Title Page

The additive impact of pre-liver transplant metabolic factors on survival post-liver transplant.

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Background: Diabetes at time of liver transplantation is associated with reduced post-transplant survival. We aimed to assess whether additional metabolic conditions such as obesity or hypertension, had additive prognostic impact on post-transplantation survival.

Methods: A multi-center cohort study of 617 adult subjects undergoing liver transplantation between 2003-2009. Dry-body mass index was calculated following adjustment for ascites.

Results: After a median follow-up of 5.8 years (range 0-10.5), 112 (18.2%) patients died. Diabetes was associated with reduced post-transplant survival (hazard ratio 1.89, 95%CI 1.25-2.86, p=0.003), whereas obesity, hypertension, dyslipidemia and the metabolic syndrome itself, were not (p>0.3 for all). Patients with concomitant diabetes and obesity had lower survival (aHR 2.40, 95%CI 1.32-4.38, p=0.004), whereas obese non-diabetic patients or diabetic non-obese patients had similar survival compared to non-diabetic, non-obese individuals. The presence of hypertension or dyslipidemia did not impact on survival in patients with diabetes (p>0.1 for both). Obese diabetic patients had longer intensive care and hospital stays than non-obese diabetic or obese, non-diabetic patients (p<0.05). The impact of concomitant obesity and diabetes on survival was greater in subjects aged 50+years (52.6% five-year survival, aHR 3.04, 95%CI 1.54-5.98) or those

transplanted with hepatocellular carcinoma (HCC) (34.1% five-year survival, aHR 3.35, 95%CI 1.31-5.57). Diabetes without obesity was not associated with an increased mortality rate in these sub-groups.

Conclusions: Concomitant diabetes and obesity but not each condition in the absence of the other, is associated with reduced post-liver transplant survival. The impact of diabetes and obesity is greater in older patients and those with HCC.

Keywords: Liver transplantation , Obesity , Diabetes

Introduction

Obesity, diabetes and other metabolic conditions such as hypertension and dyslipidemia are highly prevalent risk factors for death in the general world-wide population (1, 2). Consequently, metabolic disease is commonly encountered among subjects being considered for orthotopic liver transplantation (OLT). Careful evaluation of metabolic factors is necessary due to their potential impact upon patient and graft survival post-transplant and therefore impact upon suitability for transplantation.

Pre-transplant diabetes has been reported from single center studies as being associated with either reduced post-OLT survival, or having no impact on survival.(3-6) However, the most recent analysis of the Scientific Registry of Transplant Recipients (SRTR) database demonstrated a history of type 2 diabetes was associated with a 20% increase in mortality risk post-transplant.(7) Earlier studies utilizing the SRTR database have demonstrated diabetes to impact survival only if insulin requiring or in subjects with underlying chronic hepatitis C infection.(8,

9) Other metabolic conditions including obesity and hypertension frequently co-exist in patients with diabetes, however the additive effect of these factors on survival is not well-defined.

The impact of pre-operative obesity on survival following liver transplantation is controversial with retrospective cohort studies demonstrating conflicting results.(10-13) This may in part be due the confounding impact of ascites which may increase body weight.(14) Despite this, class 3 obesity (body mass index [BMI] ≥40 kg/m^2) is considered a relative contra-indication to OLT.(15)

The inconsistent impact of obesity on post-OLT survival may be due to the interacting and potentially additive effects of other co-morbid metabolic conditions such as diabetes, hypertension and dyslipidemia. A few single center studies with relatively short follow-up have examined the effect of multiple metabolic co-morbidities, however have yielded inconsistent results.(16) Notably, patients with nonalcoholic steatohepatitis (NASH) related cirrhosis who have a high rate of metabolic disease are less likely to be listed for transplantation due to co-morbid conditions.(17) Thus, determination of the additive prognostic significance of multiple metabolic co-morbidities is clearly needed to aid the selection and denial of liver transplant recipients and guide utilization of resources. Therefore, we performed a multi-center cohort study to determine the impact of pre-transplant metabolic conditions upon patient survival and complications post-liver transplantation.

Materials and Methods

Overview

The study cohort consisted of patients who underwent liver transplantation in Australia between 2003-2009, thus allowing a median follow-up of five years. Subjects were identified from the Australian and New Zealand Liver Transplant Registry (ANZLTR). Baseline and outcome data were obtained from the prospectively collected ANZLTR database. In addition, investigators at each adult liver transplantation unit in Australia (Sir Charles Gairdner Hospital, Perth; The Austin Hospital, Melbourne; Princess Alexandria Hospital, Brisbane; Flinders Medical Centre, Adelaide; Royal Prince Alfred Hospital, Sydney) provided additional baseline and follow-up data when these were not available through the ANZLTR database. Subjects from New Zealand were not included as they had previously been analysed.(5) Ethics approval was obtained from the Sir Charles Gairdner Hospital Human Ethics committee. A waiver of consent was granted according to the principals of the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research.

Study Population

Adult subjects were included if they underwent OLT performed between 1/1/2003-31/12/2009 in Australia. Exclusion criteria included, living related transplant, second (or subsequent) transplant, multi-organ transplant, transplantation for fulminant liver failure or for hepatocellular carcinoma (HCC) outside UCSF criteria.(18)

A total of 840 subjects were identified from the ANZLTR database as fulfilling the inclusion and exclusion criteria. Subjects were further excluded due to lack of information regarding diabetes or body weight (n=153), loss to follow-up (n=65) or

prior liver or kidney transplant (n=5), leaving a total of 617 subject in the study.

Data Variables

Variables collected at time of transplant included; baseline demographics (age, gender, ethnicity); history of metabolic disease (diabetes, hypertension, dyslipidemia); *dry* body weight (adjusted for ascites by liters of ascites removed at time of transplant or previous therapeutic paracentesis); history of coronary artery disease or prior abdominal surgery excluding prior appendicectomy and hernia repair, liver disease details (aetiology, presence of HCC, Childs-Pugh score); pre-transplant laboratory results (liver function tests, creatinine, INR, glucose, lipids, ferritin, MELD); requirement for intensive care unit (ICU) admission or dialysis at time of transplant; donor variables (age, gender, height, weight); cold and warm ischemic time, and units of blood products. Lipid variables were taken from time of activation if not available at time of transplant. Body mass index was calculated using dry body weight. Thirty-eight subjects had body weight recorded but not height, meaning BMI was not able to be calculated in these subjects. Among these subjects, those with a dry weight of less than 70kg or greater than 120kg were classified as non-obese or obese in the categorical analysis. The metabolic syndrome (MetS) was defined as three of more of the following five factors; obesity (dry BMI≥30kg/m^2), clinical diagnosis of diabetes, clinical diagnosis of hypertension, low HDL-cholesterol (<40mg/dl males, <50md/dl females) or hypertriglyceridemia (≥150 mg/dl or lipid lowering therapy).(19) Follow-up data included; duration of ICU stay and hospitalization, last recorded creatinine, requirement for dialysis and graft and patient survival.

Outcomes

The primary outcome of the study was overall patient survival. Secondary outcomes were graft survival, intra-operative units of blood transfused, duration of ICU stay and hospitalization.

