



Improvement in Non-alcoholic Fatty Liver Disease Score Correlates with Weight Loss in Obese Patients Undergoing Laparoscopic Sleeve Gastrectomy: a Two-Centre Study from an Asian Cohort

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Abstract

Purpose Incidence of non-alcoholic fatty liver disease (NAFLD) is on the rise and is one of the most common causes of chronic liver disease worldwide. Obesity and metabolic syndrome are considered the most significant risk factors. Bariatric surgery is the only treatment modality in morbid obesity which allows long-term weight loss with improvement in associated co-morbid conditions. However, the effects of bariatric surgery on NAFLD are not well established. NAFLD fibrosis score (NFS) is a validated non-invasive scoring system used to assess advanced fibrosis. We used the NFS to analyse the impact of weight loss on NAFLD following sleeve gastrectomy.

Materials and Methods 174 patients who underwent bariatric surgery between 2010 and 2016 were retrospectively reviewed. Multivariate analysis was performed using pre-operative patient characteristics, biochemical markers and TANITA body analysis measurements to determine significant risk factors for NFS > 0.675. Additionally, the NFS was calculated at 6 months, 1 year and 2 years post-operatively to determine correlation with weight loss.

Results Pre-operatively, 13.8% of our patients had significant fibrosis by NFS. Mean change in NFS was -0.46 ± 1.02 , -0.55 ± 0.98 and -0.55 ± 1.12 at 6 months, 1 year and 2 years respectively. This was significantly correlated with percent of total weight loss with R coefficients of 0.253, 0.292 and 0.274 respectively ($P < 0.05$). 79.2% of patients with NFS > 0.675 achieved resolution by 2 years post-operatively.

Conclusion Based on our study, we conclude that sleeve gastrectomy may be a viable treatment option for management of NAFLD in the obese.

Keywords Bariatric surgery · Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Obesity · Sleeve gastrectomy

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become one of the most common causes of chronic liver disease worldwide, affecting Caucasians and Asians of all ethnicities [1–8].

It is a hepatic manifestation of metabolic syndrome and has been shown to be frequently associated with central obesity, hypertension, insulin resistance (IR), diabetes mellitus (DM), hypertriglyceridemia and low levels of high-density lipoprotein (HDL) [9]. Various studies from Asian countries have delineated the significant association between obesity and the development of NAFLD. These studies are consistent with the global obesity epidemic and its increasing prevalence in Asia. Many of the metabolic changes associated with obesity are also seen with NAFLD. These include abnormal hepatic uptake of fatty acids, lipotoxicity, insulin resistance and state of chronic inflammation [10–15]. NAFLD is a risk factor for development of end-stage liver disease and liver cancer [16–18]. The clinical spectrum of NAFLD ranges from bland steatosis to those with NASH and advanced fibrosis. The latter two groups are at risk of progression to cirrhosis, hepatocellular carcinoma and

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decompensated liver failure, underlying the importance of developing surveillance and measures to prevent progression in this disease entity.

Majority of patients with NAFLD are clinically asymptomatic, and it is usually diagnosed by abdominal ultrasonography. Liver histology is required for staging of disease severity which clearly differentiates NAFLD from NASH and liver fibrosis, which is not possible by any other imaging modality. The invasive nature of biopsies with its inherent risks, however, drove the need for non-invasive testing for which Angulo et al. devised the NAFLD score (NFS) using routine biochemical markers. This demonstrated a positive predictive value (PPV) of 90% for liver fibrosis when $NFS > 0.675$ and a negative predictive value (NPV) of 93% when $NFS < -1.455$ [17]. Several studies have shown its reliability and usefulness as a simple tool in clinical practice [18–21]. The effectiveness of NFS in evaluating fibrosis was validated in a meta-analysis by Xiao et al. and in bariatric patients by Pimental et al. [21, 24].

It has been demonstrated in some studies that NAFLD improves after weight loss induced by bariatric surgery in the morbidly obese. The aim of our study was to evaluate the correlation between percentage total weight loss (%TWL) and change in the NFS in obese Asian patients following laparoscopic sleeve gastrectomy (LSG). This would support the routine use of NFS in following up patients with obesity and NAFLD, with a view that LSG may be demonstrated to be an effective treatment tool.

Materials and Methods

Analysis of prospectively collected data was conducted of patients who had undergone primary LSG between January 2010 and December 2016 in two specialised bariatric centres in Singapore.

