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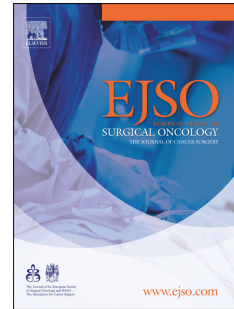
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Title Page
Conflicts Statement

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Abstract

Background: Hepatic Steatosis (HS) is as an independent risk factor for morbidity and mortality post-hepatectomy. Recent studies report significant correlation between chemotherapy (now frequently employed pre-hepatectomy for Colorectal liver metastases (CRLM)), HS and steatohepatitis. Furthermore, raised body mass index (BMI) predisposes to HS. However, no previous study has analysed the effect of HS on long-term survival.

Method: A retrospective analysis of a prospective consecutive cohort of 102 patients undergoing hepatectomy with 60 months follow-up data was performed. Resection specimens were examined histologically and the degree of steatosis graded accordingly. The data was compared to BMIs and other clinical characteristics. Statistical analyses included Log-Rank, Contingency, Logistic Regression and Fisher's Exact Tests.

Results: No detectable fatty change in 27 patients; 1 patient had cirrhosis; 57 had HS: 26 graded mild; 10 moderate, 21 severe and 17 not graded. 1 patient (BMI 29.5 kg/m²) had steatohepatitis but survived surgery. No significant difference in median survival between patients with and without HS (28.6 vs. 32.3 months, log rank $p>0.05$). Results were similar between patients with BMI <25 and BMI ≥ 25 (32.3 vs. 36.8 months, log rank $p>0.05$). Analyses of BMI against steatosis grade showed that patients with a higher BMI were at an increased risk of having a more severe HS (Logistic Regression, $p<0.01$; Fisher's Exact, $P<0.01$). Contingency analyses on the influence of diabetes, chemotherapy and increasing number of risk factors on the likelihood of obtaining HS were insignificant (Fisher's Exact, all $p>0.05$).

Conclusion: While patients with higher Body Mass Index values are at increased risk of having more severe hepatic steatosis, neither BMI nor hepatic steatosis significantly influences long-term survival. We conclude therefore that neither obesity nor hepatic steatosis has significant prognostic relevance on long-term survival of CRLM patients undergoing hepatectomy

Introduction

Hepatic steatosis is a histopathological state in which there is infiltration and excessive accumulation of lipids within hepatocytes ⁽¹⁾. The true incidence of hepatic steatosis remains unknown, however it has been reported that 34% of adult Americans have hepatic steatosis as detected by magnetic resonance spectroscopy⁽²⁾, increasing to 93% in severely obese subjects in one recent case series study ⁽³⁾.

The aetiology of hepatic steatosis is multi factorial and can be categorised into seven main categories (alcohol induced, primary, nutritional, metabolic, drug-induced, toxin induced and infectious) ⁽⁴⁾. With the current prevalence of obesity in the UK increasing, it is expected that these figures will be comparable to those obtained in studies conducted in the USA and hence it remains the single most concerning aetiological factor for development of non-alcoholic fatty liver disease (NAFLD).

The pathophysiology of NAFLD disease remains uncertain; however the most supported theory postulates that insulin resistance is the key mechanism in the pathogenesis of NAFLD. Hepatic steatosis results if free fatty acid synthesis exceeds triglyceride exportation. This may occur via a variety of mechanisms but is most commonly seen due to insulin resistance and increased hepatocellular free fatty acid neosynthesis from acetate following increased alcohol exposure. ⁽⁴⁻⁷⁾