Statistical Analysis

Baseline descriptive variables are presented as median and inter-quartile range (IQR) and number (percentage). Survival outcomes including patient and graft survival were assessed using Kaplan-Meier analysis. The influence of baseline pre-transplant metabolic and other parameters upon patient and graft survival were assessed using log-rank testing and cox-proportional hazards. A multi-variate prognostic algorithm of prognostic metabolic variables was developed using Cox-proportional hazard modeling with appropriate adjustment of other prognostic variables. Results are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Analysis was performed using SPSS 22.0.0.

Results

Cohort Characteristics

The cohort consisted of 617 subjects whose average (standard deviation) age was 51 (9.2) years. Subject and donor organ details are outlined in Table 1. Subjects were more likely to be male and Caucasian. The median MELD score unadjusted for HCC was 15. Chronic hepatitis C infection was the commonest cause of liver disease whereas 21% of individuals had HCC. The average donor age was 42 (16) years and the median (IQR) BMI and 25.4 (23.0-28.0) kg/m^2 respectively.

Pre-Transplant Metabolic Factors

Diabetes

A significant proportion of the cohort had diabetes at time of transplantation (113/617, 18.3%). The majority had type 2 (104/113) with only nine patients having type 1 diabetes.

Body Weight and Obesity

Mean dry body weight was significantly lower after adjustment for ascites (78.0 kg vs. 79.8 kg, $p<0.001$). The prevalence of pre-OLT overweight (BMI 25-29.9 kg/m^2), grade I obesity (BMI 30-34.9 kg/m^2) and grade II obesity (BMI 35-39.9 kg/m^2) was 36.1%, 16.2% and 4.7% respectively. Only five subjects (0.8%) had grade III morbid obesity (BMI>40 kg/m^2). Two percent of subjects were underweight (BMI<18 kg/m^2).

Hypertension, Dyslipidemia and the Metabolic Syndrome

In contrast to diabetes and obesity, the prevalence of hypertension (9.7%) was low. The prevalence of hypertriglyceridemia and low HDL-cholesterol levels was 9.2% and 22.7% respectively among the 409 individuals who had a complete lipid profile available. Twenty-seven subjects were on anti-hypertensive medication and 24 subjects were on lipid-lowering therapy. A total of 31/402 (5.0%) individuals fulfilled criteria for the MetS.

Overall and Graft Survival

Over a median follow-up of 5.8 years (range 0-10.5), 112 (18.2%) patients died. Overall one and five year survival rates were 92.6% and 83.2% respectively. One and five year graft survival rates were 91.7% and 82.4% respectively. The

commonest causes of death were liver related causes including recurrent HCC (n=43), followed by non-HCC malignancy (n=21), infections (n=14), intra-operative/ cardiovascular causes (n=13). The cause of death was unknown in four individuals.

Impact of Metabolic Disease on Overall and Graft Survival

Diabetes

Diabetes was associated with reduced one and five overall survival rates at one year (89.4% vs. 94.4%) and five years (75.9% vs. 88.2%, p=0.003) with a hazard ratio of 1.86 (95% CI 1.23-2.81). Similarly, graft survival was lower at one and five years in subjects with pre-OLT diabetes than those without (87.6% vs. 92.4% and 73.2% vs. 84.5% respectively, p=0.006).

Obesity

Dry-BMI was not associated with overall or graft survival (p=0.40 and 0.68 respectively, cox-regression). Categories of dry-BMI were similarly not associated with overall or graft survival (p=0.42 and p=0.49 respectively, log-rank test).

Dyslipidemia and Hypertension

A pre-OLT history of hyperlipidemia or hypertension were not associated with poorer overall survival (p>0.3 for both) or worse graft survival (p>0.4 for both).

Metabolic Syndrome

A pre-OLT diagnosis of MetS had no impact on overall survival (p=0.33, log-rank test) or graft survival (p=0.16, log-rank test).

Predictors of Post-OLT Survival

Dry-BMI categories and other metabolic factors including hypertension, low-HDL cholesterol, hypertriglyceridemia and MetS were not associated with survival on univariate cox regression analysis (Table 2). Patient factors at time of transplant which were associated with overall post-OLT survival included age, diabetes, serum creatinine level, requirement for dialysis, diagnosis of HCC and hepatitis C virus (HCV) infection. Donor factors that were significant associated with overall post-OLT survival were age and BMI. On multivariate analysis including donor and recipient factors, diabetes, serum creatinine and a diagnosis of HCC and HCV remained significantly inversely associated with overall survival.

Additive Impact of Obesity and Diabetes on Overall Survival

Patients with concomitant diabetes and obesity had lower survival (aHR 2.40, 95% CI 1.32-4.38, p=0.004, Figure 1, Table 3) compared to non-diabetic, non-obese individuals, whereas survival was not different in obese non-diabetic patients or diabetic non-obese patients (p>0.2 for both). Obese diabetics had the poorest overall survival with a five-year survival rate of 65.6% compared to non-obese diabetics (80.3%), obese non-diabetics (89.8%) and non-obese non-diabetics (87.7%). Deaths that were due to recurrent HCC or infection were numerically but not statistically more common in subjects with concomitant diabetes and obesity (Table 4). The presence of hypertension or dyslipidemia did not impact on survival in patients with diabetes (p>0.1 for all, data not shown).

Impact of Obesity and Diabetes According to Age, HCV Status and HCC.

As age, diagnosis of HCV and diagnosis of HCC were independent predictors of survival (Table 1), the potential additive impact of obesity and diabetes were examined after stratification by these factors (Table 5).

Among individuals aged less than 50 years, diabetes and obesity had no independent impact on survival (p=0.9, log-rank test, Figure 2A). In contrast, subjects aged 50 or older at time of transplant had a significantly poorer five-year survival if they were obese and diabetic compared to those who were non-diabetic and non-obese (Figure 2B, p=0.001). Five-year survival in these individuals approached 50% and they were more than 3 fold more likely to die compared to non-obese, non-diabetic individuals after adjustment for baseline creatinine and diagnosis of HCV and HCC (Table 5).

Among subjects without HCV infection, the combination of obesity and diabetes was associated with a significantly poorer five-year survival (Figure 3A, p<0.001, log-rank test). After adjustment for age, diagnosis of HCC and baseline creatinine, HCV negative individuals who were obese and diabetic were four fold more likely to die than those who were non-obese and non-diabetic (Table 5). Unexpectedly, obesity and diabetes had no impact on survival among subjects with HCV (p=0.98, log-rank test, Figure 3B).

Among subjects who did not have HCC at time of transplant, obesity and diabetes were not associated with poorer survival (p=0.16, log rank testing, Figure 4A). Among those with HCC at time of transplant, concomitant diabetes and obesity was associated with poorer overall survival (p=0.01, log-rank test, Figure 4B). In these individuals, five year survival was less than 50% and the hazard ratio was 3.4

(95% CI 1.31-8.57, p=0.01) compared to non-obese, non-diabetic individuals (Table 5).

Duration of Intensive Care and Hospital Stay

Concomitant diabetes and obesity was associated with greater likelihood of a complicated admission with a longer median intensive care stay (4 days) and median duration of hospitalization (22 days) (Supplemental Table 1). The median amount of red blood cells transfused during the operation was not different according to the presence of obesity or diabetes.

