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ORIGINAL SCIENTIFIC REPORT

Incidence and Impact of Non-alcoholic Fatty Liver Disease (NAFLD) in Patients with Adenocarcinoma of the Esophagus Treated with Curative Intent

John V. Reynolds[1] · Noel E. Donlon[1] · Jessie A. Elliott[1] · Brendan Moran[1] · Hugo Temperley[1] · Tim S. Nugent[1] · Maria Davern[1] · Sinead King[1] · Melissa Conroy[1] · Joanne Lysaght[1] · Narayanasamy Ravi[1] · Carmel Ryan[2] · Stephen Finn[2] · Suzanne Norris[3] · Clare L. Donohoe[1]

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Abstract

Background and Aims Esophageal adenocarcinoma (EAC) is associated with visceral obesity (VO). Non-alcoholic fatty liver disease (NAFLD) is common within this phenotype; however, its incidence and clinical significance in EAC have not been studied.

Study design A total of 559 patients with hepatic stetatosis (HS) defined by unenhanced CT were enrolled. In a sub-study, in 140 consecutive patients a liver biopsy was taken intraoperatively to study HS and non-alcoholic steatohepatitis (NASH). Postoperative complications were defined as per the Esophageal Complications Consensus Group (ECCG). Liver biochemistry was measured peri-operatively, with an ALT > 5 defined as acute liver injury (ALI). Mann–Whitney U test or Fisher's exact test was utilized and the Kaplan–Meier method for survival.

Results 42% (n = 234/559) of patients had CT-defined HS. HS was associated with VO in 56% of cases, metabolic syndrome (Met S) in 37% and type 2 diabetes in 25%, compared with 44, 21, and 15% in non-HS patients ($p < 0.01$). Pathologic HS was present in 32% (45/140) and graded as mild, moderate, and severe in 73, 24, and 3%, respectively, with NASH reported in 16% and indefinite/borderline NASH in 42% of HS cases. Postoperative ALI was similar (p = 0.88) in both HS (10%) and non-HS cohorts (11%). Operative complication severity was similar in both cohorts. 5-yr survival was 53% (HS) vs 50% (p = 0.890).

Conclusion This study establishes for the first time the incidence and clinical impact of NAFLD in EAC patients undergoing surgery and highlights no major impact on oncologic outcomes, nor in the severity of complications.

Introduction

Epidemiologic studies have established a clear link between esophageal adenocarcinoma (EAC) and obesity [1–6] of the adipose compartments; visceral adipose tissue (VAT) is closely aligned with metabolic dysregulation and inflammation. Visceral obesity (VO) is associated with type 2 diabetes mellitus (T2DM), hypertension, and hyperlipidemia in the metabolic syndrome (Met S) and with non-alcoholic fatty liver disease (NAFLD) [6, 7].

The incidence of NAFLD in EAC and its impact on outcomes, both operative and oncologic, are unknown. NAFLD has an estimated population prevalence of 25–30% in USA and Europe and represents a risk factor for progression to steatohepatitis (NASH), cirrhosis, and hepatocellular cancer (HCC) [7–11]. A liver biopsy remains the gold standard to investigate NAFLD. Non-invasive modalities include transient elastography (Fibroscan™), MRI, and unenhanced CT scans [7, 12]. [13]. In cancer

✉ John V. Reynolds
reynoljv@tcd.ie

[1] Department of Surgery, Trinity College Dublin, and the Trinity St. James's Cancer Institute Dublin, Dublin, Ireland

[2] Department of Pathology, St. James's Hospital and Trinity College Dublin, Dublin, Ireland

[3] Hepatology Department, Department of Medicine, St. James's Hospital and Trinity College Dublin, Dublin, Ireland

populations, the routine use of CT alone in staging enables a radiologic determination of HS. The attenuation value of liver parenchyma, expressed as Hounsfield Units (HU), decreases as HS progresses, and may be reported as the attenuation difference between liver and spleen [13, 14].

The liver is central to the immune and inflammatory response to major surgery, with a characteristic heightened acute phase response proportional to the magnitude of surgery [15–17]. In the setting of post-operative sepsis, liver failure as measured by increases in the serum bilirubin is a component of the sequential organ failure score (SOFA) [18]. What is unknown at this time is whether NAFLD impacts on the hepatic response to surgery, predisposes to other complications, or adversely affects the outcome of patients with postoperative infection or sepsis.