Steatosis independently is considered reversible to some extent if the underlying aggravating factor is removed. However, if the steatosis is severe and accompanied by inflammation, it may develop into steatohepatitis. In 1998, Day CP *et al* ⁽⁸⁾ proposed the “two-hit” model of steatohepatitis, whereby the “first-hit” involves the progression to hepatic steatosis via the insulin resistance mechanism. Once developed, the majority (70-75%) will continue with steatosis, whilst 20-25% will progress to steatohepatitis- the “second-hit”. These authors suggest that steatosed hepatocytes act as a reservoir of hepato-toxic agents and are subsequently more susceptible to oxidative stress caused by endotoxin, cytokines and environmental toxins– the “second-hit”. As our population is becoming increasingly obese, and liver resection plays an ever-more important role in the management of metastatic colorectal cancer, this problem is now of even greater clinical relevance. The initiation of various

chemotherapy regimens for colorectal cancer may predispose to further oxidative stress causing progression of benign steatosis to steatohepatitis. Additionally, it is widely perceived that post-operatively fatty accumulation affects hepatocyte homeostasis and thus potentially impairs the recovery of steatotic livers, post liver resection (steatosis as RF in liver surg: ann surg 2007 aug). Hence, unsurprisingly it would appear logical that most clinicians would be hesitant to administer aggressive chemotherapy regimens in such patients for fear of intra-operative and post operative complications.

A recent report showed that the use of chemotherapy, and in particular Irinotecan, is associated with an increased risk of hepatic steatosis and steatohepatitis⁽⁹⁾. The authors concluded that steatohepatitis is associated with an increased mortality after hepatectomy and the use of Irinotecan should be carefully considered. Recent studies reported steatosis as an independent factor for morbidity and mortality rates in patients undergoing hepatectomy^(10, 11, 12). Considering the pathophysiology and risk factors for steatohepatitis, and in view of the evidence given above, it would appear that hepatic steatosis and obesity are relative contraindications in patients undergoing hepatectomy for CRLM. However, none of the studies above evaluated the effect of hepatic steatosis on the long-term survival of CRLM patients.

Therefore, the primary objective of this study is to evaluate the prognostic significance of hepatic steatosis, on a microscopic level, and increased body mass index (BMI) value in the long term survival of CRLM patients and to assess whether these patients should be offered surgery.

Methods

Clinical and follow-up data were retrieved retrospectively from a prospective consecutive cohort of 102 CRLM patients who underwent hepatectomy with intention-to-treat at Aintree University Hospital between April 2002 and October 2006. Data collected include patient demographics, survival data, relevant clinical characteristics (BMI values, alcohol consumption, medications, diabetes, triglyceride measurements and chemotherapy regimen) and operative details.

Two consultant pathologists with hepatobiliary expertise were blinded to the clinical data and independently determined the degree of hepatocellular steatosis in the resected specimens. The degree of steatosis was graded as defined by Kleiner *et al*²⁵ (Figure- 4^{25, 26}): no fatty change (<5%), mild (5 to <33%), moderate (33 to <66%) or severe (\geq 66%). Steatohepatitis and cirrhotic livers were also described. Steatosis data were then analysed against survival, Body Mass Index (BMI) and other relevant prognostic factors such as chemotherapy regimens.

Statistical analyses were performed using Fisher's exact test for nominal data, Log-rank test for survival data and logistic regression when analysing ordinal data with continuous data. A p-value of <0.05 was considered to be statistically significant. Deaths within 30 days are excluded from all analyses. JMP version 6 (SAS Institute, Cary, NC, USA), Microsoft Excel (Microsoft Office 2007) were used to perform the various statistical functions

Results

Patient demographics

Table 1 summarises the demographics and clinical pathological characteristics of the 102 patients in this study. There were 40 women and 62 men with median survivals of 28.7 months (95% CI 19.4-37.6) and 32.3 months (95% CI 23.8-50.2) respectively. The median age of the population was 64.9 years (IQR 57.3-70.5 years).

Clinicopathological Characteristics

In 16 patients the degree of steatosis was not graded, 1 was cirrhotic, 1 had steatohepatitis, 27 had no detectable fatty change, 57 were steatotic: 26 graded mild; 10 graded moderate; 21 graded severe. BMI value was irretrievable for 29 patients, 44 had normal BMI ($<25 \text{ kg/m}^2$), 29 had raised BMI ($>25 \text{ kg/m}^2$): 15 were overweight (BMI 25-29.9 kg/m^2), 10 were obese (30-34.9 kg/m^2) and 4 were severely obese ($\geq 35 \text{ kg/m}^2$).

