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ORIGINAL CONTRIBUTIONS

Influence of Insulin Resistance Status on the Development of Gallstones Following Roux-En-Y Gastric Bypass: a Prospective Cohort Study

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Abstract
Background The occurrence of gallstones following Roux-en-Y gastric bypass (RYGB) has been extensively reported. As RYGB promotes improvement in insulin resistance (IR), which is one of the factors enrolled in the pathophysiology of gallstones, this study aims to determine the influence of IR and its post-RYGB course on the development of gallstones.
Methods This is a prospective cohort study that enrolled 108 morbidly obese subjects free of gallstones which underwent RYGB and were followed up for 24 months, through clinical, laboratory, and ultrasound examinations. IR was assessed through the surrogate marker homeostasis model assessment (HOMA).
Results Of the individuals evaluated, 29 (26.8 %) developed gallstones following RYGB. In the univariate analysis, postsurgical gallstones were associated with preoperative HOMA ($p<0.0001$), preoperative fasting glucose ($p=0.0019$), preoperative fasting insulin ($p=0.0001$), and preoperative triglycerides ($p=0.0001$). Multivariate analysis revealed that preoperative HOMA was the only factor independently associated with gallstones ($p<0.0001$). The incidence of gallstones among individuals with IR was 46.8 %; in the non-IR subjects, the incidence was 7.4 % ($p<0.0001$). Preoperative IR led to a relative risk of 6.02 (95 % CI=2.1–17.3; $p=0.0009$) of gallstones.
Conclusions As gallstones often occur following RYGB, there is controversy regarding their management. Some authors propose systematic cholecystectomy along with RYGB, while others suggest that the aggregate risk of the concomitant approach is significantly higher. As IR was a significant risk factor in this study, an individualized approach for this population may be proposed. Further research is needed to confirm these findings.

Keywords Gallbladder diseases · Gallstones · Gastric bypass · Insulin resistance · Obesity · Bariatric surgery

Introduction

Bariatric surgery has become the standard treatment for morbid obesity, and Roux-en-Y gastric bypass (RYGB) is the most commonly performed technique worldwide nowadays [1]. The occurrence of following RYGB has been previously reported, and its postoperative incidence exceeds that expected for subjects which do not undergo surgery, varying from 6.7 to 52.8 % [2–9]. Symptomatic gallstones were observed in 7–16 % of these individuals [7]. Gallstones usually tend to appear in the first 6–12 months following surgery and rarely after 2 years [10].

The pathogenesis of gallstones is a not completely understood phenomenon. In the general population, several risk factors have been identified, and they include advanced age, female gender, multiparity, obesity, hereditary features, hypocaloric diets, short gut syndrome, type 2 diabetes mellitus (T2DM), drug usage, and gastrointestinal surgeries [11]. Insulin resistance (IR) has been reported to be related to gallstones through several mechanisms. They relate to impairment in

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gallbladder motility, especially in ejection function, and bile composition, as it increases the cholesterol content of the bile due to a direct increase in gene expression of bile carriers of cholesterol, as well as decreasing the expression of enzymes that synthesize bile acids [12–16].

The exact pathways that lead to increased incidence of gallstones following RYGB are not completely known. Various factors have been implied as potentially enrolled in this process. The postoperative changes include cholesterol hypersaturation in the bile due to the rapid weight loss, decreased secretion of bile acids caused by restriction of food intake, raise in the mucin production (which increases bile crystallization), and hypomotility of the gallbladder due to a decrease of cholecystokinin secretion [16–18].

The impact of RYGB on IR has been widely reported, and it is observed even before significant weight loss. RYGB often leads to a great increase in insulin sensitivity and pancreatic function, commonly leading to resolution of its associated clinical features, especially metabolic syndrome (MetS) and T2DM [19–25]. The pathophysiologic pathways which cause this early improvement are not completely known, but they may enroll factors as increases in incretin and adipokine activity and decrease of chronic inflammation. Weight loss itself appears to be important too, probably maintaining the early benefits achieved in a long time setting [26, 27]. Complete resolution of the IR-related metabolic disturbances is common among subjects who undergo surgery, but some patients may develop postoperative persistent or refractory IR, a phenomenon which is even less understood [28, 29].