Inclusion Criteria

- Obese patients who underwent LSG between 18 and 70 years irrespective of gender
- Patients with follow-up data at two encounters or more post-surgery (6 months, 12 months or 24 months)

Exclusion Criteria

- Patients with inadequate follow-up as defined in the inclusion criteria
- Patients who underwent bariatric surgery other than sleeve gastrectomy
- Patients who underwent sleeve gastrectomy following a previous bariatric surgery

- Patients with acute or chronic viral hepatitis or existing gallstones
- Previous biliary surgery or obstruction excluding uncomplicated cholecystectomy
- Recent or previous alcohol abuse

Detailed analysis of medical records was done. Patients with inadequate or improper documentation of history and with discrepancies in clinical or diagnostic test records were excluded.

NAFLD Fibrosis Score

NFS was calculated at each time point during follow-up and compared with the pre-operative value. NFS was calculated using the following formula:

$$NFS = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (} \times 10^9\text{/l)} - 0.66 \times \text{albumin (g/dl)}$$

Staging of using the NFS was determined using the cut-off points determined by the original author:

$NFS < -1.455$	No significant fibrosis
$-1.455 < NFS \leq 0.675$	Indeterminate score
$NFS > 0.675$	Significant fibrosis

Statistical Analysis

Data collected from each centre included sex, age, ethnicity, height, weight (at the time of surgery and follow-up), biochemical markers for scoring, measures of insulin resistance and dyslipidemia and TANITA body analysis measurements where available.

Baseline data was expressed as frequencies and percentages for categorical characteristics, and the differences in distributions between patients with significant fibrosis and those without based of pre-operative NFS score were compared using the χ^2 test. The means and standard deviations were used to summarise continuous variables, and compared using the independent *T* test.

Linear regression modelling was used to demonstrated correlation between %TWL and change in NFS at 6 months, 1 year and 2 years. Subgroup analysis was performed on patients with significant fibrosis based on pre-operative NFS, who failed to demonstrate improvement in NFS post-surgery to determine risk factors.

Results

The study population consisted of 174 patients undergoing primary laparoscopic sleeve gastrectomy. Their mean age was 43.2 ± 10.9 years with a mean pre-operative weight and BMI

of 114.1 ± 27.2 kg and 42.6 ± 8.32 kg/m² respectively. 58% of patients were class III obese. 63.2% of patients were known to have diabetes mellitus prior to surgery who had opted for LSG over gastric bypass. 13.8% of patients had significant liver fibrosis pre-operatively based on NFS > 0.675.

In our univariate analysis, significant pre-operative factors associated with a NFS > 0.675 include older patients, male gender, heavier weight, higher BMI and class III obesity, larger waist circumference, presence of diabetes mellitus, higher fasting glucose level, lower platelet and albumin count, lower total cholesterol and LDL level, lower impedance and higher fat free mass and total body water. After multivariate analysis, only higher weight, higher BMI, class III obesity, lower platelet count and lower impedance were found to be significant risk factors for a higher NFS score. The results of univariate and multivariate analysis are detailed below in Table 1.

Of our patient cohort, 94.3% and 59.8% were available for follow-up at 1 and 2 years respectively. Mean %TWL was 22.2 ± 5.36 , 27.0 ± 8.08 and 27.1 ± 9.27 at 6 months, 1 year and 2 years respectively. Corresponding mean changes in NFS were -0.46 ± 1.02 , -0.55 ± 0.98 and -0.55 ± 1.12 at these time points. Among the 24 patients who had significant fibrosis based on pre-operative NFS, 79.2% achieved resolution based on NFS. Descriptive statistics during follow-up are detailed in Table 2.

There was significant correlation ($P < 0.05$) between %TWL and change in NFS after LSG at 6 months, 1 year and 2 years. The predicted change in NFS can be calculated using the following formulae: $0.618 + (-0.048 [\% \text{ total weight loss in } \%])$, $0.408 + (-0.035 [\% \text{ total weight loss in } \%])$ and $0.340 + (-0.033 [\% \text{ total weight loss in } \%])$ at 6 months, 1 year and 2 years respectively. The correlation between %TWL and change in NFS score have been detailed in Chart 1. Subgroup analysis on patients with significant fibrosis based on pre-operative NFS demonstrated having higher pre-operative weight and BMI as well as lower %TWL to be significant risk factors in predicting failure of resolution of fibrosis.