Neoadjuvant chemotherapy was administered in 51 patients: 14 had Fluorouracil with Folinic Acid (5FU/FA), 15 had 5FU/FA with Oxaliplatin, 1 had 5FU/FA with Irinotecan, 1 had 5FU/FA with Irinotecan and Oxaliplatin, 20 had unspecified chemotherapy.

Correlation with Hepatic Steatosis

Contingency analyses on the correlation between neoadjuvant chemotherapy and hepatic steatosis, diabetes mellitus and hepatic steatosis, BMI value and steatosis and the extent of hepatectomy (major hepatectomy defined as resection of >3 segments) and steatosis are shown in *Figure 1*. Statistically, adjuvant chemotherapy, diabetes and extent of hepatectomy are not significantly correlated to hepatic steatosis (Fisher's exact $P>0.05$). However results showed that the presence of hepatic steatosis is more likely in patients with raised BMI ($>25 \text{ kg/m}^2$), than in patients with normal BMI (Fisher's Exact Test $P<0.01$). The significance is maintained when steatosis is further stratified by severity. It can be seen that the proportion of patients with raised BMI increases with increasing severity of steatosis (Pearson's Test and Likelihood Ratio, $P<0.05$) (*see Table 2*).

Figure 2 shows the Logistic Cumulative Probability Plot of BMI Value against steatosis grade. Here, the BMI value is plotted along the x axis and the probability of each steatosis grade on the y axis. Clearly, as the BMI value increases, the probability of a having a more severe degree of steatosis also increases (Whole model Tests $P < 0.001$).

Survival analyses

Subsequent analyses compared the difference in survival between patients stratified by BMI grades (*Figure 3a*), by the degree of hepatic steatosis (*figure 3b*) and by the extent of hepatectomy. Statistically there is no significant difference in survival between patients with different BMI grades, the degrees of hepatic steatosis or the extent of hepatectomy (Log Rank, $p > 0.05$). Similar results were found on subgroup analyses where patients were stratified according to BMI cut-off value of 25 kg/m^2 (Log Rank, $P > 0.05$) and where patients were stratified according to the presence of hepatic steatosis (Log Rank, $P > 0.05$). Moreover, survival analysis on the patients who had major hepatectomy stratified by the steatosis status yield insignificant results (Log Rank $P > 0.05$) (*see Table 3*).

In Summary, neither hepatic steatosis nor BMI values significantly influences the long term survival of patients with CRLM who underwent hepatectomy.

Discussion

The effect of hepatic steatosis on short term post operative outcomes has been widely investigated⁽⁹⁻¹³⁾. The general underlying theme in these studies seemed to indicate that patients with steatosis were susceptible to a more arduous post operative course with respect to complication rates and short term morbidity. It was postulated that steatosis may have interfered with post operative hepatic regeneration and hence would result in an adverse outcome for patients undergoing partial hepatectomy. Resultantly, this has led to concerns that moderate to severe steatosis are relative contraindications to hepatectomy, and that surgeons should avoid the temptation to resect aggressively in this scenario.

Recent studies have challenged the theory that obese patients predispose to post operative complications or mortality⁽¹⁴⁾. Counter to these observations, there is only one study in the literature that reported that steatosis did not affect 60 day mortality rates⁽¹⁵⁾.

To our knowledge, our study is the first to analyse the long-term relationship between hepatic steatosis, raised BMI and survival of patients with CRLM undergoing hepatectomy. Whilst we report that patients with higher BMI values are at increased risk of developing more severe hepatic steatosis, it must be noted that neither BMI nor hepatic steatosis is an independent prognostic factor of long-term survival after resection of CRLM.

