Carvedilol is associated with improved survival in patients with liver cirrhosis and ascites

Title page

Carvedilol use is associated with improved survival in patients with liver cirrhosis and ascites.

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RS collected data, performed statistical analysis and wrote the manuscript. KAL assisted in statistical analysis, data collection, manuscript revision and presentation. NM and MR contributed to data collection. PCH conceptualised the study. All authors reviewed and approved the final manuscript.

Abstract

Background and aims: Carvedilol, a non-selective beta-blocker (NSBB) with additional anti-alpha 1 receptor activity, is a potent portal hypotensive agent. It has been used as prophylaxis against variceal bleed. However, its safety in decompensated liver cirrhosis with ascites is still disputed. In this study, we examined whether long-term use of carvedilol in the presence of ascites is a risk factor for mortality.

Methods: This was a single-centre retrospective analysis of 325 consecutive patients with liver cirrhosis and ascites presenting to our Liver Unit between 1st of January 2009 to 31st August 2012. The primary outcome was all-cause and liver-specific mortality in patients receiving or not receiving carvedilol as prophylaxis against variceal bleeding.

Results: The final cohort after propensity score matching comprised 264 patients. Baseline ascites severity and UK End Stage Liver Disease (UKELD) score between carvedilol (n=132) and non-carvedilol (n=132) groups were comparable. Median follow-up time was 2.3 years. Survival at the end of the follow-up was 24% and 2% for carvedilol and non-carvedilol group respectively (Log Rank p<0.0001). The long-term survival was significantly better in carvedilol than non-carvedilol group (Log Rank p<0.001). The survival difference remained significant after adjusting for age, gender, ascites severity, aetiology of cirrhosis, previous variceal bleed, spontaneous bacterial peritonitis prophylaxis, serum albumin and UKELD with hazard ratio of 0.59 [CI 0.44, 0.80] (p=0.001), suggesting 41% reduction in mortality risk. When stratified as per the severity of ascites, carvedilol therapy resulted in hazard ratio of 0.47 [0.29, 0.77] (p=0.003) in those with mild ascites. Even with moderate or severe ascites, carvedilol use was not associated with increased mortality risk.

Conclusion: Long-term carvedilol therapy is not harmful in decompensated cirrhosis with ascites.

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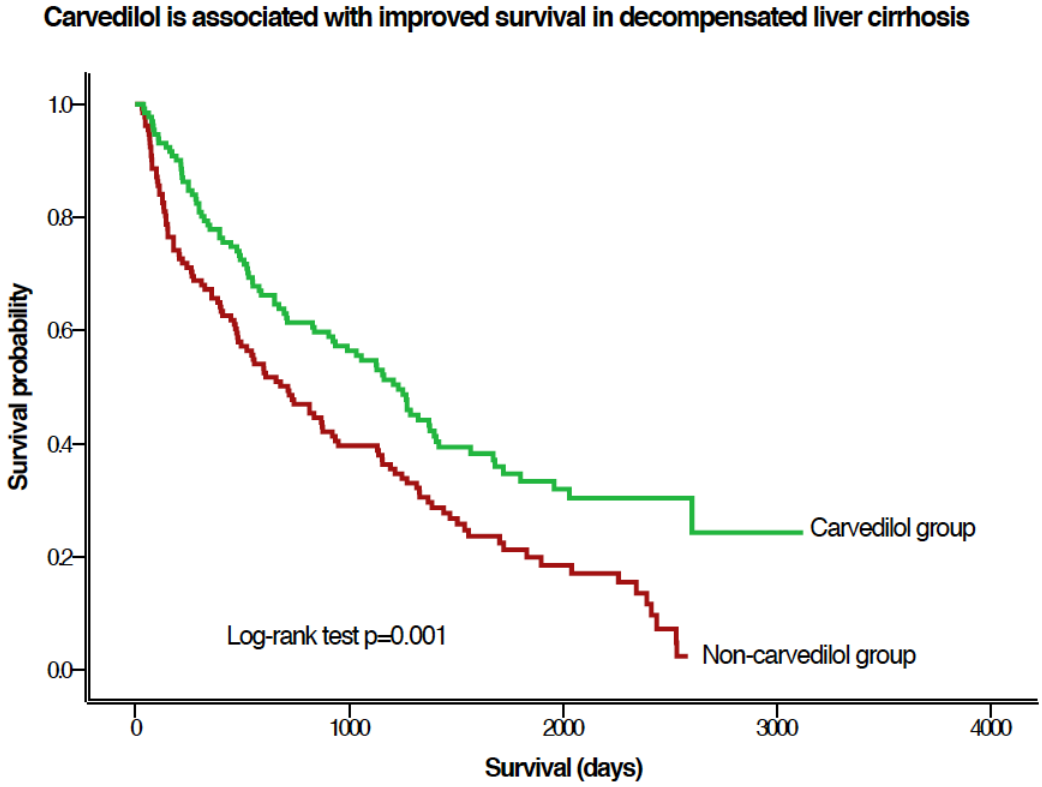
Graphical abstract



Lay summary:

The safety of carvedilol and other non-selective beta blocker in liver cirrhosis with ascites is still debated. In this study, we have shown that carvedilol therapy in patients with liver cirrhosis and ascites was associated with reduced risk of mortality, particularly in those with mild ascites. We concluded that low dose, chronic treatment with carvedilol in patients with liver cirrhosis and ascites is not detrimental.