As part of the Esophageal Cancer and Visceral Obesity Clinical and Translational Research Program in Dublin, a detailed CT-measure of body composition and HS is routinely performed in all patients with EAC being treated with curative intent, and a liver biopsy is taken intra-operatively in consenting patients. This study, the first to systematically address NAFLD in EAC, had the following aims: (i) to determine the incidence and associations of NAFLD in a western EAC population; (ii) to characterize NAFLD severity by histologic assessment; (iii) to determine whether NAFLD impacts on operative complications; (iv) to determine whether NAFLD impacts the liver response to surgery; and (v) to assess impact on oncologic outcomes.

Methods

Patient selection and study design

The Esophageal and Gastric Centre at St. James's Hospital, Dublin, is a high-volume National Centre, and a detailed clinical, pathologic, and body composition database is prospectively maintained for all patients by a full time data manager. All patients with EAC diagnosed between 2007 and 2019 and treated with curative intent were included. All eligible patients with at least one preoperative computed tomography (CT) scan capturing the level of the L3 vertebra conducted at this center were included. This study was approved by the IRB and registered on ClinicalTrials.gov (NCT03061370).

Treatment protocol

Patients with locally advanced esophageal adenocarcinoma were treated with neoadjuvant chemoradiation or peri-operative chemotherapy [19, 20]. The standard operative approach was an open *en bloc* esophagectomy with gastric conduit and thoracic or cervical anastomosis, with a transhiatal esophagectomy or an extended total gastrectomy in selected cases.

Computed Tomography assessment of hepatic steatosis

PET-CT/CT scans were routinely obtained at diagnosis using a Discovery ST^{TM} PET/CT scanner (GE Healthcare, Little Chalfont, UK). HS was defined as the measurement of attenuation value of liver parenchyma, expressed as Hounsfield Units (HU), where a cutoff was set at -9 [14]. Images at L3 were analyzed by a single-blinded investigator [SLD] to determine the cross-sectional area (cm^2) of each tissue compartment [21]. Visceral obesity (VO) was defined as previously described [22].

Liver pathology methods

In an unselected cohort of consented patients ($n = 140$), liver biopsies were taken and formalin-fixed paraffin-embedded liver biopsies were assessed by subspecialist hepato-pathologists. Standard hematoxylin and eosin (H&E)-stained histologic sections were stratified as follows into subgroups based on quantification of intrahepatocyte lipid vacuoles: no steatosis ($< 5\%$); mild steatosis (5–33%); moderate steatosis (34–66%); and severe steatosis ($> 66\%$) (Fig. 1). Where HS was present, biopsies were further assessed for NASH, with NAFLD activity score (NAS) being assigned to each in accordance with the NASH clinical research network (CRN) scoring system [23, 24]. This semiquantitative system assigns a score from 0 to 8 based on degree of steatosis (0–3), lobular inflammation (0–3) and hepatocellular ballooning (0–2). A total score of 5 or more is designated definite steatohepatitis, scores of 3 or 4 are defined as indefinite, and less than 3 as absent steatohepatitis [23, 24].

Operative complications

Postoperative complications were coded prospectively using definitions established by the Esophageal Complications Consensus Group (ECCG), as well as the Clavien–Dindo severity classification [25–27]. CRP, albumin, WCC, ALT, AST, bilirubin, and INR were recorded preoperatively and on each day in the first week postoperatively, in addition to standard hematology and biochemical profiles. Postoperative liver dysfunction was defined as a fivefold increase in ALT or two times the upper limit of normal for bilirubin.

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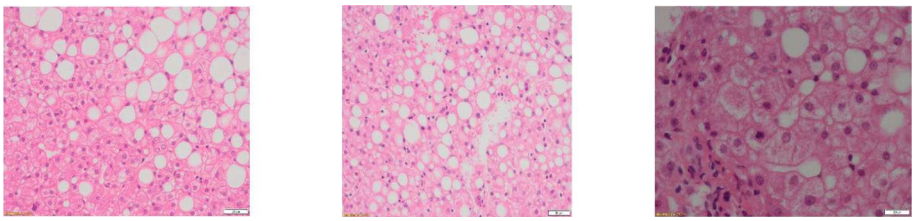

Fig. 1 Liver biopsy of non-alcoholic steatohepatitis (NASH). Histologic features of NASH include steatosis, ballooning, and lobular inflammation and associated NAS scores

Other measurements

Met S was defined using the Adult Treatment Panel III (ATPIII) definition as any two of the following: obesity, type II diabetes mellitus, hypertension, and hyperlipidemia [28]. In addition to standard metabolic profiling, all patients had measurement of fasting cholesterol, triglycerides, and glucose.