This observation could imply that hepatic steatosis does not correlate with impaired hepatic regeneration. This view is shared by others who examined hepatic regeneration following hepatectomy, and found that though alcoholic steatohepatitis and NAFLD shared similar hepatic histology, liver regeneration was not impaired in NAFLD⁽¹⁶⁾.

Secondary analyses compared the distribution of hepatic steatosis amongst patients with a positive history of diabetes mellitus or chemotherapy. Results from both analyses suggest that statistically, the likelihood of steatosis in patients with DM or patients who had chemotherapy is insignificantly different to those without. It is also

reported that increasing number of risk factors in a patient does not have a significant bearing on the risk of developing hepatic steatosis. This is most likely due to the multifactorial nature of the pathogenesis in hepatic steatosis and suggests that each singular factor does not have a synergistic effect when combined with another factor. This is somewhat surprising as one would expect patients with DM to demonstrate increased levels of steatosis secondary to them having the metabolic syndrome. Of more clinical relevance though is the fact that pre-operative chemotherapy did not appear to impinge upon development of steatosis, at the levels used.

Perhaps the most interesting finding in this study is that for a given BMI value, the Logistic Cumulative Probability Plot may be used to estimate the likelihood of the degree of hepatic steatosis in a patient. This is particularly important because although our study reports that hepatic steatosis does not influence the long-term post-operative mortality, there is no doubt that steatosis and obesity are associated with increased postoperative morbidity. The development and improvement of such a model may improve the post-operative management plan for such patients

Conclusion

In light of the results already discussed, we conclude that the long-term survival of patients with colorectal liver metastases undergoing curative hepatic surgery is not influenced by their Body Mass Index value or the degree of hepatic steatosis. Subsequently therefore, they are not contraindicated for hepatic surgery.

Furthermore, a clinical history of diabetes or chemotherapy treatment does not independently predict the presence of hepatic steatosis. In addition, the presence of an increasing number of risk factors does not have significant bearings on the likelihood or degree of hepatic steatosis.

Conflict of interest

The authors state that they have no conflict of interest.

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Table 1- Summary of demographics, clinical and histological data stratified by sex			
Variable	Female (n)	Male (n)	Combined (n)
No. of Patients	40	62	102
Age			
Median	67 yrs	63 yrs	65 yrs
Inter Quartile Range	57-73 yrs	58-70yrs	57-71 yrs
Major (>50%) Resection	17	37	54
Body Mass Index			
Median			24.9kg/m ²
Acceptable (<25 kg/m ²)	20	24	44
Overweight (25-29.9 kg/m ²)	8	7	15
Obese (30-34.9 kg/m ²)	0	10	10
Severely Obese (≥35 kg/m ²)	2	2	4
Degree of Steatosis			
Indeterminate	7	9	17
Cirrhosis, no fatty change		1	1
Steatohepatitis	1	0	1
No Fatty Change	10	17	27
Mild	8	18	26
Moderate	4	6	10
Severe	10	11	21
Survival			
Median Survival	28.7 Months	32.3 Months	30.2 Months
Neoadjuvant Chemotherapy (n=79)	31	48	79
Irretrievable data	9	14	23
Yes	19	32	51
No	14	14	28
5FU/FA	5	9	14
5FU/FA + Oxaliplatin	4	11	15
5FU/FA + Oxaliplatin + Irinotecan	0	1	1
5FU/FA + Irinotecan	1	0	1
Unspecified Chemotherapy	7	13	20
History of Diabetes Mellitus	4	6	10
Statin treatment	10	7	17

Clinical Characteristic	n	Statistical Test	R ²	p-value
BMI (continuous)	61	Whole Model Test	0.089	0.0001
BMI (<25 Vs ≥25 kg/m ²)	61	Fisher's Exact	0.088	<0.001
	61	Likelihood Ratio	0.115	0.026
	61	Pearson	0.115	0.032
Diabetes Mellitus	69	Fisher's Exact	0.002	N.S.
Chemotherapy	66	Fisher's Exact	0.002	N.S.
Hepatectomy (major Vs Minor)	79	Fisher's Exact	0.002	N.S.