Abbreviations:

NSBB, non-selective beta-blocker; ALD, Alcoholic liver disease; NAFLD, Non-alcoholic fatty liver disease; HCC, Hepatocellular carcinoma; SBP, Spontaneous bacterial peritonitis; PSM, Propensity score matching; PT, Prothrombin time; INR, International Normalised Ratio; UKELD, United Kingdom Model for End Stage Liver Disease; MELD, Model for End Stage Liver Disease.

INTRODUCTION

Liver cirrhosis remains a leading cause of death worldwide. In the United Kingdom alone mortality from liver cirrhosis has risen dramatically in the last decade tandem with the rise in alcohol consumption and the epidemic of obesity [1]. Portal hypertension underlies many of its fatal complications. For this reason, non-selective beta-blocker (NSBB) was proposed to be beneficial in the management of patients with varices. Its unselective beta-blockade reduces cardiac output and splanchnic blood flow while the unopposed effect of alpha 1 receptors leads to splanchnic vasoconstriction thus reducing portal pressure and its attendant complications [2, 3]. Indeed, NSBB therapy has been associated with a 40% reduction in the risk of variceal bleeding and in combination with endoscopic ligation, the risk of rebleeding was lower than that seen with either therapy alone [4].

Lowering of portal pressure with NSBB therapy has also been shown to reduce the development of ascites, refractory ascites and hepatorenal syndrome [5]. Furthermore, the effect of NSBB on intestinal permeability, bacterial translocation and inflammatory response has been proposed to mitigate the risk of developing spontaneous bacterial peritonitis [6, 7]. Mookerjee *et al* have demonstrated an association between short-term survival with NSBB therapy and a significant reduction in inflammatory markers [7]. Its benefit on survival was further supported by the finding of higher in-hospital mortality among those with decompensated cirrhosis without NSBB compared with those who received NSBB irrespective of the ascites severity [8].

Carvedilol, an NSBB with intrinsic anti-alpha 1 receptor activity, has been associated with a greater reduction in portal pressure than the traditional beta blocker, propranolol [9]. In a meta-analysis, the proportion of patients achieving target haemodynamic response was higher with carvedilol than propranolol [9]. Additionally, the use of carvedilol has been shown to reduce portal pressure

in those who initially failed to respond to propranolol. Its action on alpha 1 receptor reduces portocollateral resistance, and its effects on hepatic stellate cells diminished intrahepatic resistance [10]. In a rodent model of liver injury, carvedilol has been reported to mitigate the development of fibrosis by modulating inflammatory cytokines and enhancing antioxidant response [11].

However, the safety of carvedilol and other NSBB in cirrhosis with ascites is still debated. Sersté *et al* reported poor survival among patients with refractory ascites on NSBB therapy [12]. Additionally, NSBB therapy has been associated with increased risk of paracentesis induced circulatory dysfunction [12, 13]. A potential mechanism underlying these observations is that NSBB can reduce cardiac output and perfusion, especially renal blood flow. In a milieu characterised by hemodynamic derangement associated with cirrhosis, such effect can potentially compromise organ perfusion leading to a multitude of complications including hepatorenal syndrome [14]. This led to the 'therapeutic window hypothesis' which posits that the development of refractory ascites marks the point at which beta-blockade has a detrimental effect on cardiac function and mean arterial pressure [15].

In clinical practice, this debate has led to uncertainty surrounding the role of NSBB and carvedilol in decompensated cirrhosis with ascites [16]. From a practical standpoint, the main question is whether carvedilol should be continued once ascites developed and progressed. We have previously shown that carvedilol at a low dose of 12.5 mg for four weeks is well tolerated and significantly reduced portal pressure without compromising systemic haemodynamics [3, 17]. In the present study, we sought to examine whether long-term use of carvedilol (therapy of more than four weeks) in the presence of ascites is a risk factor for mortality.

PATIENTS AND METHODS

Study population

This retrospective analysis included consecutive patients with cirrhosis and ascites who were admitted to the Liver Unit at The Royal Infirmary of Edinburgh between the 1st of January 2009 to the 31st of August 2012. The Royal Infirmary of Edinburgh serves as a tertiary referral centre for Lothian as well as a local hospital for Edinburgh city (population ~800,000). In our unit, carvedilol is the NSBB of choice for primary prophylaxis for oesophageal variceal haemorrhage (grade II or above on endoscopy) [18-21] and secondary prophylaxis if endoscopic band ligation is not tolerated or preferred by patient. Carvedilol is commenced at a low dose of 6.25 mg once daily and if tolerated, it is titrated to a target dose of 12.5 mg daily.