Discussion

Many investigators have examined the association between pre-transplant diabetes or obesity on post-transplant outcomes.(3, 4, 7, 9-14, 16, 20-23) These studies have examined the independent effects of obesity and diabetes, however given the frequency with which they co-exist, it is surprising there is a lack of knowledge regarding the additive effects of concomitant metabolic factors on outcomes. This large multi-center study with long-term follow-up, examined the additive impact of pre-transplant metabolic factors on survival post-liver transplantation. We found that; 1) diabetes but not other metabolic factors were associated with reduced patient and graft survival post-liver transplant; 2) the greatest reduction in survival was observed in the setting of concomitant diabetes and obesity, whereas hypertension and dyslipidemia did not modify the risk of diabetes; 3) subjects with concomitant diabetes and obesity had greater peri-operative morbidity with longer ICU stay and

hospitalizations and; 4) the adverse impact of the combination of obesity and diabetes was significantly greater in certain patient populations, namely those aged more than 50 years, those without HCV infection and those with HCC.

Studies examining the impact of pre-OLT obesity on survival following transplantation have been conflicting; a large UNOS based study demonstrated poorer overall survival in subjects with a BMI>35 kg/m^2, however subsequent studies that have adjusted for potential confounding factors such as ascites, have not found a difference in overall survival between BMI categories.(12-14) Our study adds weight to these previous findings, as we did not detect a survival hazard of obesity or morbid obesity calculated using ascites adjusted dry-weight. Our cohort however, had very few grade III obese (BMI>40) individuals and was thus not able to examine survival in this group.

Notably, these previous studies did not examine the additive impact of on other metabolic factors. Among our cohort of patients, those who had concomitant obesity and diabetes were more likely to have longer ICU and hospital stays, but were also had significantly poorer overall survival. Obesity has been associated with poorer survival in patients with type 2 diabetes in the general population(24), however the hazard associated with obesity is significantly magnified in the post-transplantation population. Survival was particularly poor among individuals who were 50 years or older or who had a diagnosis of HCC with a five year survival approaching 30% in the latter group. Obesity is associated with increased HCC recurrence post-OLT, perhaps due to greater circulating levels of potentially oncogenic growth factors, whereas diabetes has been demonstrated to be a risk

factor for reduced post-transplant survival in patients with HCC.(20, 25) Given the poor prognosis in this subgroup, strategies to modify the risk of post-transplant death are required. Metformin has *in vitro* anti-neoplastic effects and has been proposed as a first-line hypoglycemic agent post-transplant, however clinical data is still absent.(26, 27) Unfortunately information on baseline tumor characteristics was not available, limiting our ability to assess the impact of factors such as tumor size or vascular invasion on outcomes.

No significant difference in cardiovascular mortality was found among patients with diabetes and obesity compared to those without. This may be due to lack of power to determine an association, noting that larger studies have found diabetes to be a risk factor for cardiovascular death.(7) Significantly, the proportion of deaths due to cardiovascular disease in our entire cohort was only 3.6% which is lower than reported in the SRTR (10% at five years)(28). Thus it may be that patients with obesity and diabetes are evaluated for additional adverse cardiovascular risk factors and disease more stringently and had been excluded from transplantation in the Australian cohort. Alternatively, it may also reflect more aggressive cardiovascular risk management among patients with diabetes and obesity, allowing other causes of death for which diabetes is also a risk factor (eg liver disease, malignancy and infection) to become dominant causes of death.

Two single center studies from Tennesee and New Zealand respectively examined the effect of multiple metabolic co-morbidities on post-OLT survival.(5, 16) Although post-operative events were more frequent and hospitalization significantly longer in subjects with diabetes and concomitant obesity in the New Zealand cohort,

neither study found any impact on survival, likely related to relatively small numbers and limited follow-up. In contrast, in a cohort of 98 subjects from Pittsburg, the combination of age >60 years, diabetes, BMI >30 kg/m^2 and hypertension was associated with a 50% 1 year survival (29). We found the combination of age>50, diabetes and obesity to be associated with a poorer overall survival with no effect of hypertension or increasing the age threshold to 60 years (data not shown). Nevertheless, patients with the combination of metabolic factors and older age in our cohort had significantly better survival (53% at five years), than the Pittsburg cohort. Notably survival between those with and without the metabolic syndrome was equivalent in the Pittsburg series suggesting age rather than metabolic disease may have had a dominant impact on survival.

Recently, the impact of diabetes and obesity was examined using data from the UNOS registry.(30) Survival was reduced in patients with diabetes, however was not different among diabetics who were obese compared to those who were non-obese. Other risk factors for post-transplant mortality were similar to our cohort (HCC, HCV infection). In this study, obesity was not classified according to dry body weight and the prevalence of obesity was higher compared to our cohort (33% vs. 22%). Different ethnic compositions may also account for some of the differences observed with one in five individuals transplanted in the US being Black or Hispanic which are rare in Australia.

Our study has a number of strengths, being a large multi-center study with significant follow-up and thus adequate power to detect prognostic significance of metabolic factors on survival. The potential confounding impact of ascites on BMI

was taken into account. Furthermore, we were able to examine sub-populations where the impact of metabolic factors were particularly significant. A significant limitation of our study, as with all studies examining post-transplant survival, is that the findings are inherently biased towards patients who survived assessment and waiting for a transplant. In addition, we were not able to examine the influence of severity or duration of metabolic factors or the use of medications

In summary, we found obesity exacerbates the risk of death post-liver transplantation when associated with a pre-OLT diagnosis of diabetes. The long-term survival figures of obese diabetic patient subgroups with HCC or age>50 years is sobering and should necessitate a close evaluation during transplant assessment. Incorporation of pre-transplant diabetes should be considered within guidelines for the evaluation of patients for liver transplantation.(15)

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Figure Legends

Figure 1. Pre-transplant obesity increases the impact of diabetes on survival post-liver transplantation. Overall survival was significantly worse (p=0.004, log-rank test) in diabetics who were obese compared to non-obese diabetics and non-diabetics in 655 individuals followed for a median of 6.6 years.

Figures 2A and B. The impact of pre-transplant obesity and diabetes on overall post-transplant survival is modified by age. Concomitant pre-transplant obesity and diabetes is associated with poorer survival in those greater than 50 years (p=0.001, log-rank test) compared to those less than 50 (p=0.9, log-rank test).

Figures 3A and B. The impact of pre-transplant obesity and diabetes on overall post-transplant survival is modified by hepatitis C infection. Concomitant pre-transplant obesity and diabetes is associated with poorer survival in those without HCV infection (p<0.001, log-rank test) compared to those with HCV infection (p=0.9, log-rank test).

Figures 4A and B. The impact of pre-transplant obesity and diabetes on overall post-transplant survival is modified by a diagnosis of HCC at time of transplant. Concomitant pre-transplant obesity and diabetes is associated with poorer survival in those with HCC at time of transplantation (p=0.01) compared to those without (p=0.16).