n.s. not significant p>0.05

Parameter	n	Median Survival (months)	95% CI		Log - Rank p-value
			Lower	Upper	
BMI (n=73)					
<25 kg/m ²	44	32.3	19.5	50.2	N.S.
≥25 kg/m ²	29	36.8	23.8	66.6	
BMI Graded (n=73)					
Acceptable	44	32.3	19.5	50.2	N.S.
Overweight	15	41.5	16.1	66.6	
Obese	10	27.2	12.5	NR	
Severely Obese	4	N/A	11.7	NR	
Steatosis (n=84)					
No Steatosis	27	32.3	22.6	62.0	N.S.
Steatosis	57	28.6	21.7	41.5	
Steatosis Graded (n=84)					
No fatty change	27	32.3	22.6	62.0	N.S.
Mild	26	37.5	21.1	NR	
Moderate	10	23.3	8.2	NR	
Severe	21	28.6	15.6	41.5	
Hepatectomy (n=96)					
Major hepatectomy	61	29.8	23.3	42.4	N.S.
Minor hepatectomy	35	30.3	19.4	56.8	
Major Hepatectomy (n=49)					
No Steatosis	17	45.6	17.1	62.1	N.S.
Steatosis	32	27.2	19.5	37.5	

NR= Limit not reached; N/A = unable to calculate due to insufficient data; N.S.= not significant p>0.05

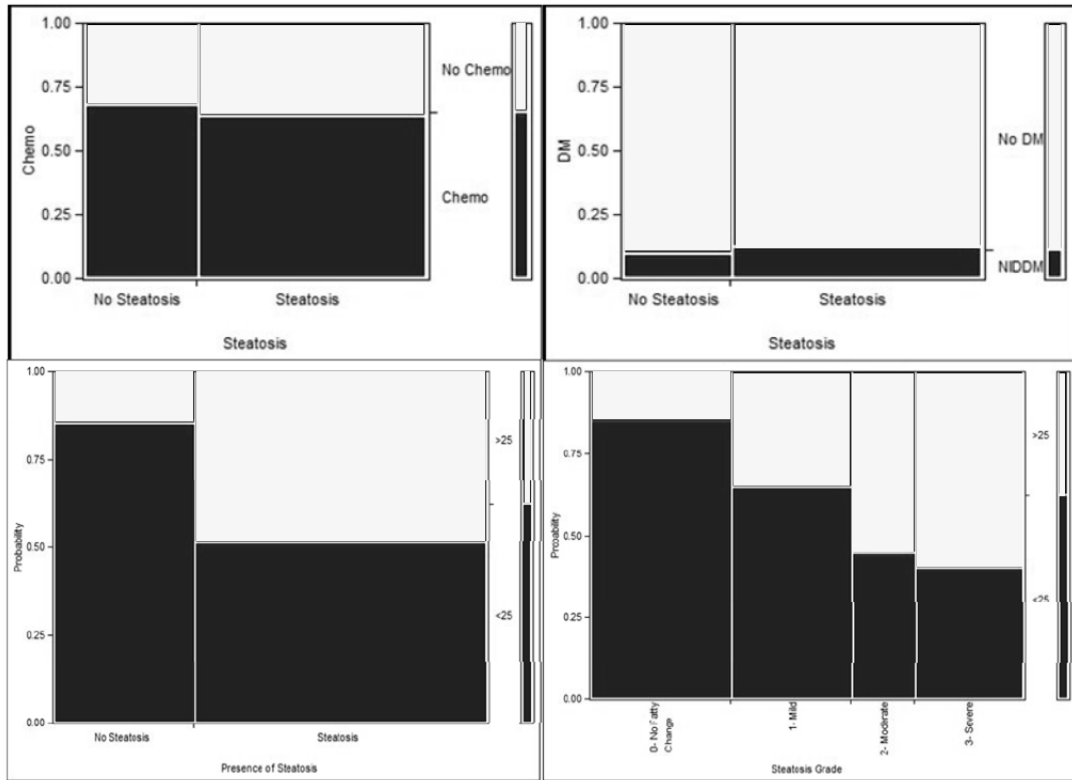


Figure 1- Contingency Analyses of neoadjuvant chemotherapy, DM and BMI against Steatosis