Statistical analysis

Data were analyzed using GraphPad Prism (v.6.0) for Windows, GraphPad software (San Diego, CA, USA), and SPSS® (v.23.0) software (SPSS, Chicago, IL, USA). Univariable comparisons between groups were performed using the Student's t or Mann–Whitney U tests for continuous or Chi-square or Fisher's exact test for categorical variables. Data are reported as mean ± standard deviation unless otherwise specified. All statistical analyses were two-tailed with the threshold of significance set at $P < 0.050$.

Results

Patient characteristics

A total of 559 consecutive patients (the majority male (455 [81%]) with a mean (+ SD) age of 63 (10) years) were enrolled. 337 (60%) were classified as cT3 and 239 (43%) as cN + . 341 (61%) underwent neoadjuvant therapy, 53% with chemoradiation and chemotherapy in 47%. The most common surgical procedure was an *en-bloc* 2-stage esophagectomy, in 64% or patients. Type2 DM, hypertension, and hyperlipidaemia was observed in 19%, 39%, and 20% of the overall cohort and Met S in 28% of patients. BMI > 30 was present in 31% of patients and CT-defined VO in 49 per cent.

Comparison of CT-defined hepatic steatosis vs no hepatic steatosis (Table 1)

Totally, 234 of 559 (42%) of patients had CT evidence of HS at diagnosis. Comparing both cohorts, mean BMI and prevalence of obesity were significantly ($P < 0.05$) increased in the HS cohort, at 28 vs 27 kg/m^2, and 32% vs 23%, respectively. VO was present in 56 vs 44% of HS vs non-HS cohorts, with T2DM, Met S, hypertension, at 25 vs 15% ($p = 0.006$), 37% vs 21% ($p < 0.001$), and 42% vs 37% (p = NS), respectively. There were no differences in age, sex, neoadjuvant therapy, or operative approach.

Operative complications

The overall complication rates, and the severity of complications, were similar in both cohorts (Table 2). Clavien–Dindo > III severity grading was observed in 24% vs 23% HS + and HS- groups, respectively, and in-hospital mortality was 1% in both cohorts. For specific complications, anastomotic leak rates were 6 vs 4% and atrial fibrillation 20 vs 17%, comparing HS with non-HS, respectively. Pneumonia and respiratory failure were, however, significantly ($p < 0.05$) increased, at 27 and 9%, compared with 18 and 4%, respectively. On univariate analysis, there was a significant association between pneumonia and visceral obesity and hepatic steatosis, but no factor was independently significant on multivariate analysis (Table 3).

Oncologic outcomes

The pCR rate overall from 144 in the HS + cohort and 197 in the HS- cohort who underwent neoadjuvant therapy prior to surgery was 7 and 12% overall, ($p = 0.08$), and 17 vs 13% in patients who had neoadjuvant chemoradiation ($p = 0.4$). A major pathologic response (MPR) defined as tumor regression grade (TRG) 1 or 2 was evident in 29 vs 30% overall ($P = 0.95$) and 41% and 40% after chemoradiation ($P = 0.86$) in HS + and HS- cohorts. Microscopically complete margins (R0) were 90% in both groups ($p = 0.72$). Median overall survival was 63.6 vs

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Table 1 Demographic, clinical details, and treatment plan in patients with CT-defined hepatic steatosis compared with no steatosis