Figure 1. Overall Survival in Obese and Diabetic Patients

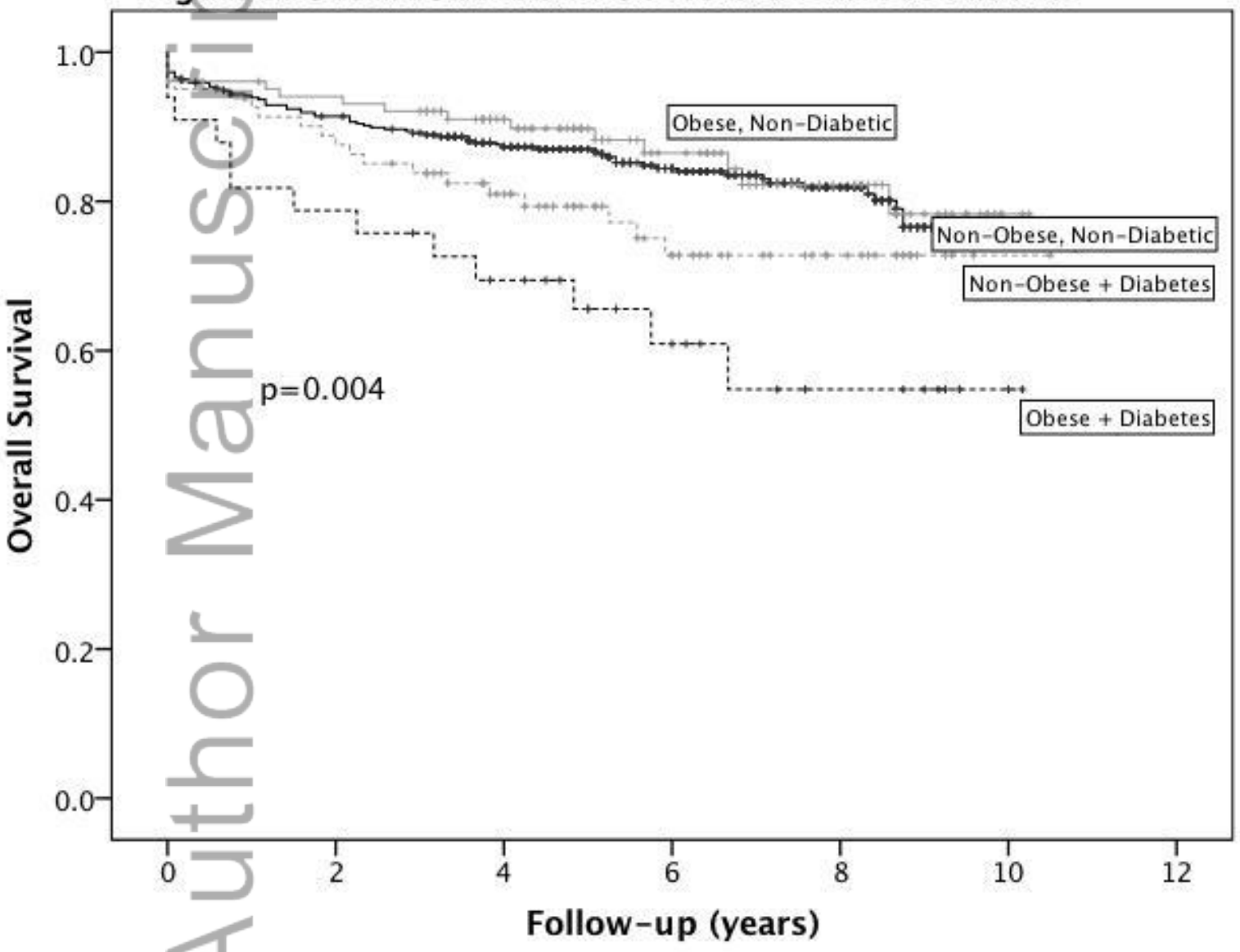

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Figure 2A. Overall Survival in Obese and Diabetic Pateints <50yrs

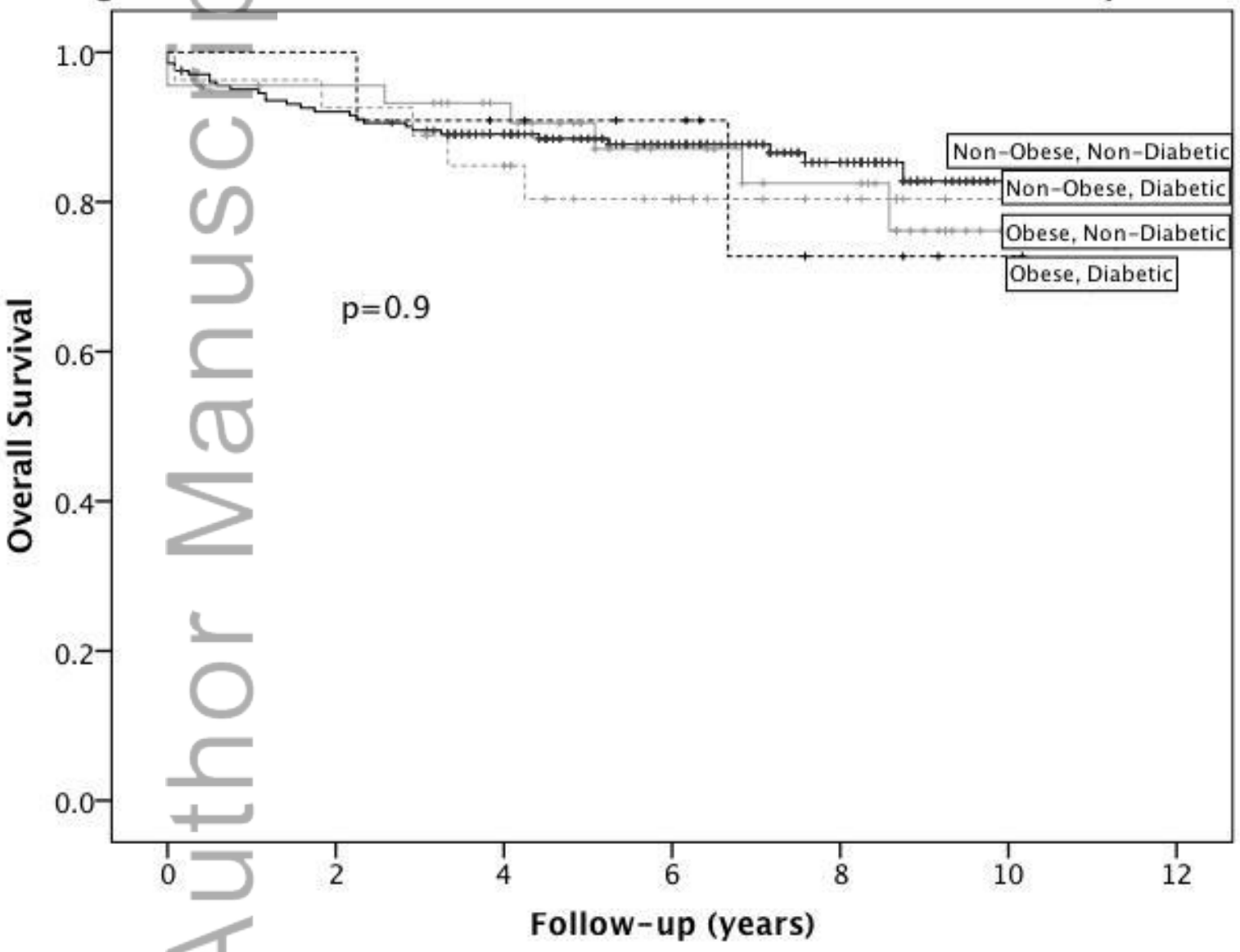

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Figure 2B. Overall Survival in Obese and Diabetic Patients >=50yrs