Gallstones following RYGB appear to be intrinsically linked to structural, functional, and weight loss effects brought by the procedure. On the other hand, IR commonly plays a role in the onset of gallstones. As RYGB provides a significant, although variable, effect on IR, the aim of this study is to evaluate the influence of IR status and its postsurgical course in the onset of gallstones and gain insight on the mechanisms that underlie its occurrence.

Materials and Methods

This is a prospective observational cohort study, which enrolled obese subjects aged 18–65 years old who underwent RYGB at Hospital de Clinicas - UNICAMP between January 2011 and December 2012. The study was submitted and approved by the local Research Ethics Committee. Surgery was indicated based on the National Institutes of Health Consensus Statement criteria. [30]. Sample size estimation was performed through single proportion formula with 95 % confidence interval. Precision was set at 10 % and the calculated sample size was 60. Exclusion criteria for this study were as follows: individuals who did not follow-up for 24 months; vulnerable groups (mentally ill, institutionalized, or aged below 18 years old); previous or actual diagnosis of bile stones; any previous surgical, endoscopic, or percutaneous procedures on the gallbladder or biliary tract; and previous use of ursodeoxycholic acid.

All subjects who undergo bariatric surgery at this institution take part in a preoperative weight loss program which lasts 4 to 12 weeks and is comprehended by weekly consultations carried out by a multidisciplinary team. Individuals undergo surgery once a minimal 10 % preoperative weight loss is achieved or since the minimal body mass index (BMI) of 35 kg/m^2 for subjects with obesity-related morbidities or 40 kg/m^2 for those free of comorbidities is reached.

All procedures were performed by the same surgical team and with the same technique. The main features of the RYGB were a 30-mL gastric pouch, a 100-cm biliopancreatic limb, a 150-cm alimentary limb, and a common limb consisting of the remainder of the small intestine.

Of 237 subjects who underwent RYGB, 108 which agreed and matched the criteria to take part in the study and achieved the 24-month follow-up were included. Main characteristics regarding demographics, anthropometric characteristics, clinical features, and laboratory studies were assessed. Percentage of excess weight loss was assessed at the following periods: 3, 6, 12, and 24 months after surgery to evaluate the significance of rapid weight loss. Comparisons were made between the periods immediately before and 24 months following surgery, in order to measure the impact of the procedure on the development of gallstones. Laboratory studies evaluated included fasting glucose (FG), fasting insulin (FI), hemoglobin A1c (HbA1c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and total cholesterol (TC). IR was evaluated by means of the homeostasis model assessment (HOMA), which was calculated through the formula of Matthews [31]. Individuals were considered insulin resistant when achieved a preoperative HOMA is higher than 2.7, as previously determined for this population by the Brazilian Metabolic Syndrome Study Group (BRAMS) [32], and/or had a previously reported diagnosis of T2DM according to the International Diabetes Federation (IDF) [33]. The presence of gallstones was assessed through ultrasound examinations. They were made the day before and 24 months after surgery in asymptomatic subjects. When a subject developed suggestive symptoms following surgery before the 24th month, an ultrasound was performed earlier; if the result was negative, the ultrasound would be performed again at 24 months. All the ultrasound examinations were performed by the same radiologist.

Statistical Analysis

The baseline characteristics of patients are described and then compared with postoperative period. Data were examined for normality according to the Pearson's chi-squared test. The univariate analysis of categorical variables was carried out

through chi-square and Fisher's exact tests. For comparisons of continuous measures, Mann–Whitney test was used. To identify possible factors associated with the studied outcomes, the stepwise Cox regression analysis was used. Relative risks were calculated by dividing the incidence rate of the studied outcome in the exposed group by the non-exposed. The significance level adopted was 5 % (p value<0.05). For the execution of analysis, Statistic Analysis System (SAS) software for Windows version 9.2 was used.

Results

Of 108 patients selected for the study, 84 (77.8 %) were female and 24 (22.9 %) were male. The mean age at surgery was 39 (range, 18–64) years. Main subject characteristics at baseline are summarized in Table 1.

Mean hospital stay was 4.1±0.2 days. Overall surgical morbidity was 9.2 % and the commonest complication was wound infection (7.4 %). There was no mortality. Patients experienced a significant mean BMI decrease from 37.1±2.9 to 26.5±3.4 kg/m^2 (p<0.0001). The mean weight loss was 28.1±8.6 kg. The mean percentage of excess weight loss 24 months following surgery was 90±25.3 %.