Discussion

Given the strong correlation between NAFLD and obesity, traditional management strategies have been directed towards weight loss, which include lifestyle modifications, behavioural modifications as well as medical therapy. Studies have demonstrated that %TWL of 5–10% improves hepatic steatosis and that in excess of 10% reduces inflammation from NAFLD [22, 23]. These studies however have been limited by the total amount of weight loss achievable from non-surgical weight loss strategies [24]. With the widespread recognition of bariatric surgery as an effective tool of weight loss in the morbidly obese, there has been increasing interest in studying its role in the management of obesity related co-morbidities, including that of NAFLD [25].

Role of Bariatric Surgery

In a large series of 236 patients, Karcz et al. from Germany demonstrated the spectrum of NAFLD in patients undergoing bariatric surgery with intra-operative liver biopsies. Seventy-seven patients had steatosis, 87 NASH, 18 fibrosis, 3 cirrhosis, 2 siderosis and 1 patient with chronic hepatitis [32].

A prospective study in a group of 21 morbidly obese Chinese patients with NAFLD showed histological and biochemical improvements 1 year after laparoscopic Roux-en-Y gastric bypass with improvements seen in NAFLD activity score, steatosis, ballooning degeneration and lobular inflammation [26]. Similar results were also found in a study comparing obese Japanese and non-Japanese patients who underwent bariatric surgery with resultant biochemical improvement in liver function [27]. In a prospective observational series from India, by Praveen Raj et al., 88 patients with pre-operative biopsy proven NAFLD were followed up. Of these, 30 patients were subjected to paired liver biopsies with a mean time between biopsies of 7.1 months (range 6–8 months). They found steatosis resolution in 19 patients, lobular inflammation resolution in 12 patients, ballooning degeneration resolution in 9 patients and fibrosis resolution in 11 patients ($P < 0.05$ for all) [28].

These studies appear to support bariatric surgery as an effective tool in the management of NAFLD. There have, however, been no conclusive large randomised controlled trials (RCT) demonstrating this. Most studies were retrospective, while the limited prospective studies lack long-term data. This is primarily a result of difficulty in routine staging of NAFLD at follow-up, for which invasive liver biopsies are the gold standard. Advanced diagnostic imaging such as magnetic resonance elastography is also prohibitive, in terms of cost, for routine use. Hence, the non-invasive NFS devised by Angulo et al., having been validated in bariatric patients [21, 24], is an attractive surrogate measure in the assessment and follow-up of these patients. The NFS has a positive predictive value (PPV) of 90% for liver fibrosis when NFS > 0.675 and a negative predictive value (NPV) of 93% when NFS < -1.455 [17].

Choice of Non-invasive Biomarker Scoring in Evaluation of NAFLD

Several other non-invasive scoring systems such as the BARD score and FIB-4 index have also been studied in the evaluation of NAFLD. The NFS however is the recommended tool by both the American Association for the Study of Liver Diseases [25] and European Association for the Study of the Liver [36]. This is given its favourable performance compared against other composite scores [37] as well as its importance in prognosticating complications and mortality in NAFLD patients [38, 39]. Additionally, it has been validated in both an Asian cohort [40] and bariatric patients [21, 24].

Table 1 Baseline characteristics, univariate analysis and multivariate analysis for predictors of having significant pre-operative NFS > 0.675