	No steatosis $N = 325$	Steatosis $N = 234$	P-value
Clinical characteristics			
Age, mean (SD)	64 (10)	63 (10)	0.25
Sex, N (%)			
Female	56 (17)	38 (16)	0.42
Male	259 (83)	196 (84)	
BMI, kg m^{-2}, mean (SD)	27.29 (5)	28.18 (5)	**0.03**
Obesity, *N* (%)	75 (23)	75 (32)	**0.04**
Viscerally obese *N* (%)	142 (44)	131 (56)	**0.005**
Metabolic syndrome *N* (%)	68 (21)	87 (37)	**< 0.001**
Diabetes, *N* (%)	50 (15)	58 (25)	**0.006**
Hypertension, *N* (%)	121 (37)	98 (42)	0.15
Respiratory disease, *N* (%)	66 (20)	40 (17)	0.2
ASA grade, N (%)			
ASA I	93 (29)	63 (27)	
ASA II	192 (59)	139 (59)	0.84
ASA III	40 (12)	32 (14)	
cT3	201 (62)	136 (58)	0.48
cN +	136 (42)	103 (44)	0.59
Neoadjuvant therapy	197 (61)	144 (62)	
Neoadj. chemotherapy	108 (54)	73 (51)	0.40
Neoadj. chemoradiation	89 (46)	71 (49)	0.60
Surgery			
En bloc transthoracic surgery	204 (63)	150 (64)	
Transmediastinal	119 (37)	84 (36)	0.59
R0	291 (90)	210 (90)	0.72

Bold values indicate significance at $P < 0.05$

55.23 months for HS + vs HS- groups with an estimated 5-year survival of 53 vs 49% ($p = 0.890$) (Fig. 2).

Liver response to surgery (Table 4 and Fig. 3)

Relevant liver function tests are shown in Table 4 along with WCC, on preoperative day 1 and postoperative days 1, 3, and 7. No significant difference was evident. A > five-fold increase in ALT (Fig. 3) was observed in 10% HS + vs 11% HS- cohorts, ($p = 0.88$). A bilirubin (1.2 to 1.9 mg/dL; 20-32 µmol;/L) was evident in 93% vs 96% (p = 0.83) and above this level in 7% vs 4% ($p = 0.83$).

Histologic study (Table 5)

In 140 unselected consecutive patients, 76% of whom had received neodjuvant therapy [chemotherapy (57%) or chemoradiation (43%)], steatosis was confirmed in 45 cases (32%), with a mean (+ SEM) score of 10 (9.3); 19 cases (13%) with CT-defined HS were negative on biopsies, and 2 (1.4%) were negative CT criteria were positive for HS on pathology. NASH/active steatohepatitis was observed in seven (16% of HS, 5% overall) cases, 19 (42% of HS, 14% overall) were borderline/indefinite for steatohepatitis, and the remaining 19 HS alone (42%; 14% overall) were negative for steatohepatitis. The degree of steatosis based on intra-hepatocyte lipid vacuoles was mild in 33 (73%), moderately severe in 11 (24.4%), and severe in one (2.2%) case.

Discussion

The rise in incidence of EAC is closely aligned with obesity trends globally [1–8]. The epidemiologic focus in particular has been on visceral obesity (VO) and dysmetabolism, and in this context, NAFLD represents the most common end-organ marker. This study explores the incidence of this association in a typical Western world cohort and explores the clinical, radiologic, and pathologic spectrum, and the oncologic and operative impact. Several findings emerge. First, CT-defined HS is prevalent in this

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Table 2 Operative complications

	No steatosis N = 325	Hepatic steatosis N = 234	*P*-value
Pneumonia	58 (18)	63 (27)	**< 0.01**
Respiratory failure requiring reintubation Acute respiratory distress syndrome	13 (4)	21 (9)	**0.01**
Dysrhythmia atrial requiring treatment	7 (2)	11 (5)	0.14
Esophagoenteric leak from anastomosis, staple line, or localized conduit necrosis Conduit necrosis/failure	54 (17)	46 (20)	0.37
Chyle leak	11 (4)	16 (6)	0.99
Multiple organ dysfunction syndrome	15 (5)	14 (6)	0.17
Clavien–Dindo severity			
CD 0	98 (30%)	64 (20%)	0.69
CD I	52 (16%)	49 (21%)	
CD II	83 (26%)	64 (27%)	
CD IIIa	44 (14%)	30 (13%)	
CD IIIb	8 (2.5%)	5 (2%)	
CD IVa	22 (7%)	9 (4%)	
CD IVb	15 (5%)	10 (4.2%)	
CD V	3 (1%)	3 (1.2%)	

Bold values indicate significance at $P < 0.05$

Table 3 Univariate and multivariate logistic regression of preoperative factors associated with postoperative pneumonia among patients with esophageal adenocarcinoma

