	56	15.4%
Cholecystitis		
Absent	103	28.4%
Present	260	71.6%
Cholelithiasis		
Absent	334	92.0%
Present	29	8.0%
Cholesterolosis		
Absent	313	86.2%
Present	50	13.8%

Table 2 – Adjusted odd-ratios (OR) for cholecystitis (dependent variable) in relation to stratified age, gender, race/ethnicity, and stratified HIDA scan ejection fraction (all independent variables) using a mixed effects logistic regression model. Pathologist was modeled as a random variable and thus does not have an OR.

	OR	95% CI Lower	95% CI Upper	p-value
Age				
16-21	-	-	-	-
11-15	0.99	0.92	1.05	0.69
6-10	1.07	0.94	1.22	0.30
0-5	1.21	0.96	1.53	0.11
Gender				
Female	-	-	-	-
Male	0.93	0.87	1.00	0.04
Race / Ethnicity				
White	-	-	-	-
Black	0.92	0.82	1.03	0.16
Hispanic	0.97	0.77	1.21	0.77
Other	1.01	0.79	1.31	0.92
HIDA Ejection Fraction				
0-15% (Very Low)				
16-34% (Low)	0.98	0.92	1.05	0.62
35-80% (Normal)	1.05	0.97	1.14	0.23
80-100% (Hyperkinetic)	1.05	0.96	1.15	0.27

Table 3 – Adjusted odd-ratios for cholelithiasis (dependent variable) in relation to stratified age, gender, race/ethnicity, and stratified HIDA scan ejection fraction (all independent variables) using a mixed effects logistic regression model. Pathologist was modeled as a random variable and thus does not have an OR.

	OR	95% CI Lower	95% CI Upper	p-value
Age				
16-21	-	-	-	-
11-15	1.02	0.96	1.08	0.59
6-10	1.10	0.97	1.24	0.14
0-5	1.45	1.14	1.84	<0.01
Gender				
Female	-	-	-	-
Male	0.96	0.89	1.02	0.20
Race / Ethnicity				
White	-	-	-	-
Black	1.00	0.89	1.12	0.99
Hispanic	1.09	0.86	1.38	0.48
Other	0.93	0.71	1.21	0.59
HIDA Ejection Fraction				
0-15% (Very Low)	-	-	-	-
16-34% (Low)	0.98	0.91	1.05	0.50
35-80% (Normal)	1.05	0.97	1.13	0.26
80-100% (Hyperkinetic)	1.06	0.97	1.15	0.19

Table 4 – Adjusted odd-ratios for cholesterolosis (dependent variable) in relation to stratified age, gender, race/ethnicity, and stratified HIDA scan ejection fraction (all independent variables) using a mixed effects logistic regression model. Pathologist was modeled as a random variable and thus does not have an OR.

	OR	95% CI Lower	95% CI Upper	p-value
Age				
16-21	-	-	-	-
11-15	0.95	0.87	1.03	0.24
6-10	0.93	0.79	1.10	0.40
0-5	0.94	0.69	1.27	0.69
Gender				
Female	-	-	-	-
Male	0.92	0.84	1.00	0.05
Race / Ethnicity				
White	-	-	-	-
Black	0.87	0.75	1.02	0.08
Hispanic	1.08	0.79	1.46	0.63
Other	1.09	0.78	1.52	0.62
HIDA Ejection Fraction				
0-15% (Very Low)	-	-	-	-
16-34% (Low)	0.95	0.86	1.04	0.24
35-80% (Normal)	0.98	0.89	1.09	0.74
80-100% (Hyperkinetic)	0.99	0.89	1.11	0.90