Patients were identified from a prospectively collected database. Date of the first radiologically confirmed ascites was taken as the time of entry into the study. The use of carvedilol was ascertained by history and medicine reconciliation obtained from electronic patient record (TrakCare, InterSystems Corp, MA, USA). Exclusion criteria were: non-liver causes of ascites, the use of selective beta-blocker (e.g. atenolol, bisoprolol) or other non-selective beta-blocker (e.g. propranolol), carvedilol therapy of less than four weeks and those who underwent liver transplantation (Figure 1). If carvedilol was discontinued during the study period, they remained in the carvedilol group as the chronic duration of the carvedilol treatment might have an impact on the long-term outcome.

Outcomes and follow-up

Primary outcomes measured were: all-cause mortality and liver-related mortality. All cases were followed up from the date of index presentation until the date of death or the 31st December 2015 whichever was earlier.

Data extraction

Demographic and imaging data were obtained from electronic integrated clinical records system (TrakCare, InterSystems Corp, MA, USA). The Information Services Division (ISD), NHS Scotland provided data linkage to the national dataset on mortality (National Records Scotland). The following variables were recorded: age, gender, aetiology of liver disease, previous variceal bleed, severity of ascites, laboratory data (serum creatinine, sodium, bilirubin, albumin, prothrombin time and international normalised ratio (INR)) and the use of antibiotics for primary or secondary spontaneous bacterial peritonitis (SBP) prophylaxis [20, 22]. Laboratory variables recorded were those obtained at the time of entry to the study. Severity of ascites was classified as mild, moderate or severe as documented in the radiology report.

Severity of liver disease was assessed using the UK model for End-stage Liver Disease (UKELD), which predicts annual mortality [23]. Given the retrospective nature of this analysis, Child-Turcotte-Pugh score was not included as the presence and the degree of hepatic encephalopathy was not reliably recorded. Model for End-Stage Liver Disease (MELD) was also calculated and compared between the groups, however, as carvedilol use of less than four weeks was excluded, the impact is somewhat biased.

Ethical approval

This study was considered as a retrospective review by the local committee in our institution hence no formal ethical approval from the NHS Research Ethics Committee was necessary. However, this study received approval from the Caldicott Guardian of NHS Lothian and the Caldicott Guardian of ISD for NHS Scotland.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Macintosh, Version 21.0. (IBM Corp., Armonk, NY, USA), except for propensity score matching (PSM) analyses, which were performed on R, version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). The approach of Tukey's boxplot was followed to detect outliers with values outside the whiskers (2.2 times the interquartile range) being considered as outliers [24]. Outliers were checked and corrected if needed or retained where appropriate. Data were presented as mean (SD) for continuous variables and as frequencies and percentages for categorical variables. Kaplan-Meier survival analysis was used to calculate the cumulative incidence of primary outcomes. Cox regression models were fitted to adjust for effects of baseline characteristics and to determine their significance as a predictor for each outcome. Covariates with $p \leq 0.200$ in univariate regression analysis were included simultaneously in the multivariate models. The risk of the outcomes was presented as hazard ratio (95% confidence intervals). An unadjusted hazard ratio (HR) indicates an association between mortality and a single predictor. An adjusted HR indicates relationship between mortality and a predictor after adjusting for other independent variables. The proportional hazard assumptions were determined using log minus log plots for each variable. A *p*-value of less than 0.05 was deemed significant. To minimise the probability of selection bias, statistical analyses were performed in a cohort of carvedilol and non-carvedilol matched using the propensity score matching (PSM). The propensity score matching is a subject's probability of treatment, conditional on observed baseline covariates [25]. PSM is a recognised method of controlling for selection bias [26]. A PSM for carvedilol use versus non-carvedilol use was generated by multiple logistic regression. This model included all variables with clinical relevance to mortality (age, gender, aetiology, previous variceal bleed, severity of ascites, SBP antibiotic prophylaxis, serum sodium, serum creatinine, serum albumin, total bilirubin, International Normalised Ratio, and UK End Stage Liver Disease). The nearest available matching (1:1) on the estimated PSM method was used to construct the control group. Balance was achieved after

matching between the carvedilol (n=132) and non-carvedilol (n=132) groups on the selected confounders (Supplementary Data Table 1). The propensity score matching was performed using the MatchIt package in R [27, 28].

RESULTS

Clinical characteristics

Mean age for the entire cohort was 59.5 (SD 12.3) years and 67% were men. A total of 132 patients were on carvedilol with a median dose of 12.5 mg (range 6.25 -12.5 mg) per day. The discontinuation rate for carvedilol was 9% (12/132) in the first year and 80.3% (106/132) continued carvedilol therapy until the end of follow-up period. Mean UKELD and MELD score were 56 (SD 6.2) and 13.9 (SD 6.1) respectively. The prevalence of mild, moderate and severe ascites was 43.3%, 32.2% and 23.5% respectively. Baseline characteristics of the study population following the PSM are outlined in Table 1. The two groups were comparable with regards to aetiology of liver disease (p=0.91), previous variceal bleed (p=0.79), severity of ascites (p=0.93), antibiotic for SBP prophylaxis (p=0.41), serum sodium (p=0.41), serum creatinine (p=0.45), serum albumin (p=0.51), serum total bilirubin (p=0.71), INR (p=0.47), UKELD score (p=0.33) and MELD score (p=0.24).