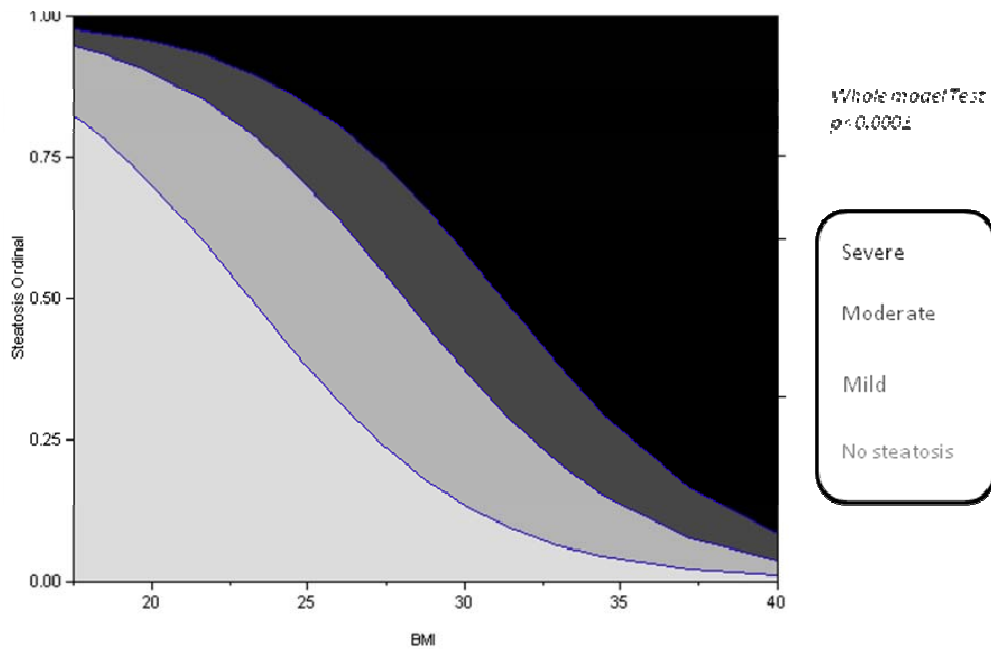


Figure 2- Logistic Cumulative Probability Plot of BMI value against steatosis grades