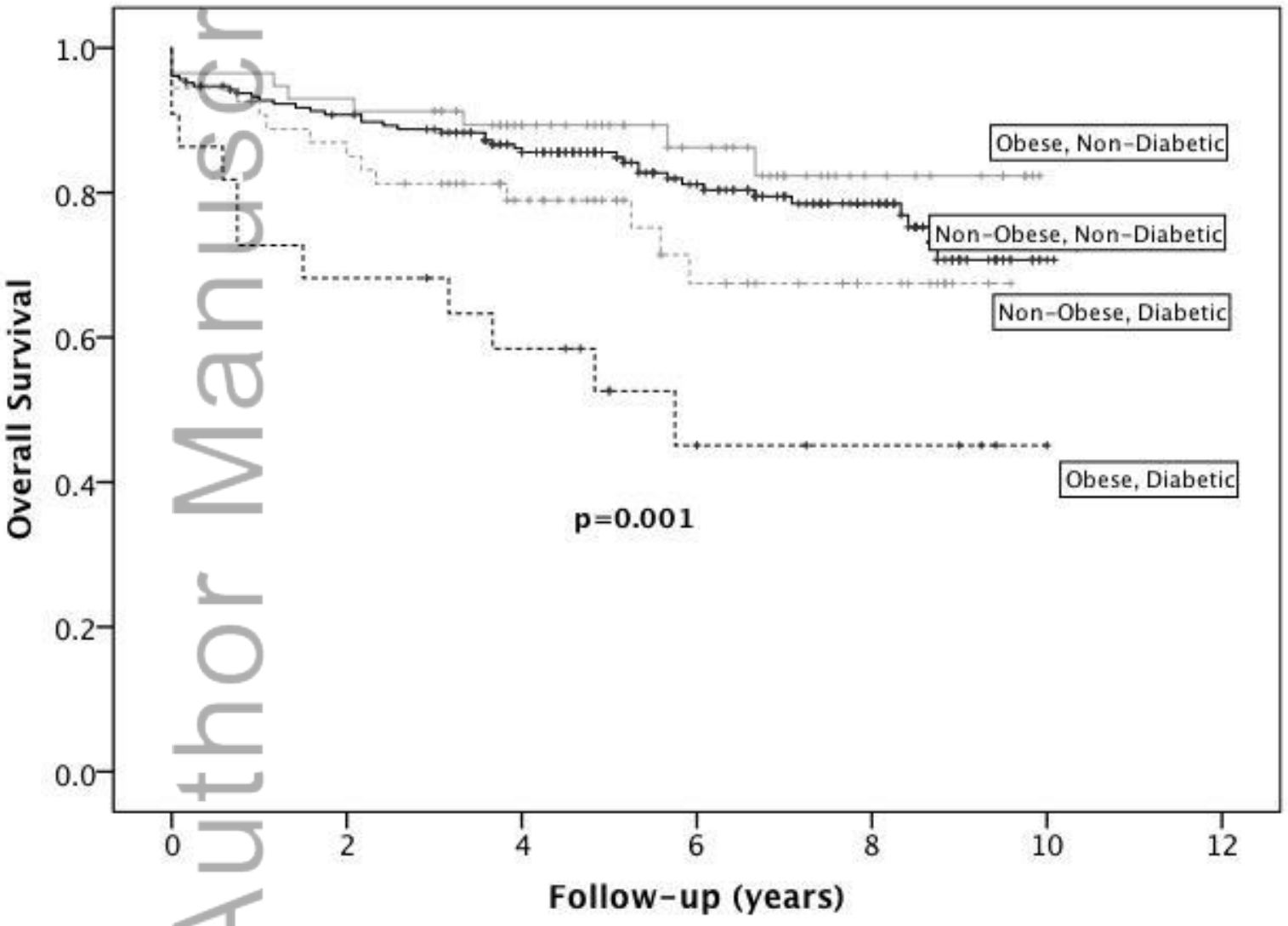

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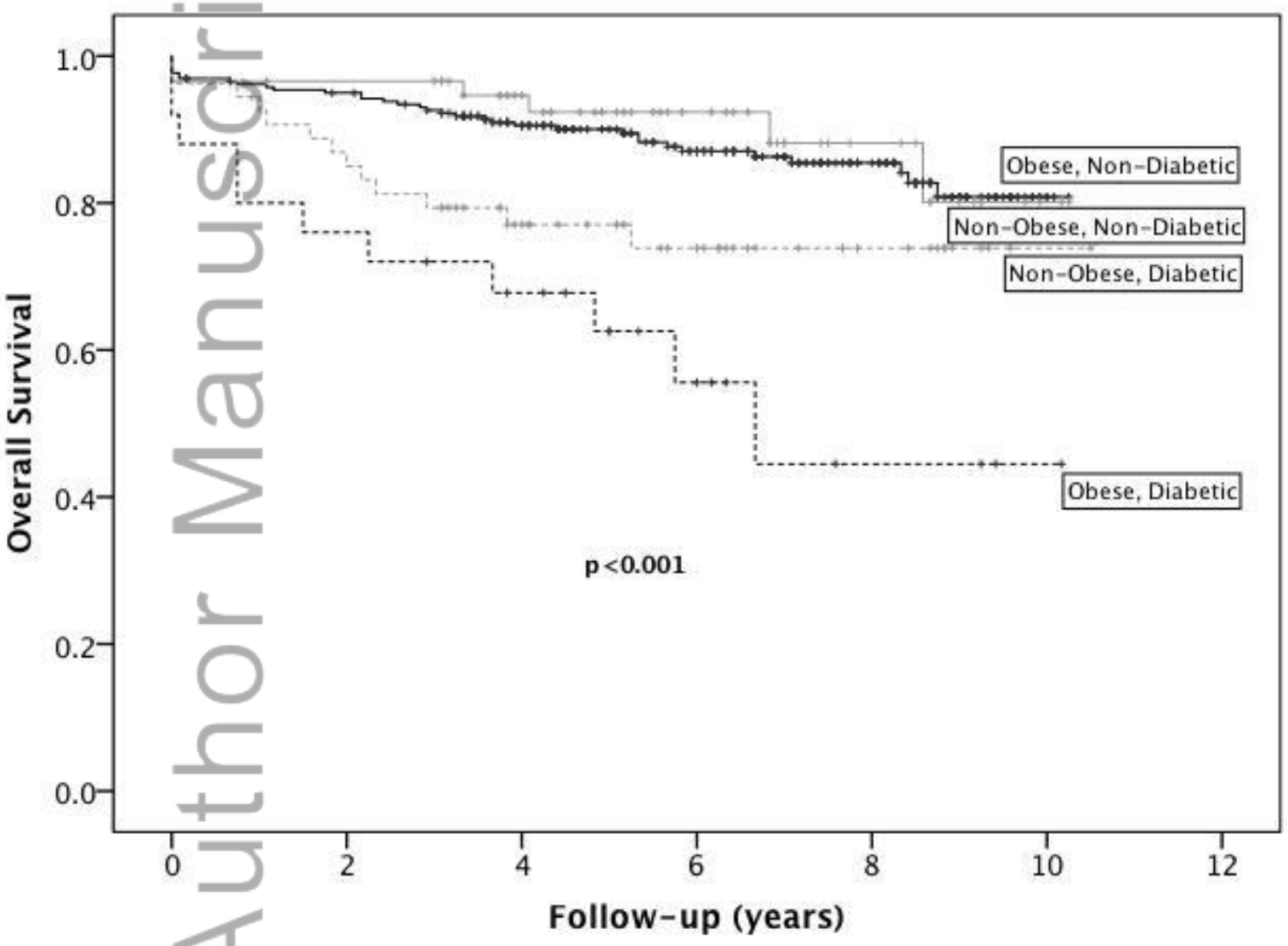