Survival

The 264 patients were followed up for a median of 2.2 (IQR 0.8-4.1) years, during which there were 191 (72.3%) deaths. Among those on carvedilol, the estimated six-month and two-year survival was 95% and 61% respectively (Table 2). For non-carvedilol group, six-month survival was 89%, which declined to 47% at two-years. Similarly, survival at the end of the follow-up period was 24% for patients on carvedilol compared with only 2% among those who did not receive carvedilol (p=0.001). Median survival time was 1230 [CI 1006.9, 1453.1] days and 713 [CI 484.9, 941.0] days for carvedilol and non-carvedilol group respectively. After the first year, the unadjusted survival advantage associated with carvedilol was between 10 to 15% per year (Table 2).

As shown in Kaplan-Meier curves (Figure 2), the unadjusted hazard for carvedilol group was significantly lower than that seen in non-carvedilol group (Log Rank p=0.001). The use of carvedilol resulted in an unadjusted hazard ratio of 0.61 [CI 0.46, 0.81], when compared with those without carvedilol. The survival difference remained significant after adjusting for age, gender, previous variceal bleed, severity of ascites, aetiology of cirrhosis, SBP prophylaxis, serum albumin and UKELD with hazard ratio of 0.59 [CI 0.44, 0.80] suggesting 41% reduction of mortality risk associated with its use.

Ascites severity modifies the effect of carvedilol

Among those with mild ascites, the use of carvedilol resulted in an unadjusted hazard ratio of 0.51 [CI 0.33, 0.79]. The relationship remained significant even after adjusting for age, gender, aetiology of cirrhosis, previous variceal bleed, SBP prophylaxis, serum albumin and UKELD with 43% reduction in risk of death with carvedilol (HR 0.47 [CI 0.29, 0.77], p=0.003) when compared with those not on carvedilol. In moderate ascites, the trend of decreased risk of death with carvedilol was not statistically significant (p=0.08) with adjusted HR 0.61 [0.36, 1.06]. Similarly, we did not observe significant difference in the risk of death between carvedilol and non-carvedilol group among those with severe ascites (HR 0.77 [CI 0.42, 1.43], p=0.41) (Table 3).

Predictors of mortality

Table 4 demonstrates the findings from univariate and multivariate analyses. In univariate analysis, the following variables; carvedilol use, age, NAFLD as aetiology of liver cirrhosis, SBP prophylaxis were significantly associated with death. However, the effect of age was rendered insignificant after adjusting for other variables in a multivariate analysis (Table 4). In contrast, the association between nonalcoholic fatty liver disease and death remained significant with a two-fold increase in mortality when compared with alcoholic liver disease (HR 2.25 [CI 1.32, 3.84]). Additionally, antibiotic use for SBP prophylaxis was an independent predictor of mortality (p=0.007).

Causes of death

There were 191 deaths in the entire cohort (72.3%; 191/264). Of these 90.6% (173/191) were liver-related deaths. The leading cause of liver-related death was alcoholic liver disease (ALD) (53.9%; 103/191) followed by variceal bleed (14.1%; 27/191), hepatocellular carcinoma (HCC) (10.5%; 20/191) and Non-alcoholic fatty liver disease (NAFLD) (9.4%; 18/191).

ALD related deaths for carvedilol and non-carvedilol group were 48.2% (40/83) and 41.7% (43/108) respectively (p=0.66). The proportion of deaths relating to variceal bleed (16.9%; 14/83) for carvedilol and (12%; 13/108) for non-carvedilol group (p=0.40). Of the 14 patients who died of variceal haemorrhage, eight were on 12.5 mg of carvedilol and the remaining were on 6.25 mg of carvedilol. Similarly, there was no difference in HCC, NAFLD, viral and sepsis related deaths between the two groups (Table 5).

The leading cause of non-liver related deaths was cardiovascular disorders (18.8%; 36/191). Cardiovascular related deaths occurred in 16.9% (14/83) of patients on carvedilol and in 20.4% (22/108) of those in non-carvedilol group (p=0.58). We did not observe significant difference in cardiovascular-related death between patients with NAFLD on carvedilol and those with NAFLD without carvedilol. Similarly, there was no difference in deaths relating to extrahepatic malignancy, respiratory or renal disorders between the carvedilol and non-carvedilol groups (Table 5).

DISCUSSION

In this study, we examined for the first time whether long-term, low dose carvedilol therapy influences mortality in established cirrhosis with ascites. It also addressed an important clinical question-should carvedilol be continued in the presence of ascites. Our data highlight two important points. First, we have shown that long-term use of low dose carvedilol in cirrhosis with ascites was associated with reduced risk of mortality. Second, this association was modified by the severity of ascites; carvedilol therapy was associated with decreased risk of death in mild ascites but did not affect the outcome of those with moderate or severe ascites. Importantly, even in the presence of severe ascites, carvedilol therapy was not associated with excess mortality.