Anthropometric, clinical, and laboratory features before and after surgery are described in Table 2.

Gallstones were present in 29 (26.8 %) individuals in the first 24 months following surgery. The presentation was the following: acute cholecystitis was present in 3 (10.3 %), suggestive symptoms with no acute inflammation in 4 (13.8 %), and the remaining 22 (75.9 %) were asymptomatic and diagnosed at the 24th month ultrasound scan. No case of main duct stones or pancreatitis was observed. Mean time of diagnosis was 20.2±6.8 (range, 4–24) months. In the univariate analysis, the occurrence of gallstones was statistically associated with preoperative HOMA (p<0.0001), preoperative FG (p=0.0019), preoperative FI (p=0.0001), and preoperative TG (p=0.0001). Age, gender, pre- and postoperative BMI, percentage of excess weight loss at any postoperative period, postoperative FG, postoperative FI, pre- and postoperative HbA1c, pre- and postoperative TC, postoperative TG, and postoperative HOMA did not differ significantly between individuals which developed gallstones and the ones which did not (Table 3). Multivariate analysis was carried out enrolling the significant variables, and preoperative HOMA was the only factor independently associated with gallstones (p<0.0001).

Mean preoperative HOMA was 2.3±1.3; postoperatively, it decreased to 0.9±0.6 (p<0.0001). There were 55 (50.9 %) individuals classified as insulin resistant as evaluated by HOMA before surgery; postoperatively, there were still eight (7.4 %) with persistent IR (p<0.0001). Thus, the postoperative resolution rate of IR was 85.4 %. Gender, preoperative BMI, preoperative weight, percentage of excess weight loss, postoperative weight loss, and postoperative weight did not differ significantly between IR and non-IR group. The mean age of IR group was significantly higher than the observed in the non-IR group (42.6±11.4 vs. 35.3±8.4; p=0.00132). These findings are detailed in Table 4.

Among subjects with preoperative IR, the observed incidence of postsurgical gallstones was 45.4 %; in the non-IR group, the incidence was 7.4 % (p<0.0001). The relative risk of subjects with preoperative IR to develop postsurgical gallstones in the 24 months following surgery was 6.02 (95 % CI=2.1–17.3; p=0.0009). Presence of hypertension, T2DM, and dyslipidemia did not generate significant risk ratios. A forest plot presenting this data is shown in Fig. 1. In the IR group, the incidence of gallstones did not differ significantly between subjects which presented a resolution of IR (46.8 %) and those with persistent IR (37.5 %) (p=0.7153).

All 29 subjects which developed gallstones underwent laparoscopic cholecystectomy. There was not any case that required conversion to open surgery. Mean hospital stay was 1.1±0.4 (range, 1–3) days. The commonest complication was wound infection at the umbilical trocar site (6.9 %), and there were neither major morbidity nor mortality.

Table 1 Subjects' characteristics at baseline

Age (years)	39±10.8 (range, 18–64)
Gender	Female, 84 (77.8 %) Male, 24 (22.2 %)
BMI (kg/m^2)	37.1±2.9 (range, 35–50)
Weight (kg)	99±12 (range, 71.8–126)
Comorbidity profile	T2DM, 30 (27.8 %) Hypertension, 57 (52.8 %) Dyslipidemia, 28 (25.9 %) MetS, 49 (45.5 %)
Medication usage	Oral antidiabetics, 27 (25 %) Antilipidemic drugs, 6 (5.5 %) Antihypertensives, 51 (47.2 %) Insulin, 7 (6.5 %)

BMI body mass index

Discussion

Due to its efficacy, bariatric surgery is currently considered the standard treatment option for morbid obesity, since it brings great improvements in weight loss outcomes and obesity-related comorbidities. The last survey carried out by the International Federation for the Surgery of Obesity and Metabolic Diseases (IFSO) revealed that 468,609 bariatric procedures were performed worldwide in 2013, which means that about 0.01 % of the world's population underwent bariatric surgery.