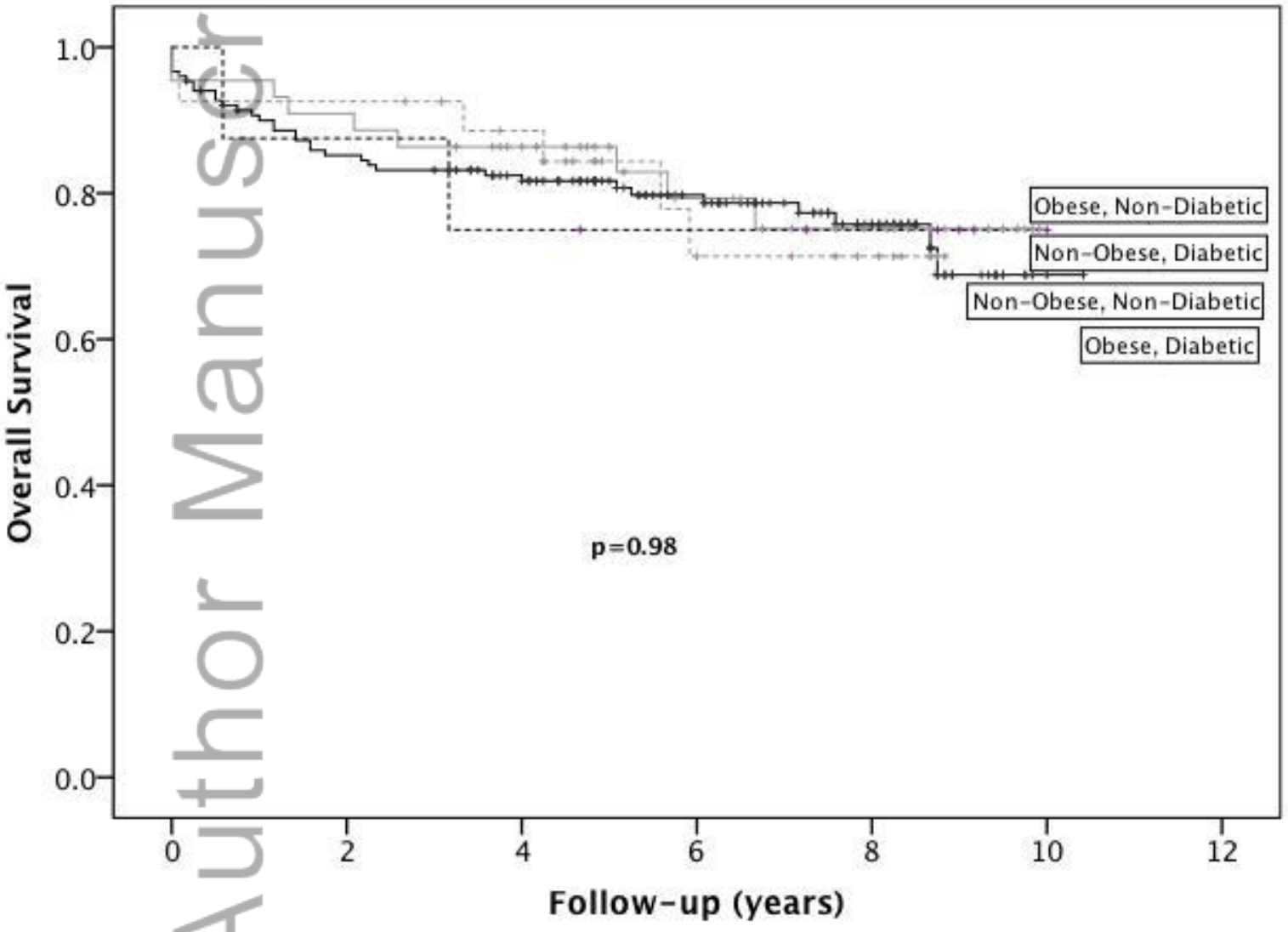
Figure 3A. Overall Survival in Obese and Diabetic Patients without HCV