	Pneumonia Univariate		
	P-value	OR (95% CI)	
Age, years	0.713	1.21 (0.56 – 1.87)	
Sex, male vs female	0.815	1.58 (1.21 – 2.65)	
ASA grade	0.365		
ASA II vs I	0.216	1.72 (1.15 – 1.92)	
ASA III vs I	0.292	1.26 (0.89 – 2.82)	
Diabetes	0.786	1.94 (1.64 – 2.10)	
Respiratory comorbidity	0.479	1.65 (0.98 – 1.89)	
Metabolic syndrome	0.967	0.99 (0.62 – 1.59)	
Visceral obesity	0.021	1.29 (1.03 – 2.42)	P = 0.102 MVA
BMI 25–30 vs < 25	0.091	1.45 (1.34–2.69)	
$kg/m^2 > 30$ vs < 25	0.451	1.67 (1.1–2.10)	
Hepatic stetatosis	0.010	1.11 (1.23 – 2.18)	P = 0.091 MVA

OR odds ratio; *CI* confidence interval; *ASA* American Society for Anesthesiologists; *BMI* body mass index, *MVA* multivariate analysis

cohort, strongly associated with VO, Met S, and T2DM. Second, most cases have mild steatosis on histologic assessment, the majority being "indefinite for NASH." Third, HS has a modest impact on operative outcomes, with no impact on mortality or the severity of complications. Finally, standard oncologic outcomes, and survival, are not impacted.

Risk assessment for esophageal surgery focuses predominantly on respiratory and cardiac co-morbidities. In the absence of known liver disease, or excessive alcohol intake, currently there is little pre-operative investigation of liver function. This study took advantage of the pre-operative CT imaging available in all EAC cases at our institute. The $CT_{L\text{-}S}$ detects moderate or severe degree HS

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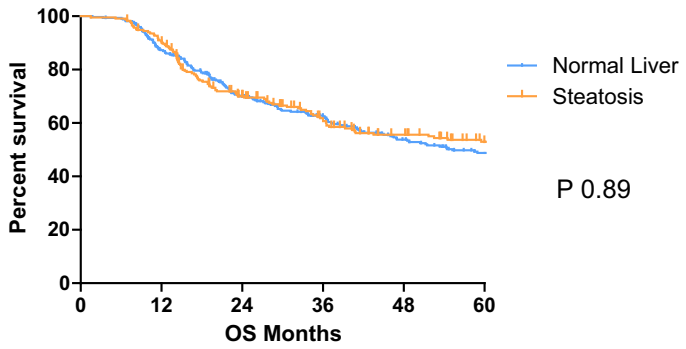

	Normal Liver Parenchyma			Hepatic Steatosis		
Survival (years)	No at risk	Deaths	% survival	No at risk	Deaths	% survival
1	325	41	87	234	21	91
3	277	73	63	211	63	62
5	161	33	50	114	15	53

Fig. 2 Overall survival: HS vs no HS

Table 4 Liver biochemistry in the perioperative period

Routine laboratory markers	No Steatosis *N* = 325				Hepatic Steatosis *N* = 234			
	Pre-op	POD1	POD3	Max	Pre-op	POD1	POD3	Max
Marker	(Mean (SD)	(Mean (SD)	(Mean (SD)	(Mean (SD)	(Mean (SD)	(Mean (SD)	(Mean (SD)	(Mean (SD)
WCC (10^9 /L)	6.43 (2.33)	13.31 (4)	10.9 (3.67)	15.6 (6.59)	6.62 (2.02)	13.46 (3.67)	11.06 (3.72)	16.76 (5.56)
CRP (mg/L)	7.59 (19.08)	129.1 (53.89)	187.6 (89.17)	207.9 (99.93)	7.2 (19.64)	130.8 (55.72)	181.8 (73.43)	211.2 (86.86)
Bilirubin (μmol/L)	7.86 (4.09)	7.41 (8.46)	9.21 (7.65)		8.18 (5.07)	6.54 (6.56)	8.45 (7.56)	
AST (IU/L)	22.12 (14.39)	99.68 (290.2)	135 (220.4)		24.5 (16.48)	95.41 (177.8)	155.4 (240.5)	
ALT (IU/L)	19.81 (9.04)	89.27 (145)	101.23 (101.23)		24.24 (17.43)	127.6 (225)	132 (156.4)	
Alk Phos (IU/L)	77.28 (21.8)	63.6 (43.01)	78 (89.2)		78.73 (23.51)	62.4 (27.31)	88 (76.4)	
GGT (IU/L)	31.41 (26.27)	43.31 (46.84)	65.3 (67.45)		38.38 (39.42)	47.82 (50.03)	67.4 (45.4)	
INR	1.01 (0.17)	1.23 (1.6)	1.32 (1.9)		0.99 (0.15)	1.14 (0.15)	1.5 (1.2)	
Albumin (g/L)	41.22 (4.01)	28.3 (9.3)	26.76 (7.71)	24.56 (4.55)	42.1 (3.62)	28.43 (3.73)	25.87 (6.72)	23.65 (6.5)