Table 2 Anthropometric and laboratory features before and after RYGB

Feature	Presurgery	Postsurgery	Value of *p*
BMI (kg/m^2)	37.1±2.9 (range, 35–50)	26.5±3.4 (range, 20.7–38.5)	<0.0001
Weight (kg)	99±12 (range, 71.8–126)	70.8±10.5 (range, 43.6–97.2)	<0.0001
Fasting glucose (mg/dL)	92.5±17.3 (range, 65–160)	81.4±13.8 (range, 62–174)	<0.0001
Fasting insulin (uU/dL)	10±5 (range, 2–26.3)	4.6±2.7 (range, 2–12.6)	<0.0001
Hemoglobin A1C (%)	5.7±1 (range, 4.4–9.5)	5.2±0.6 (range, 3.5–7.9)	0.0003
HOMA-IR	2.3±1.3 (range, 0.4–6.5)	0.9±0.6 (range, 0.4–2.7)	<0.0001
Triglycerides (mg/dL)	111.4±46.9 (range, 38–461)	79.9±26.3 (range, 36–263)	<0.0001
HDL cholesterol (mg/dL)	42.8±10.4 (range, 26–102)	57.1±11.4 (range, 26–94)	<0.0001
Total cholesterol (mg/dL)	177.6±40.5 (range, 107–350)	149.3±33.2 (range, 95–292)	<0.0001

BMI body mass index, *HOMA-IR* homeostasis model assessment-insulin resistance, *HDL* high-density lipoprotein

Table 3 Univariate analysis of gallbladder disease among RYGB subjects

Feature	Gallbladder disease group	Non-gallbladder disease group	Value of *p*
Age (years)	40.6±9.2 (range, 27–64)	38.5±11.3 (range, 17–63)	0.28
Gender	Female, 82.8 % Male, 17.2 %	Female, 75.9 % Male, 24.1 %	0.45
Preoperative BMI (kg/m^2)	37.3±3.3 (range, 35–50)	37.1±2.8 (range, 35–49.6)	0.93
Postoperative BMI (kg/m^2)	26±3 (range, 21–32)	26.6±3.5 (range, 20.7–38.5)	0.50
Preoperative Weight (kg)	97.9±12.6 (range, 71.8–125)	99.4±11.8 (range, 73–124)	0.54
Postoperative Weight (kg)	69.4±10.7 (range, 43.6–97.2)	71.4±10.4 (range, 47.2–96.6)	0.39
Preoperative FG (mg/dL)	101.5±20.9 (range, 67–160)	89.2±14.5 (range, 65–140)	0.0019
Postoperative FG (mg/dL)	83±14.7 (range, 62–174)	77.1±9.7 (range, 60–115)	0.08
Preoperative FI (uU/dL)	14.1±4.6 (range, 7.2–26.3)	8.5±4.4 (range, 2–21.4)	<0.0001
Postoperative FI (uU/dL)	4.7±2.7 (range, 2–12.6)	4.4±2.6 (range, 2–10.7)	0.55
Preoperative HbA1c (%)	6±1.2 (range, 4.4–9)	5.6±0.9 (range, 4.4–9)	0.09
Postoperative HbA1c (%)	5.3±0.6 (range, 4.2–7.9)	5.1±0.6 (range, 3.5–7.2)	0.22
Preoperative HOMA-IR	3.5±1.2 (range, 2.2–6.5)	1.9±1 (range, 0.4–4.2)	<0.0001
Postoperative HOMA-IR	1±0.5 (range, 0.3–2.7)	0.8±0.5 (range, 0.3–2)	0.22
Preoperative TG (mg/dL)	142±69.3 (range, 38–461)	100.2±28.6 (range, 38–151)	0.0001
Postoperative TG (mg/dL)	79.4±28.5 (range, 37–263)	81.2±19.1 (range, 36–117)	0.25
Preoperative HDL-c (mg/dL)	39.4±7 (range, 26–52)	44±11.1 (range, 30–102)	0.11
Postoperative HDL-c (mg/dL)	56.8±10.9 (range, 26–94)	57.8±12.8 (range, 36–90)	0.90
Preoperative TC (mg/dL)	179.7±41.6 (range, 117–295)	176.8±40.3 (range, 107–350)	0.78
Postoperative TC (mg/dL)	151.3±36.2 (range, 95–292)	144±22.4 (range, 101–186)	0.54
% EWL, 3 months (%)	25.1±6.4 (range, 15–36.4)	25.5±6 (range, 10.3–38.4)	0.74
% EWL, 6 months (%)	51.5±10.1 (range, 36.1–66.8)	49.4±12.1 (range, 18.4–74.4)	0.50
% EWL, 12 months (%)	92.5±16.8 (range, 51.4–124.2)	89.9±20.7 (range, 41.3–130.4)	0.65
% EWL, 24 months (%)	93.2±25 (range, 32.1–135.7)	88.9±25.6 (range, 21.6–133.3)	0.43
Preoperative T2DM	17.2 %	24.1 %	0.15
Postoperative T2DM	10.3 %	6.3 %	0.70
Preoperative hypertension	58.6 %	50.6 %	0.46
Postoperative hypertension	13.9 %	6.3 %	0.75
Preoperative dyslipidemia	31 %	24.1 %	0.46
Postoperative dyslipidemia	5 %	3.4 %	1.00