	Baseline characteristics N = 174	Univariate analysis for predictors of having significant pre-op NFS > 0.675		Multivariate analysis			
		NFS ≤ 0.675 N = 150	NFS > 0.675 N = 24	Coefficient	p – value	Coefficient	p – value
Gender (%)							
○ Male	74 (42.5)	59 (39.3)	15 (62.5)	RR = 2.25	P < 0.05	F = 0.01	0.92
○ Female	100 (57.5)	91 (60.7)	9 (37.5)				
Mean age, years (SD)	43.22 (10.9)	42.07 (10.8)	50.5 (8.66)	T = -3.64	P < 0.05	F = 2.35	0.13
Mean height, m (SD)	1.64 (0.10)	1.64 (0.10)	1.64 (0.13)	T = -0.01	P = 0.994		
Mean weight, kg (SD)	114.1 (27.2)	109.5 (22.8)	142.3 (35.0)	T = -4.44	P < 0.05	F = 2.71	0.10
Mean BMI, kg/m ² (SD)	42.6 ± 8.32	41.0 (6.94)	52.6 (9.36)	T = -5.82	P < 0.05	F = 7.12	< 0.05
Obesity (%)							
○ Class 2	73 (42.0)	71 (47.3)	2 (8.3)	RR = 7.94	P < 0.05	F = 3.45	< 0.05
○ Class 3	101 (58.0)	79 (52.7)	22 (91.7)				
Diabetes Mellitus							
• Present	64 (36.8)	49 (32.7)	15 (62.5)	RR = 2.87	P < 0.05	F = 4.51	0.567
• Absent	110 (63.2)	101 (67.3)	9 (37.5)				
HbA1c, % (SD)	6.62 (1.95)	6.58 (2.03)	6.82 (1.38)	T = -0.55	P = 0.58	-	-
Fasting glucose, mmol/L (SD)	6.58 (2.82)	6.39 (2.74)	7.80 (3.05)	T = -2.15	P < 0.05	F = 1.20	0.28
Insulin, mIU/L (SD)	31.3 (30.0)	27.7 (19.8)	55.4 (62.8)	T = -1.69	P = 0.11	-	-
HOMA-IR	10.2 (13.6)	8.38 (6.15)	23.3 (33.8)	T = -1.53	P = 0.15	-	-
AST, IU/L (SD)	28.3 (15.5)	28.1 (15.3)	29.3 (17.3)	T = -0.33	P = 0.74	-	-
ALT, IU/L (SD)	37.2 (26.5)	38.5 (27.1)	29.3 (21.6)	T = 1.58	P = 0.12	-	-
Platelet, x10 ⁹ /L (SD)	279.9 (68.2)	290.2 (66.0)	215.5 (42.7)	T = 7.28	P < 0.05	F = 5.83	< 0.05
Albumin, g/L (SD)	41.8 (3.62)	42.5 (3.03)	37.9 (4.45)	T = 4.90	P < 0.05	F = 3.09	0.08
Total cholesterol, mmol/L (SD)	4.87 (0.96)	4.97 (0.96)	4.32 (0.76)	T = 3.08	P < 0.05	F = 2.51	0.12
LDL, mmol/L (SD)	3.02 (0.89)	3.09 (0.91)	2.60 (0.62)	T = 2.51	P < 0.05	F = 2.00	0.16
HLD, mmol/L (SD)	1.22 (0.30)	1.22 (0.30)	1.21 (0.26)	T = 0.15	P = 0.88	-	-
TG, mmol/L (SD)	1.60 (0.78)	1.65 (0.82)	1.33 (0.44)	T = 1.81	P = 0.07	-	-
Waist circumference, cm (SD)	122.9 (17.4)	121 (16.7)	135 (18.5)	T = -3.05	P < 0.05	F = 1.77	0.19
Basal metabolic rate	1597.5 (327)	1578 (316)	1788 (382)	T = -1.96	P = 0.05	-	-
Impedance	354.0 (76.3)	365 (70.6)	248 (40.9)	T = 5.12	P < 0.05	F = 8.92	< 0.05
Fat %	42.7 (9.8)	42.8 (9.57)	41.9 (11.8)	T = 0.39	P = 0.70	-	-
Fat mass, kg (SD)	46.3 (11.5)	45.9 (10.6)	50.0 (18.2)	T = -0.70	P = 0.50	-	-
Fat free mass, kg (SD)	67.0 (18.1)	65.2 (16.6)	84.9 (22.7)	T = -3.45	P < 0.05	F = 2.94	0.09
Total body water, % (SD)	48.6 (13.3)	47.3 (12.3)	61.4 (16.4)	T = -3.36	P < 0.05	F = 2.55	0.11
NFS (%)							
○ x < -1.455	76 (43.7)						
○ -1.455 < x ≤ 0.675	74 (42.5)						
○ x > 0.675	24 (13.8)						

Risk Factors for Predicting Significant Fibrosis Based on NFS

In our study, male gender, advanced age, heavier weight, higher BMI and class III obesity, larger waist circumference, presence of diabetes mellitus, higher fasting glucose level, lower platelet count, low serum albumin levels, lower total cholesterol and LDL level,

lower impedance and higher fat free mass and total body water were found to be independent risk factors for a higher NFS score. HOMA-IR, as a measure of insulin resistance, was higher in patients with pre-op NFS > 0.675 (23.3 ± 33.8 versus 8.38 ± 6.15); this was however not significant ($P = 0.15$). Higher BMI was the most significant risk factor predicting a higher NFS score ($P < 0.05$).