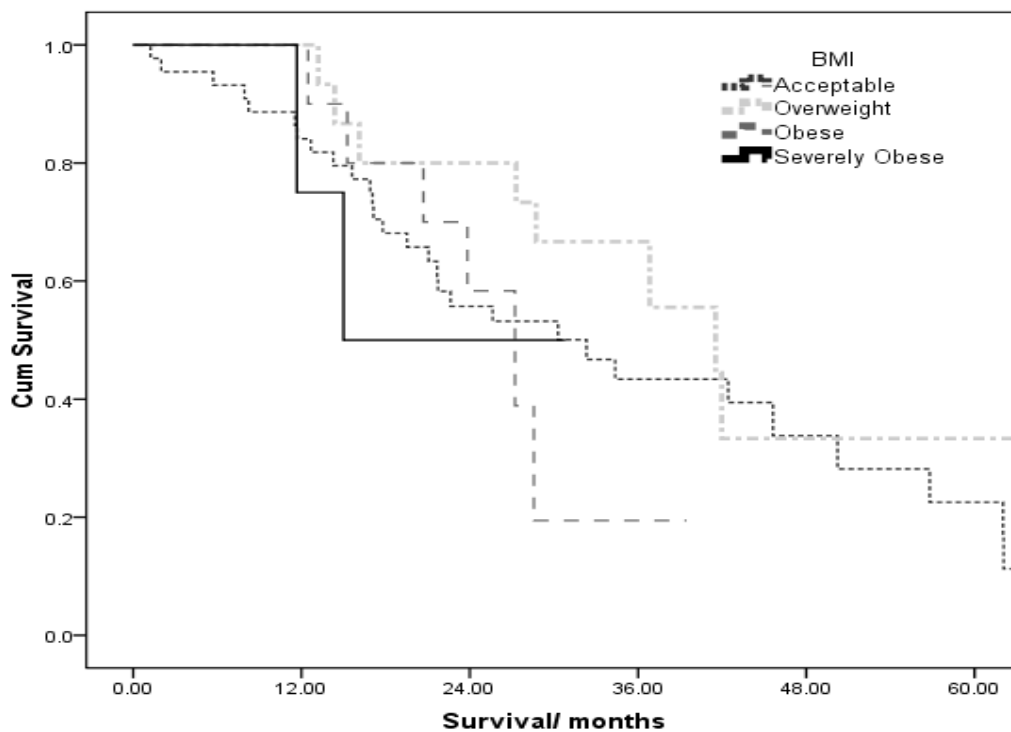


Figure 3a- Kaplan-Meier Survival Curve for BMI grades

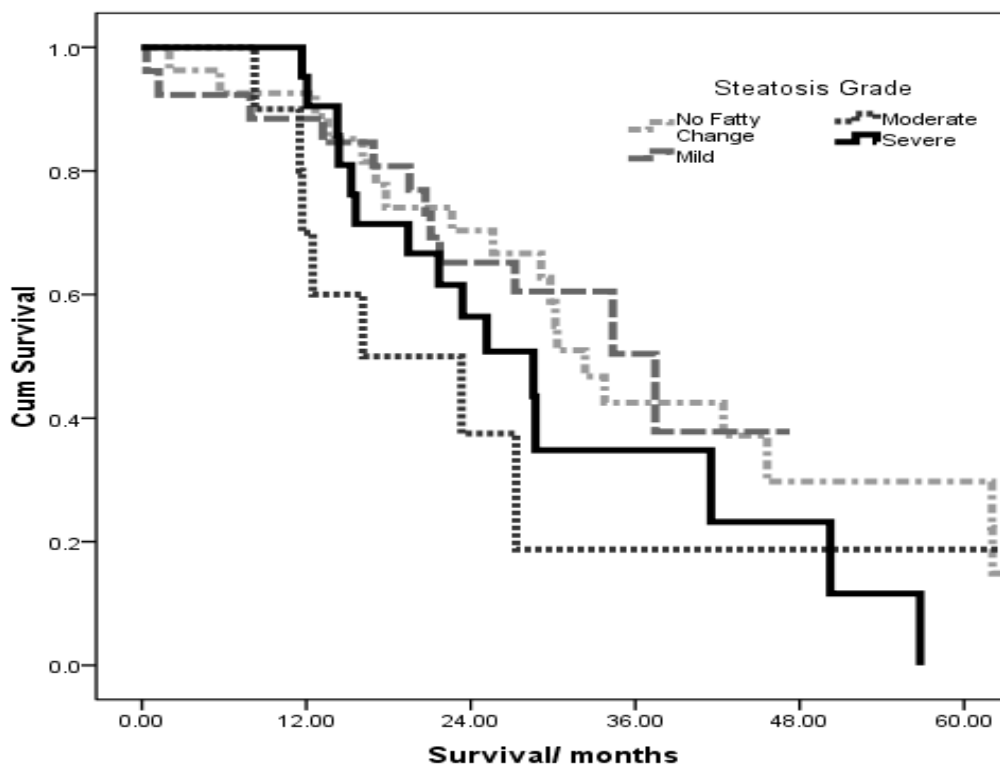


Figure 3b- Kaplan-Meier Survival Curve for steatosis grades