Our findings are in agreement with previous studies which largely focused on the role of propranolol in cirrhosis. The use of NSBB in cirrhosis with ascites has been associated with improved survival in various population ranging from hospital admission [8] to those on transplant waiting list [29]. Our study exclusively examined the impact of carvedilol in the presence of ascites. Carvedilol is the NSBB of choice in the preventative strategy against variceal bleed in our centre. Its safety in decompensated cirrhosis with ascites is still debated, for instance, its use in two of the studies examined in a recent meta-analysis was associated with increased mortality [30].

It was postulated that the vasodilatory effect from the concomitant alpha-blockade can potentially exacerbate arterial hypotension in the already precarious haemodynamic state. The effects of carvedilol on systemic haemodynamics are dose dependent [3, 17] and we have previously shown that carvedilol at 12.5 mg for four weeks led to a marked reduction in portal pressure without significantly altering the mean arterial pressure [3]. In the present study, carvedilol therapy at a median dose of 12.5 mg per day for a median duration of 49 months was associated with reduced risk of death. The estimated survival throughout the follow-up period was favourable with

carvedilol. Indeed, the survival at one-year was 78% for carvedilol and 65% for non-carvedilol despite the similarities in the baseline UKELD score. These groups were also similar with regards to liver disease severity, aetiology of liver disease and the degree of ascites.

The disparities between our findings and that of Njei *et al* may also have been attributed to the differences in population studied [30]. Specifically, our study population comprised all grades of ascites rather than solely focused on refractory ascites. Our data suggest that the severity of ascites modifies the effect of carvedilol. The use of carvedilol in mild ascites was associated with 53% reduced risk of long-term mortality. Although the risk of death in moderate and severe ascites was statistically similar between carvedilol and non-carvedilol group, the trend was that the impact of carvedilol decreased with increasing severity of ascites. This is consistent with the 'therapeutic window hypothesis' which stipulates that NSBB therapy may be effective only within a particular clinical window of advanced liver disease [15].

The underlying mechanisms for the protective effect of carvedilol in our study is unclear. It is plausible that similar to the traditional NSBB, the benefits incurred hinge on its portal hypotensive effect. Despite the similarities in variceal bleed related mortality between the two groups, the long-term effects of its portal pressure lowering on ascites related complications, bacterial translocation, anti-inflammatory and anti-fibrotic cannot be excluded [7, 11]. The cause of death documented reflects the progression of the underlying liver disease compounded by concurrent comorbidities, in particular, ischaemic heart disease.

Some limitations must be acknowledged. First, the retrospective nature of this study precludes the analysis of spontaneous bacterial peritonitis, evidence of autonomic dysfunction, interaction of concomitant drugs, blood pressure measurements, hepatic encephalopathy, ongoing alcohol consumption and compliance with carvedilol. Second, degree of ascites severity was based on radiology reports, which was subject to operator bias. Additionally, we did not have a reliable

information on the clinical course of ascites following the treatment with carvedilol. Similarly, we do not have reliable data regarding the safety of carvedilol in patients with refractory ascites. Information regarding concomitant use of diuretics and paracentesis were also not available.

However, our cohort represents real-world insight of patients with established cirrhosis and ascites. We used propensity score matching to minimise any potential bias. Our data have important implications for clinical management of patients with established cirrhosis and ascites. Long-term treatment with carvedilol at a low dose, even in the presence of severe ascites, is not associated with increased mortality. Therefore, our data support continuing carvedilol therapy in patients with ascites unless there are features to suggest significant haemodynamic perturbation compromising organ perfusion. As such, prospective randomised controlled trial is required to evaluate the efficacy of carvedilol in well characterised spectrum of cirrhosis and ascites. Further studies on the effects of carvedilol on the underlying disease progression and systemic inflammatory response modulation might unravel its effect on long-term survival.

In conclusion, we have demonstrated that low dose, chronic treatment with carvedilol in patients with decompensated cirrhosis and ascites is not detrimental. Furthermore, we have shown that carvedilol therapy in this setting was associated with reduced mortality, particularly in those with mild ascites. Our data support the need of prospective studies to determine its impact in severe and refractory ascites.