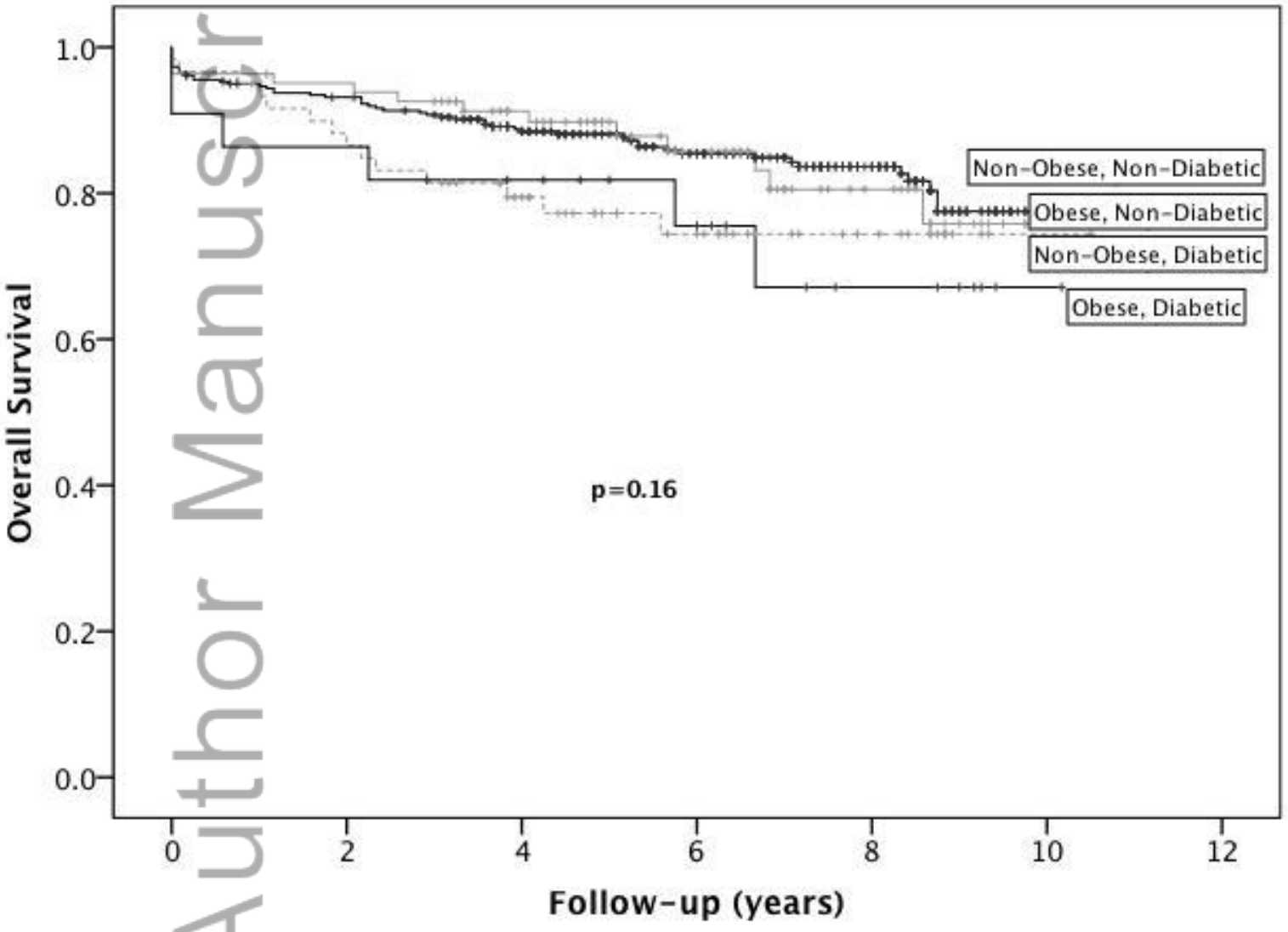
JGH_13240_F3A.jpeg

Figure 3B. Overall Survival in Obese and Diabetic Patients with HCV



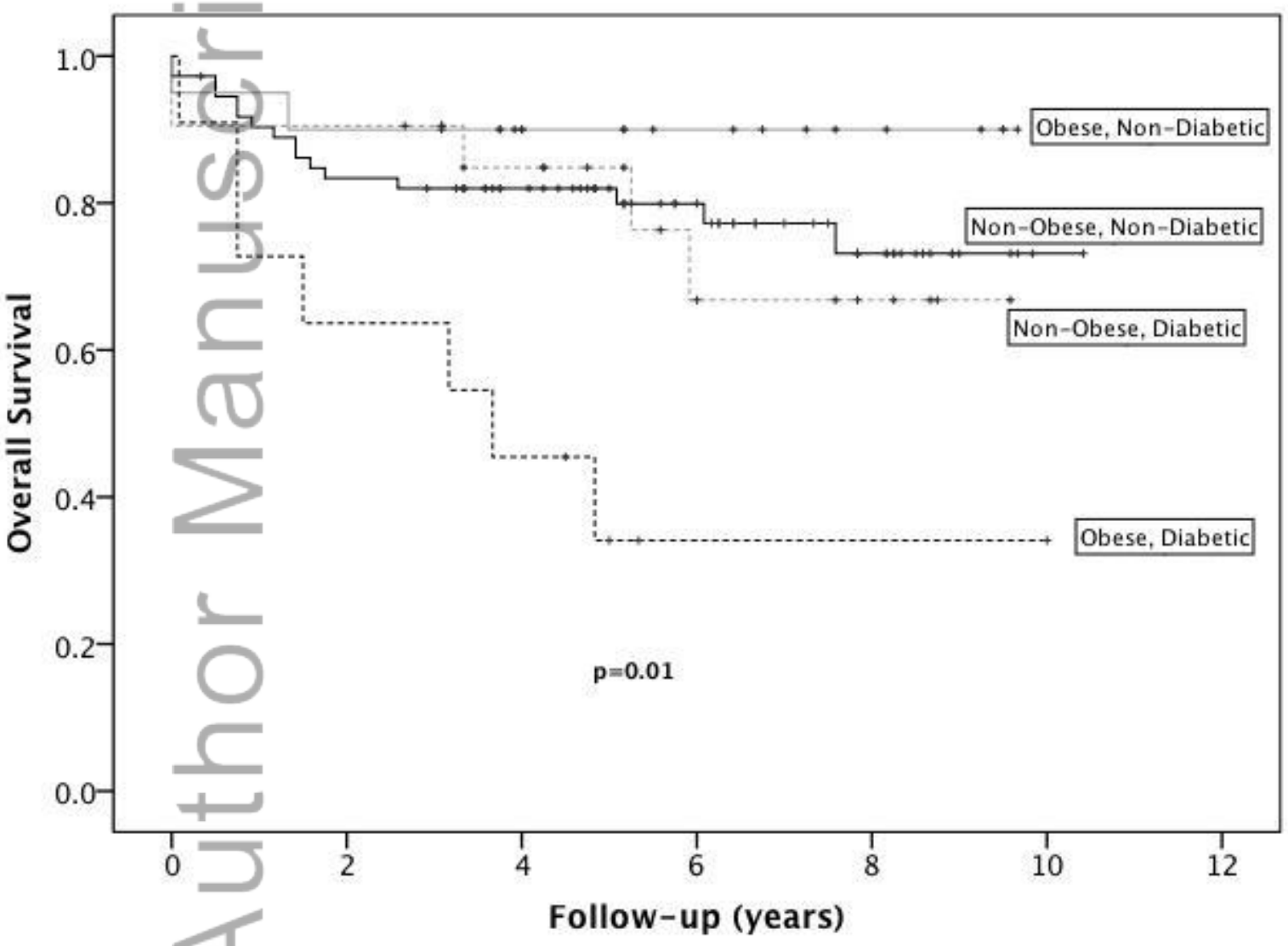
JGH_13240_F3B.jpeg

Figure 4A. Overall Survival in Obese and Diabetic Patients without HCC



JGH_13240_F4A.jpeg

Figure 4B. Overall Survival in Obese and Diabetic Patients with HCC



JGH_13240_F4B.jpeg

Table 1. Cohort and Donor Organ Characteristics at Time of Transplant.

Characteristic		**Overall (n=617)**
Recipient Factors	Age (years)	50.7 (9.2)
	Gender (male)	466 (71%)
	Caucasian	511 (78%)
	Prior Upper Abdo. Surgery	62 (9.5%)
Liver Disease	Hepatitis C	246 (37.6%)
	Alcohol	84 (12.8%)
	NAFLD/CC	65 (9.9%)
	HCC	136 (20.8%)
Liver /Renal Function	Bilirubin (mg/dl)	3.1 (1.6-6.1)
	Albumin (g/dl)	3.0 (0.7)
	Creatinine (mg/dl)	0.90 (0.72-1.14)
	INR	1.5 (1.3-1.8)
	MELD	15 (10-20)
	CTP Class A/B/C	19% / 47% / 34%
Metabolic Factors	Wet-weight (kg)	80.0 (17.6)
	Dry-weight (kg)	78.0 (17.7)
	Wet-BMI (kg/m^2)	27.1 (5.0)
	Dry-BMI (kg/m^2)	26.6 (5.0)
	Cholesterol (mg/dl)	131 (104-170)
	Triglyceride (mg/dl)	71 (53-106)
	HDL-Cholesterol (mg/dl)	44 (31 -61)
	Prior IHD	14 (2%)
Donor Factors	Donor sex (male)	366/630 (56%)
	Donor Age (years)	42.1 (16.2)
	Donor BMI (kg/m^2)	25.4 (23.0-28.0)
	CIT (hours)	7.7 (2.4)
	WIT (minutes)	43 (33-53)

Footnote: Data presented as mean (standard deviation) or median (interquartile range) according to normality of distribution and number and percentage. Note, MELD is not been adjusted for the presence of hepatocellular carcinoma (HCC). CC=cryptogenic cirrhosis, CTP=Child Turcot Pugh, BMI=body mass index, IHD=ischemic heart disease, CIT=cold ischemic time, WIT=warm ischemic time.