RYGB Roux-en-Y gastric bypass, *BMI* body mass index, *FG* fasting glucose, *FI* fasting insulin, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model assessment-insulin resistance, *HDL-c* high-density lipoprotein cholesterol, *TC* total cholesterol, *% EWL* percentage of excess weight loss, *T2DM* type 2 diabetes mellitus

Table 4 Comparison between IR and non-IR groups

Feature	IR	Non-IR	Value of *p*
Age (years)	42.6±11.4	35.3±8.4	0.0013
Gender	Female, 78.2 % Male, 21.8 %	Female, 77.4 % Male, 22.6 %	1.00
Preoperative BMI (kg/m^2)	37±2.7 (range, 35–50)	37.3±3.1 (range, 35–49.6)	0.52
Postoperative BMI (kg/m^2)	26.6±3.5 (range, 20.7–36.6)	26.3±3.2 (range, 21.6–38.5)	0.57
Preoperative weight (kg)	98.5±13.1 (range, 71.8–125)	99.6±10.8 (range, 81–124)	0.68
Postoperative weight (kg)	70.9±11.3 (range, 43.6–97.2)	70.8±9.7 (range, 50–95)	0.92
Weight loss, 24 months (kg)	27.5±9.5 (range, 7.6–48.8)	28.8±7.5 (range, 14.7–49.3)	0.54
% EWL, 24 months (%)	87.7±27.7 (range, 21.6–135.7)	92.5±22.3 (range, 39.2–133.3)	0.47
Gallbladder disease incidence	45.4 %	7.5 %	<0.0001

IR insulin resistance, *BMI* body mass index, *% EWL* percentage of excess weight loss

Also, the overall number of surgeries has been increasing continuously over time [1].

The occurrence of gallstones following RYGB has been extensively reported [2–9]. Deitel and Petrov [34] firstly observed an incidence of about 10 % in the first 24 months following varied bariatric procedures. This finding was later confirmed and consolidated in a prospective study carried out by Shiffman et al. [35].

Among the factors potentially implicated in the postsurgical development of gallstones, rapid weight loss (especially in the first 3 months after surgery) is one the most studied, with mixed results. Li et al. [7], Coupaye et al. [36], and Tsirline et al. [37] revealed a significant relationship, while Iglézias-Brandão et al. [5] and Nagem et al. [2] did not find any significant predictors. In this study, neither early nor late excess weight losses were associated with gallstone development.

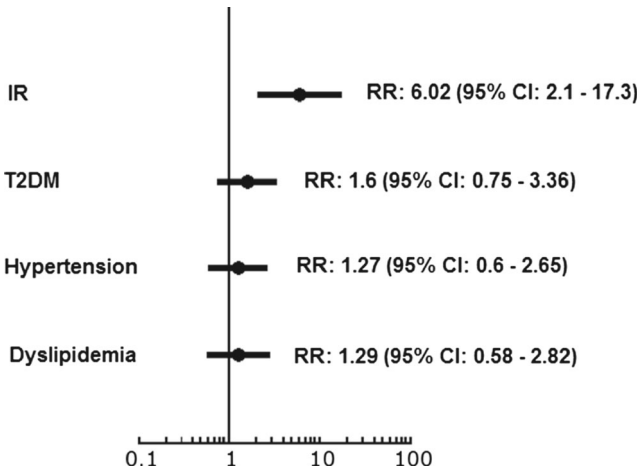

Fig. 1 Forest plot of possible preoperative risk factors for gallbladder disease in RYGB subjects. *IR* insulin resistance, *RR* relative risk, *CI* confidence interval, *T2DM* type 2 diabetes mellitus