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Table 1

Clinical characteristics	Pre-match			Post-match		
	Carvedilol group (*n*=132)	**Non-carvedilol group (*n*=193)**	***p*-value**	**Carvedilol group (*n*=132)**	**Non-carvedilol group (*n*=132)**	***p*-value**
Age (years)	59.1 (12.7)	59.9 (12.0)	0.55	59.1 (12.7)	59.8 (11.9)	0.62
Men	87 (65.9)	116 (60.1)	0.29	87 (65.9)	89 (67.4)	0.89
Aetiology			0.31			0.91
ALD	94 (71.2)	157 (81.3)		94 (71.2)	101 (76.5)	
NAFLD	15 (11.4)	15 (7.8)		15 (11.4)	12 (9.1)	
Viral	5 (3.8)	4 (2.1)		5 (3.8)	4 (3.0)	
Others	12 (9.1)	12 (6.2)		12 (9.1)	10 (7.6)	
HCC	6 (4.5)	5 (2.6)		6 (4.5)	5 (3.8)	
Previous variceal bleed	42 (31.8)	66 (34.2)	0.72	42 (31.8)	45 (34.1)	0.79
Severity of ascites			0.13			0.93
Mild	60 (45.5)	67 (34.7)		60 (45.5)	57 (43.2)	
Moderate	42 (31.8)	69 (35.8)		42 (31.8)	43 (32.6)	
Severe	30 (22.7)	57 (29.5)		30 (22.7)	32 (24.2)	
Antibiotic for SBP prophylaxis	40 (30.3)	34 (17.6)	0.01*	40 (30.3)	33 (25.0)	0.41
Serum sodium (mmol/L)	134.8 (5.1)	134.6 (5.2)	0.81	134.8 (5.1)	134.3 (5.5)	0.41
Serum creatinine (mmol/L)	71.8 (31.2)	77.5 (51.1)	0.26	71.3 (26.2)	74.3 (37.8)	0.45
Serum albumin (g/L)	28.6 (7.8)	28.0 (6.9)	0.48	28.1 (5.6)	27.6 (6.9)	0.51
Total bilirubin (mmol/L)	87.8 (107.1)	88.4 (106.2)	0.96	88.3 (108.3)	93.2 (104.3)	0.71
INR	1.5 (0.5)	1.5 (0.5)	0.55	1.5 (0.4)	1.6 (0.5)	0.47
UKELD	55.7 (6.1)	55.9 (6.1)	0.76	55.7 (6.2)	56.5 (6.3)	0.33
MELD	12 (9)	13 (9)	0.26	13 (6)	14 (6)	0.24

Table 2

Time interval	Estimated survival in percentage	
	Carvedilol	Non-carvedilol
30-day	98	95
6 month	95	89
1-year	78	65
2-year	61	47
3-year	55	40
4-year	39	27
5-year	33	20

Table 3

Severity of ascites	Carvedilol	Non-carvedilol	*p*-value
Mild			
Mortality (*n*, %)	35 (58.3)	50 (87.7)	0.000*
Unadjusted HR	0.51 (0.33 – 0.79)	Ref	0.003*
Adjusted HR	0.47 (0.29 – 0.77)	Ref	0.003*
Moderate			
Mortality (*n*, %)	26 (61.9)	34 (79.1)	0.09
Unadjusted HR	0.59 (0.35 – 0.99)	Ref	0.05*
Adjusted HR	0.61 (0.36 – 1.06)	Ref	0.08
Severe			
Mortality (*n*, %)	22 (73.3)	24 (75.0)	1.00
Unadjusted HR	0.90 (0.50 – 1.61)	Ref	0.73
Adjusted HR	0.77 (0.42 – 1.43)	Ref	0.41

Table 4

	Univariate analysis		Multivariate analysis	
	Hazard ratio		**Adjusted hazard ratio**	
Variables	**(95% confidence interval)**	***p*-value**	**(95% confidence interval)**	**Adjusted *p*-value**
Carvedilol	0.61 (0.46 – 0.81)	0.001*	0.59 (0.44 – 0.80)	0.001*
Age	1.01 (1.00-1.02)	0.04*	1.00 (0.99 – 1.02)	0.34
Men	1.09 (0.81 – 1.48)	0.55	1.06 (0.77 – 1.47)	0.69
Aetiology				
ALD	Ref		Ref	
NAFLD	1.82 (1.18 – 2.81)	0.007 *	2.25 (1.32 – 3.84)	0.003*
HCC	0.44 (0.14 – 1.39)	0.16	0.51 (0.16 – 1.64)	0.26
Viral	0.91 (0.52 – 1.59)	0.75	1.14 (0.63 – 2.07)	0.65
Others	1.85 (0.90 – 3.78)	0.09	1.87 (0.89 – 3.94)	0.09
Previous variceal bleed	0.80 (0.52 – 1.09)	0.16	0.77 (0.56 – 1.06)	0.11
Severity of ascites				
Mild	Ref		Ref	
Moderate	1.06 (0.76 – 1.48)	0.71	0.93 (0.65 – 1.33)	0.66
Severe	1.20 (0.84 – 1.72)	0.31	1.26 (0.87 – 1.84)	0.22
SBP prophylaxis	0.64 (0.45- 0.89)	0.009*	0.62 (0.43 – 0.88)	0.007*
Serum sodium	1.01 (0.98 – 1.04)	0.37		
Serum creatinine	1.00 (0.99 – 1.00)	0.88		
Serum albumin	0.98 (0.95 – 1.00)	0.063	0.98 (0.95 – 1.00)	0.09
Total bilirubin	1.00 (0.99 – 1.00)	0.67		
INR	1.09 (0.81 – 1.45)	0.57		
UKELD	1.00 (0.98 – 1.02)	0.93	0.46 (1.01 – 0.98)	0.46
MELD	1.00 (0.97 – 1.32)	0.44		