Table 2 Descriptive statistics after 6 months, 1 year and 2 years follow up

	Pre-op	6 months	1 year	2 years
Follow-up, n (%)	174 (100)	156 (89.7)	164 (94.3)	104 (59.8)
Mean weight, kg (SD)	114.1 (27.2)	88.8 (20.1)	83.0 (18.5)	81.7 (18.2)
Mean TWL, kg (SD)	-	25.7 (9.71)	31.5 (13.9)	31.0 (14.3)
Mean %TWL (SD)	-	22.2 (5.36)	27.0 (8.08)	27.1 (9.27)
Mean NFS (SD)	-1.19 (1.75)	-1.65 (1.50)	-1.74 (1.41)	-1.71 (1.56)
Mean change in NFS (SD)	-	-0.46 (1.02)	-0.55 (0.98)	-0.55 (1.12)
Fibrosis score group (%)				
○ $x < -1.455$	76 (43.7)	96 (61.5)	97 (59.1)	59 (56.7)
○ $-1.455 < x \leq 0.675$	74 (42.5)	48 (30.8)	61 (37.2)	42 (40.4)
○ $x > 0.675$	24 (13.8)	12 (7.70)	6 (3.70)	5 (4.80)

Correlation Between Weight Loss and Resolution of NAFLD

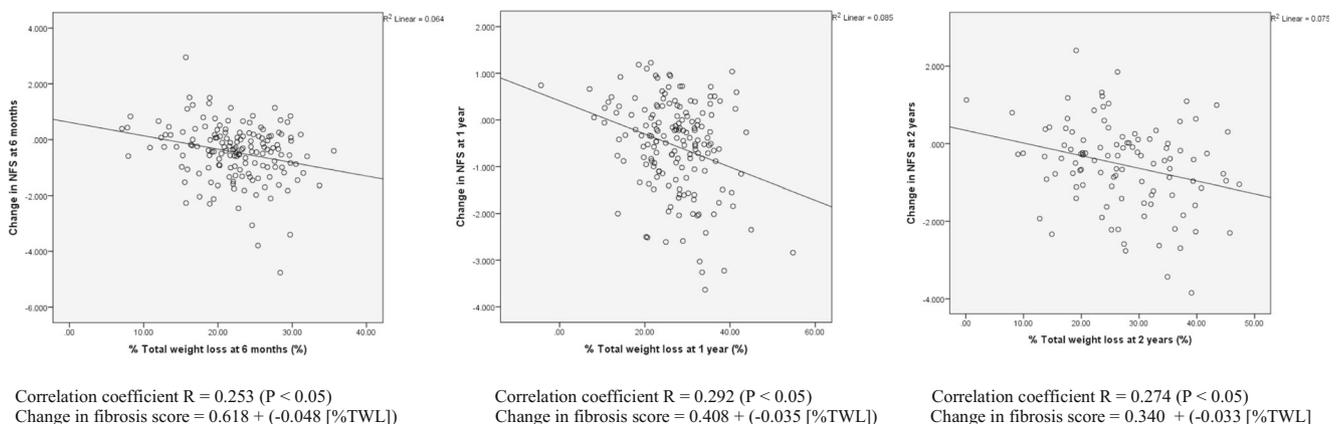
In our study, surgery-induced weight loss correlates directly with improvement in NFS. In our cohort of 174 patients, 164 (94.3%) and 104 (59.8%) patients followed up at 1 and 2 years respectively. During follow-up assessment, the mean %TWL was 22.2 ± 5.36 , 27.0 ± 8.08 and 27.1 ± 9.27 at 6 months, 1 year and 2 years respectively. During the same time, the mean change in NFS was -0.46 ± 1.02 at 6 months, -0.55 ± 0.98 at 1 year and -0.55 ± 1.12 at 2 years. Significant positive correlation ($P < 0.05$) was demonstrated at all three time points with correlation coefficients of 0.253, 0.292 and 0.274 at 6 months, 1 year and 2 years respectively.

Twenty-four patients (13.8%) had a pre-operative NFS > 0.675 , which was suggestive of significant fibrosis. Of these, 79.2% achieved resolution after LSG based on NFS ($P < 0.05$). In the remaining patients, the general trend was towards improvement in the NFS score corresponding with %TWL. Heavier weight, higher BMI and lower %TWL were found to be significant risk factors in predicting failure of resolution of fibrosis.