with a specificity and sensitivity of 10% and 82%, respectively, when a cutoff is set at -9 [14]. In this study, 234/559 (42%) of patients had radiologic evidence of HS by this criteria. In a sub-study of consecutive patients, liver biopsies were also taken, and 32% of patients had proven HS, with the degree of steatosis moderate or severe in 26.6% of cases, and definite or indefinite for NASH in 57.7% of HS cases [7]. These assessments corroborate each other and provide a clinico-pathologic profile in a Western series. Notably, CT-defined HS is clearly not dichotomized, as 44% of non-HS patients had VO, and 15% had Type2 DM, thus highlighting the spectrum of obesity and metabolic dysfunction across this patient cohort, and also that HS may be mild and below the sensitivity of CT imaging. HS is thus likely to represent a continuous rather than categorical variable, limiting findings of independent impact in multivariable analysis where so many variables co-exist.

NAFLD did not influence standard oncologic metrics, including response to therapy, R0 margins, and survival. A

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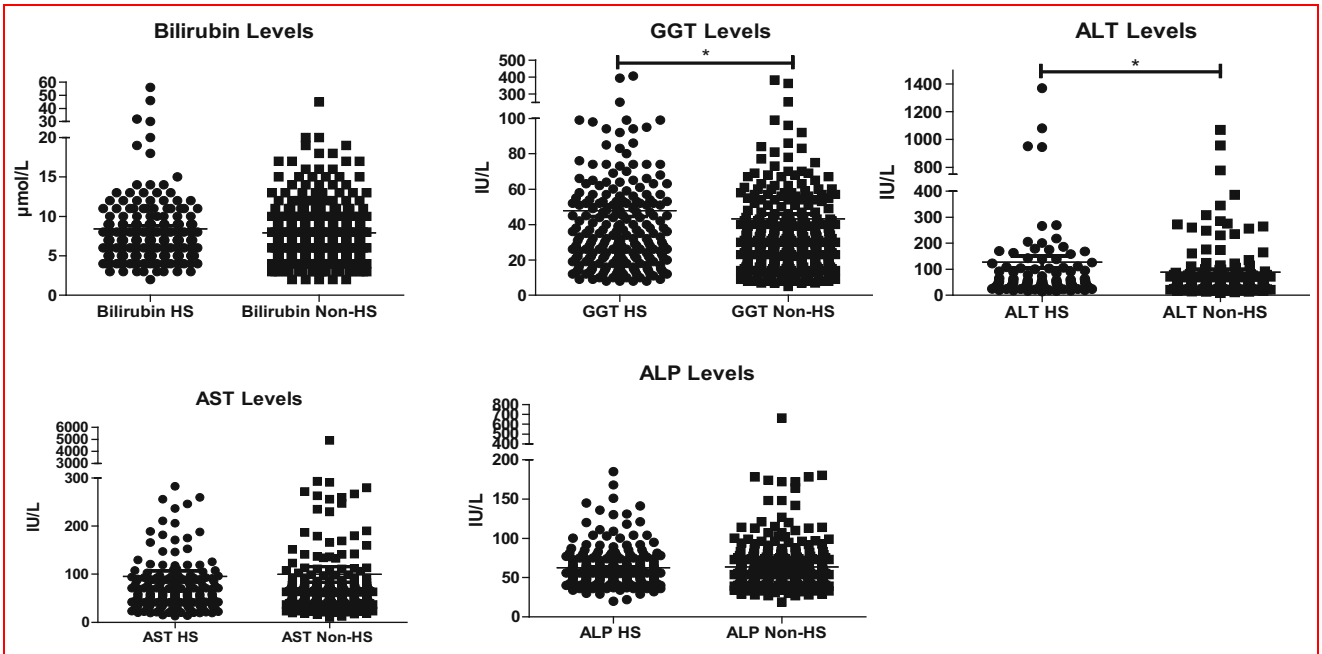