Table 2. Predictors of overall survival (n=617)

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (years)	1.03 (1.01-1.05)	0.02	1.00 (0.98-1.03)	0.73
Gender (male)	0.91 (0.61-1.36)	0.65		
Caucasian	1.04 (0.61-1.77)	0.87		
Hepatitis C	1.49 (1.03-2.17)	0.03	1.68 (1.09-2.59)	0.02
Alcohol	0.63 (0.33-1.21)	0.17		
NAFLD/CC	0.81 (0.41-1.59)	0.54		
HCC	1.83 (1.22-2.75)	0.004	1.67 (1.05-2.67)	0.03
Bilirubin (mg/dl)	1.00 (0.99-1.00)	0.91		
Albumin (gm/l)	0.99 (0.96-1.02)	0.44		
Creatinine (mg/dl)	1.01 (1.00-1.01)	0.001	1.01 (1.00-1.01)	0.001
INR	0.98 (0.83-1.15)	0.81		
MELD	1.01 (0.99-1.04)	0.22		
CTP points (3-15)	1.04 (0.94-1.14)	0.47		
Dry-BMI <18kg/m^2	1.58 (0.57-4.39)	0.38		
18-24.9 kg/m^2	Reference	-		
25-29.9 kg/m^2	0.84 (0.54-1.32)	0.46		
30-34.9 kg/m^2	1.07 (0.62-1.82)	0.81		
35.0+ kg/m^2	1.52 (0.74-3.12)	0.38		
Diabetes	1.89 (1.25-2.86)	0.003	1.66 (1.05-2.65)	0.03
Hypertriglyceridemia	0.90 (0.45-1.78)	0.75		
Low HDL-Cholesterol	0.89 (0.55-1.44)	0.63		
Hypertension	1.31 (0.74-2.34)	0.36		
Metabolic Syndrome	1.44 (0.69-3.01)	0.33		
Prior IHD	0.89 (0.22-3.98)	0.89		
Prior abdominal surgery	1.64 (0.93-2.88)	0.09		
Donor sex (male)	0.92 (0.63-1.36)	0.68		
Donor Age (years)	1.02 (1.01-1.03)	0.003	1.01 (0.99-1.03)	0.06
Donor BMI (kg/m^2)	1.05 (1.01-1.09)	0.02	1.02 (0.98-1.07)	0.34
CIT (hours)	1.05 (0.97-1.13)	0.23		
WIT (minutes)	1.00 (0.99-1.01)	0.42		

Table 3. Combination of obesity and diabetes on overall post-transplant survival.

	Hazard Ratio (95% CI)	P value
Whole Cohort (n=617)*		
Non-Obese, No Diabetes	reference	-
Obese, No Diabetes	0.82 (0.46-1.46)	0.49
Non-Obese, Diabetes	1.40 (0.82-2.37)	0.22
Obese + Diabetes	2.40 (1.32-4.38)	0.004

*Adjusted for age, creatinine and diagnosis of HCV and HCC.

Table 4. Cause of death according to presence of obesity and diabetes.

Cause of Death	Non-Obese, No Diabetes (n=65/402)	Obese, No Diabetes (n=16/102)	Non-Obese, Diabetes (n=18/80)	Obese, Diabetes (n=13/33)	P value
Liver	27 (41%)	6 (38%)	6 (33%)	4 (31%)	0.88
Recurrent HCC	*10 (15%)*	*1 (6%)*	*1 (6%)*	*4 (31%)*	0.20
Infection	7 (11%)	2 (12.5%)	2 (11%)	3 (23%)	0.64
Malignancy	11 (17%)	3 (19%)	6 (33%)	1 (8%)	0.34
Cardio-vascular	3 (5%)	0 (0%)	1 (6%)	0 (0%)	1.00
Intra-operative	4 (6%)	2 (12.5%)	1 (6%)	2 (15%)	0.48
Other	13 (20%)	3 (19%)	2 (11%)	3 (23%)	0.83

Comparisons performed with Fishers Exact test. Death due to recurrent HCC included in 'Liver' related death category.

Table 5. Overall post-OLT survival associated with obesity or diabetes according to baseline age or diagnosis of HCV or HCC.

	Five year survival	Hazard Ratio (95% CI)	P value	Five year survival	Hazard Ratio (95% CI)	P value	Five year survival	Hazard Ratio (95% CI)	P value
	Age ≤50 years (n=282)*			**Hepatitis C Negative (n=390)****			**HCC Negative (n= 491)^**		
Non-Obese, No Diabetes	88.8%	reference	-	91.4%	reference	-	89.6%	reference	-
Obese, No Diabetes	90.6%	1.12 (0.46-2.74)	0.81	92.4%	0.91 (0.38-2.18)	0.82	91.0%	0.97 (0.50-1.87)	0.92
Non-Obese, Diabetes	80.4%	1.20 (0.46-3.15)	0.70	78.6%	1.89 (0.95-3.75)	0.07	78.6%	1.64 (0.88-3.04)	0.12
Obese + Diabetes	90.9%	1.37 (0.32-5.91)	0.67	62.6%	3.87 (1.91-7.82)	<0.001	81.8%	1.71 (0.72-4.02)	0.22
	Age >50years (n=335)*			**Hepatitis C Positive (n=229)****			**HCC Positive (n=128)^**		
Non-Obese, No Diabetes	86.7%	reference	-	81.4%	reference	-	79.8%	reference	-
Obese, No Diabetes	89.3%	0.72 (0.33-1.54)	0.39	86.4%	0.80 (0.36-1.74)	0.55	85.4%	0.48 (0.14-1.65)	0.24
Non-Obese, Diabetes	80.5%	1.48 (0.79-2.80)	0.22	84.3%	0.94 (0.39 -2.25)	0.89	84.8%	0.98 (0.35-2.73)	0.97
Obese + Diabetes	52.6%	3.04 (1.54-5.98)	0.001	75.0%	0.94 (0.22-4.00)	0.94	34.1%	3.35 (1.31-8.57)	0.01

Cox-regression analysis. * Adjusted for creatinine and diagnosis of HCV and HCC; ** Adjusted for age, creatinine and diagnosis of HCC; ^ Adjusted for age, creatinine, diagnosis of HCV.

Supplemental Table 1. Post transplant peri-operative factors associated with obesity and diabetes.

	Non-Obese, No Diabetes	Obese, No Diabetes	Non-Obese, Diabetes	Obese, Diabetes	P value
RBC infused (units)	2 (0-5)	2 (0-6)	2 (0-5)	2 (0-9.25)	0.90
ICU stay (days)	2 (1-4)	3 (2-4)	3 (2-4)	4 (2-7)	0.04
Hospital stay (days)	16 (13-25)	19.5 (13-25)	17 (12.25-22)	22 (15-38)	0.01

Data presented as median (inter-quartile range), compared with Kruskal-Wallis test.