Our study findings are supportive that NAFLD severity, based on the NFS, improves with LSG and is directly correlated with %TWL. Additionally, a plateau in change of NFS score is seen at 2 years which corresponds with the known plateau in %TWL after bariatric surgery. It also demonstrates patients who are of heavier pre-operative weight and higher BMI to be at higher risk of having significant liver fibrosis and are at risk of lack of resolution after surgery.

Current Guidelines and Future Research

The American Association for the Study of Liver Diseases, American College of Gastroenterology and American Gastroenterological Association recommend that in otherwise eligible obese individuals with NAFLD or NASH, bariatric surgery should not be contraindicated. However, they commented that it is premature to consider bariatric surgery as an established option to manage NASH [25]. Mummadi et al. in their systemic review documented improvement as well as resolution in the entire spectrum of NAFLD following bariatric surgery. In the 15 studies reviewed with 766 paired liver biopsies after bariatric surgery, improvement or

**Chart 1** Correlation coefficient between total weight loss, kilograms and change in NFS score at 6 months, 1 year and 2 years

resolution rates were 91.6% for steatosis, 81.3% for steatohepatitis and 65.5% for fibrosis patients. Similarly, 69.5% patients with NASH showed complete resolution [41]. But Chavez-Tapia et al. in Cochrane review concluded that due to lack of RCTs, a definitive assessment of the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH cannot be drawn [42].

While our study supports that LSG may be an effective tool in improving NAFLD, prospective RCTs are still necessary to be conclusive in its efficacy, safety and in guiding patient selection. The direct correlation between %TWL and change in NFS score that we have demonstrated, however, support the use of the NFS score as a severity assessment and staging tool for follow-up as opposed to routine invasive liver biopsies, in these study designs.

Moreover, the exact mechanisms through which LSG may improve NAFLD are not yet well understood. Myronovych et al., in his two animal studies, demonstrated NAFLD improvement in obese mice, subjected to vertical sleeve gastrectomy (VSG). They demonstrated changes in receptor level interactions which downregulate the lipogenesis pathway after VSG [33, 34]. Similar findings were also demonstrated by Du et al. on obese mice after VSG. They suggested that VSG induces global regulatory changes through epigenetic modifications which impact hepatic inflammation and lipid metabolism pathways [35]. Further studies, including human models, are needed to demonstrate the interactions and improve our understanding of the underlying mechanisms.

Strengths of Study

To our knowledge, the present study is the first from Asia evaluating the role of LSG in obese patients with NAFLD and using a non-invasive validated scoring system NFS to assess improvement in liver function. The reported data is from two bariatric centres, involving four surgeons with experience in performing standardised bariatric surgery. A significant proportion of our patients have been followed up for 2 years. The setting of study is in Singapore where the prevalence of obesity defined by body mass index (BMI) ≥ 30 kg per square meter (kg/m^2) in the adult population has shown a steady increase, currently affecting 10.8% of population as per the national health survey in 2010 [43]. The same survey found obesity to be most prevalent in Malays (24.0%), followed by Indians (16.9%) and Chinese (7.9%). Hence, the study group with a mixed ethnic population can be approximated to be representative of an Asian cohort.

Limitations of Study

Firstly, being a retrospective study, reporter and observer bias cannot be ruled out. Secondly, in the absence of a control group, the efficacy of LSG cannot be compared against other

weight management programs or weight loss procedures. Lastly, histology remains the gold standard investigation in confirming the presence of NAFLD and it would be premature to generalise our findings based on NFS. We are only suggesting that LSG induced weight loss correlates with improvement of NAFLD and that the NFS can be used to design prospective studies evaluating the role of bariatric surgery as an effective treatment option for NAFLD.

Conclusion

In summary, LSG is safe and efficacious in obese patients with NAFLD. LSG causes an improvement in NAFLD based on the NFS which correlates with the %TWL. A particularly safe and standardised bariatric intervention, LSG can be considered for obese patients with NAFLD. Further randomised control trials with larger patient groups and longer follow-up are required to lay down definitive guidelines for management of NAFLD in obese patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Statements This study has been approved by the institutional research ethics committee. No formal consent was required as this was a retrospective study.

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