Symptomatic gallstones are frequently observed among obese individuals, and it is a current indication for surgical treatment [38, 39]. Cholecystectomy can be performed along with bariatric procedures. However, its routine concomitant execution is still highly controversial. In a retrospective cohort, Weiss et al. [40] found a significantly higher risk of complications and mortality when it was performed later, suggesting that it should be systematically performed along with RYGB. Fobi et al. [4], Amstutz et al. [41], and Tarantino et al. [42] also defended the routine concomitant cholecystectomy. On the other hand, Warschkow et al. [9] reported that prophylactic concomitant cholecystectomy during RYGB should be avoided in patients without gallstones and exclusively be performed in patients with symptomatic biliary disease, since the rate of subsequent cholecystectomy was only 6.8 % based on 6,048 obese patients who underwent RYGB without concomitant cholecystectomy. Worni et al. [8] analyzing a nationwide data bank of 70,287 patients observed that the proportion of patients undergoing concomitant cholecystectomy decreased significantly from 26.3 % in 2001 to 3.7 % in 2008; it was observed that there are higher rates of postoperative complications, reoperations, mortality, as well as longer hospital stay when concomitant cholecystectomy was performed, such that they concluded that it should only be considered in patients who are symptomatic. Tucker et al. [6], Patel et al. [43], and Taylor et al. [44] observed quite similar results and also suggested that concomitant cholecystectomy should be reserved for individuals with symptomatic gallstones. Evaluating the cost-effectiveness of each strategy, Benarroch-Gampel et al. [45] recommended against routine cholecystectomy during RYGB in asymptomatic patients.

IR has been linked to gallstones in the general population through two main pathways: gallbladder dysmotility and changes in bile content [17, 18, 46]. These pathways evolve over a long time, so it is possible to propose that the early postsurgical changes in insulin metabolism brought by RYGB are not enough to immediately break off the pathophysiologic chain.

Post-RYGB gallstones are associated with significant risks. Kumaravel et al. [47] reported a 50-fold higher risk of acute pancreatitis (AP) in a bariatric surgery cohort compared to the general population (1.04 vs. 0.017 %). They also observed that gallstones and rapid weight loss were significantly associated with AP within this cohort. Furthermore, when migration of stones to main duct occurs in RYGB patients, endoscopic treatment may be problematic, leading to complex biliary surgical interventions [48, 49]. Hence, it is important to identify groups more likely to develop gallstones among RYGB patients, avoiding future risk.

There is controversy regarding the best approach to manage asymptomatic gallstones following RYGB. In this study, cholecystectomy was performed in all individuals which developed stones, based on the specific risks of AP and limitations for the endoscopic treatment of main duct stones within this population. Moreover, the possibility of noncompliance to follow-up of this group must be taken into account [2, 47–49]. Nonetheless, there is evidence that an expectant approach in asymptomatic subjects may be safe and effective if carefully conducted [43, 45, 48].

Since preoperative IR as assessed through HOMA was independently associated with gallstones and generated a significant risk ratio in this study, it is reasonable to hypothesize that the surgery may trigger gallstone development in this group of subjects exposed to greater risk due to their metabolic disturbance. Moreover, the postsurgical resolution of IR had no protective effect. Hence, it is possible to propose that this particular group of subjects may benefit from a specific strategy, be it routine postsurgical use of ursodeoxycholic acid, which has a demonstrated protective effect on gallstone formation after RYGB in a meta-analytical study [50], but would imply a significant economic impact once it is such an expensive drug in our social context, or systematic prophylactic cholecystectomy along with RYGB. It is necessary to emphasize that, once this study included only subjects which completed the 2-year follow-up, it is subjected to selection bias, since symptomatic individuals were more likely to be present during the whole follow-up, thus potentially increasing the proportion of affected patients. Further research, especially in prospective settings enrolling a larger number of individuals and using other accurate and direct methods of IR assessment, is needed to verify the findings of this study in order to possibly establish an algorithm for this group in the future.

Conflict of Interest The authors declare that they have no competing interests.

Statement of Informed Consent Informed consent was obtained from all individual participants included in the study.

Statement of Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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