Table 5

Cause of death	Carvedilol (*n*=83) *n* (%)	Non-carvedilol (*n*=108) *n* (%)	*p* value
Liver related			
ALD	43 (51.8)	60 (55.6)	0.66
Variceal bleeding	14 (16.9)	13 (12.0)	0.40
Sepsis	12 (14.5)	20 (18.5)	0.56
NAFLD	7 (8.4)	11 (10.2)	0.80
HCC	11 (13.3)	9 (8.3)	0.34
Viral	9 (10.8)	9 (8.3)	0.62
Others	29 (34.9)	28 (25.9)	0.20
Non-liver related			
Vascular event	14 (16.9)	22 (20.4)	0.58
Respiratory	12 (14.5)	19 (17.6)	0.69
Renal	5 (6.0)	6 (5.6)	1.00
Extra-hepatic malignancy	6 (7.2)	8 (7.4)	1.00

Figure 1

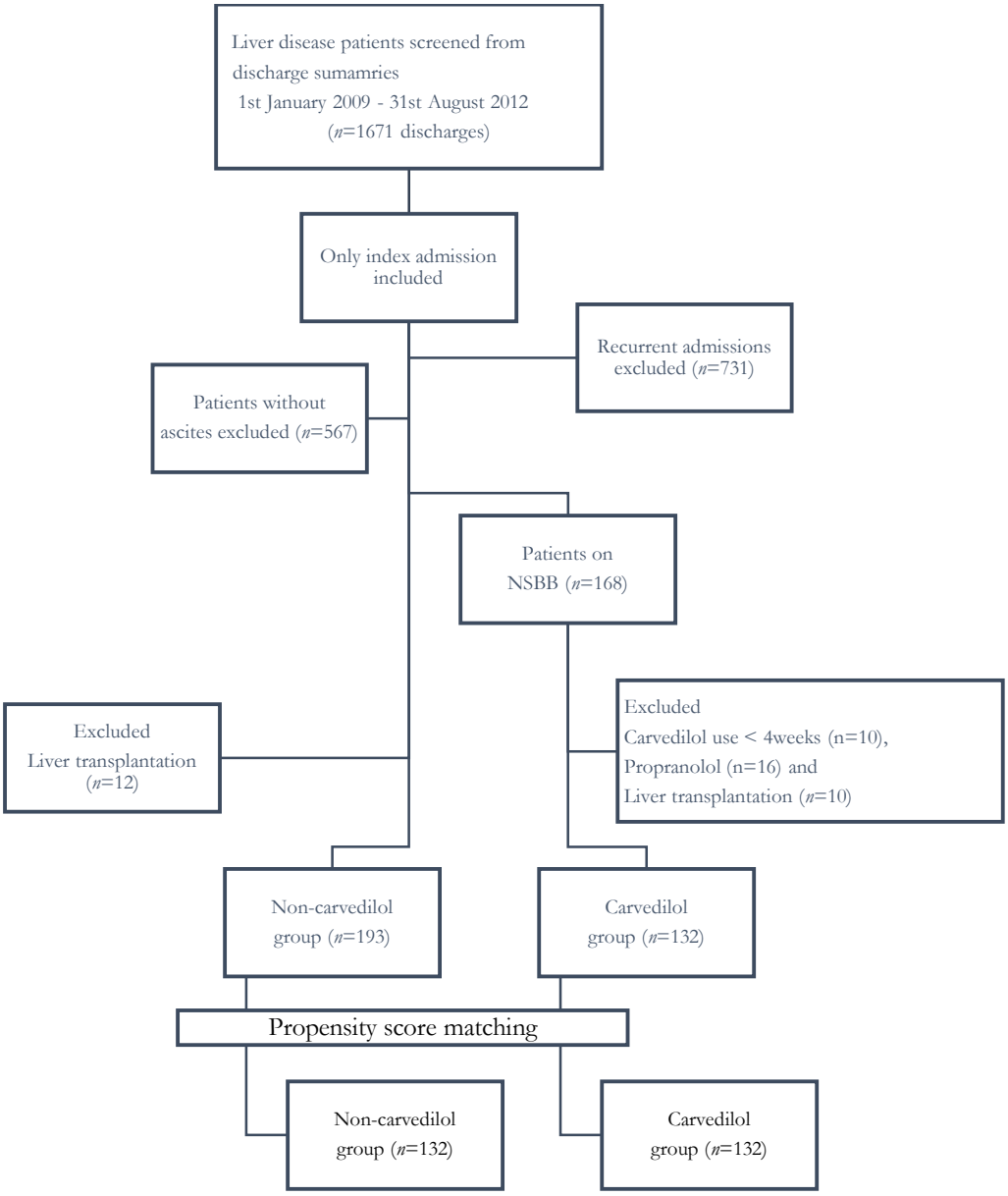
Liver disease patients screened from discharge sumamries
1st January 2009 - 31st August 2012
(n=1671 discharges)
Only index admission included
Recurrent admissions excluded (n=731)
Patients without ascites excluded (n=567)
Patients on NSBB (n=168)
Excluded
Liver transplantation (n=12)
Excluded
Carvedilol use < 4weeks (n=10),
Propranolol (n=16) and
Liver transplantation (n=10)
Non-carvedilol group (n=193)
Carvedilol group (n=132)
Propensity score matching
Non-carvedilol group (n=132)
Carvedilol group (n=132)