Fig. 3 Maximum liver biochemical response postoperatively in steatosis (HS) vs non-steatosis (NS) cohorts. *S* = steatosis, *NS* = non-steatosis. *$p < 0.05$

Table 5 Pathologic classification of NAFLD

Degree of steatosis (% Intrahepatocyte lipid vacuoles)	Number	Definite NASH	Borderline/Indefinite NASH	Not NASH
Mild (5–33)	33	2	14	17
Moderate (> 33—66)	11	4	5	2
Severe (> 66)	1	1	0	0

3- and 5-year survival of 62% and 53%, and a median survival of 63.6 months, is consistent with optimum reported outcomes [19]. A major pathologic response (TRG1/TRG2) at 29% for the HS compared with 30% for HS cohorts was observed and a pCR rate of 7% vs 12%. This may be consistent with some evidence that both obesity at least in the in the BMI range $> 30 < 35$ kg/m^2 and visceral obesity have no detrimental effect and may possibly be associated with improved survival in EAC [29, 30].

The liver plays a central in cytokine-mediated pro-inflammatory changes after major surgery, in part via increased TNF-α, IL-6, and IL-1β elaborated by Kupffer cells [31, 32]. Where the liver is compromised, outcomes for general surgery have been studied extensively and mostly risk-stratified by the Child–Turcott–Pugh (CTP) classification. Even for CTP-A cohorts, mortality rates of up to 10% are reported [33]. In a recent review of 157 patients (87% CTP-A) undergoing esophagectomy with cirrhosis, the mortality rate was 18% [34]. Since this is several-fold greater than modern benchmarks of between 1 and 5%, it is probable that few patients with cirrhosis undergo esophageal cancer surgery [15]. In contrast, in this study of NAFLD where no hepatic risk classification is made preoperatively, a low in-hospital mortality rate of just 1% is encouraging, as well as no increase in the severity of complications, nor of added risk of anastomotic leaks or sepsis. However, there was a significant increase in pneumonia, as defined per the CDC criteria, and in respiratory failure, in line with reported observations in visceral obesity [30]. Notwithstanding, neither was independently significant by multivariable analysis, suggesting a combination of mechanical, metabolic, and immunologic that may underpin postoperative pulmonary complications.

The spectrum of NAFLD observed, mostly mild, with NASH infrequently observed, suggests a sufficient hepatic reserve to withstand the stress of surgery and have little impact on complications. Liver function can be simply

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measured, as in this study, or it can be supplemented by tests of maximum liver function capacity (LiMAx) and indocyanine green plasma disappearance rate (PDR) [35, 36]. Elevated transaminases, in particular ALT, are a marker of liver injury. In a study of 215 patients after gastric cancer surgery, a two–fourfold increase in transaminases was observed on postoperative day 1, which returned to normal by day 5 to 7, and this was influenced by BMI, operation time, and intraoperative hepatic injury. [36]. In that study, 6% of patients had a five-fold increase in ALT levels on postoperative day 1, which compares with 10 and 11% in the HS + and HS- cohorts in this study, highlighting the lack of a specific marker of injury associated with HS. Moreover, bilirubin, a proxy of liver failure and applied in the SOFA score, was not differentially impacted by the presence of HS, with 93 and 96% having a bilirubin of 1.2 to 1.9 mg/dl (20–32 µmol/L), and 7 and 4% having levels above this in HS and non-HS cohorts, respectively.

This study has some limitations. First, the spectrum of NAFLD is predominantly on the mild/ moderate end of the spectrum, likely reflecting the reality of everyday practice, but inferences cannot be extended to severe NAFLD including NASH and liver fibrosis. Second, it is an observational study and not designed ab initio to categorize patients at baseline and study liver function and immune activity prospectively. We suggest that both of these aspects are explored in study designs informed by such baseline data.

In conclusion, at a time where international bodies focused on liver health, obesity, or diabetes are increasingly focused on NAFLD and mitigating its progression to NASH and fibrosis through surveillance and intervention, this profile of the disease in EAC provides for the first time data on its incidence and consequences in patients treated with curative intent [37]. Although NAFLD is prevalent in EAC patients proceeding to surgical interventions, the presence of hepatic steatosis does not predispose to added mortality or severity of complications, or worse cancer outcomes, and fatty liver with or without NASH does not significantly impact the stress response to esophageal cancer surgery.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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