Figure 2

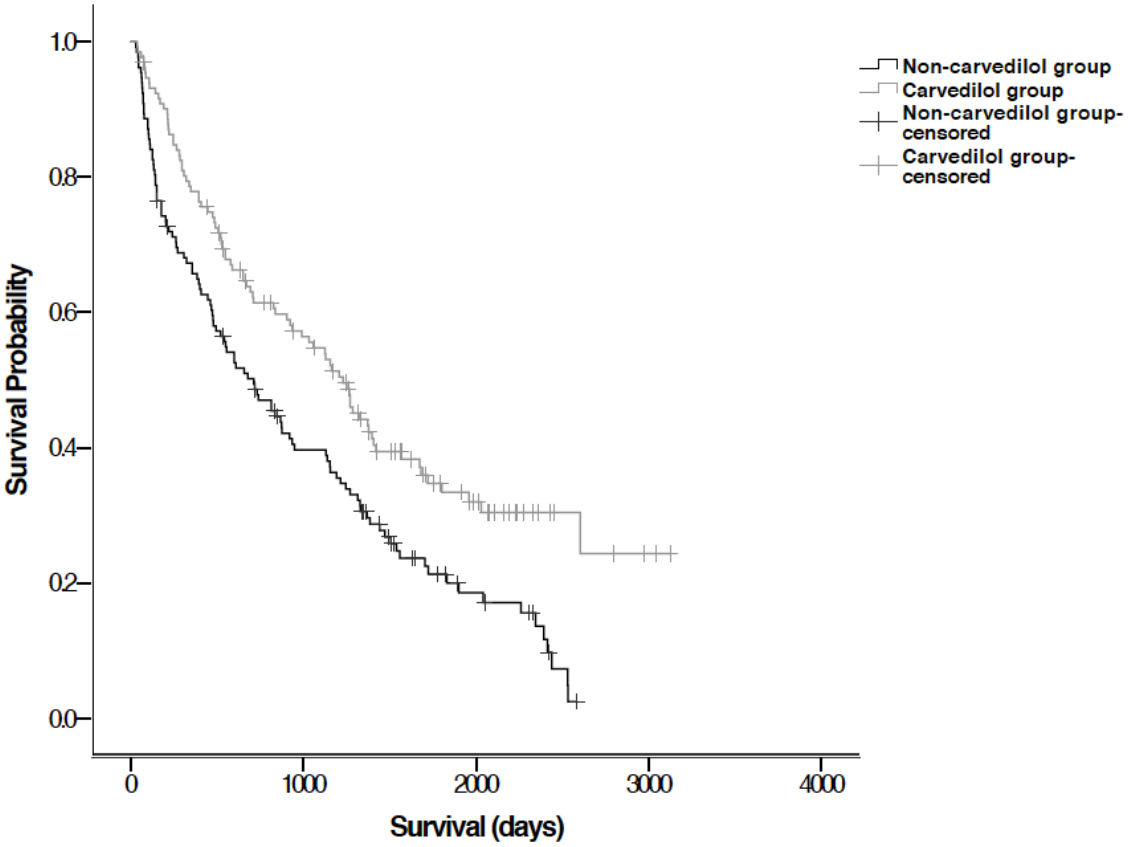
1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
1000
2000
3000
4000
Survival (days)
Non-carvedilol group
Carvedilol group
Non-carvedilol group-censored
Carvedilol group-censored

Figure and Table Legends

Table 1: Baseline characteristics of study population. Data presented as mean and standard deviation (SD) or frequency (*n*) and percentage where appropriate. *p<0.05 is significant. ALD, Alcoholic liver disease; NAFLD, Non-alcoholic fatty liver disease; Viral, Viral hepatitis; HCC, Hepatocellular carcinoma; SBP, Spontaneous bacterial peritonitis; PT, Prothrombin time; INR, International Normalised Ratio; UKELD, United Kingdom Model for End Stage Liver Disease.

Table 2: Estimated survival over time.

Table 3: Risk of mortality stratified by the severity of ascites. Adjusted hazard ratio is obtained from Cox-regression analysis adjusted to the following variables (carvedilol, age, gender, aetiology, severity of ascites, previous variceal bleed, SBP prophylaxis, serum albumin and UKELD); Data presented as frequency (*n*) and percentage of each study group or hazard ratio (HR) and 95% confidence interval. *p <0.05 is significant; Ref, reference group. SBP, Spontaneous bacterial peritonitis; UKELD, United Kingdom Model for End Stage Liver Disease.

Table 4: Independent predictors of mortality across study population. Unadjusted and adjusted hazard ratios are obtained from univariate and multivariate analysis respectively. The following variables were considered in multivariate analysis (carvedilol, age, gender, aetiology, severity of ascites, previous variceal bleed, SBP prophylaxis, serum albumin and UKELD); Data presented as hazard ratio (HR) and 95% confidence interval. *p <0.05 is significant; Ref, reference group. SBP, Spontaneous bacterial peritonitis; UKELD, United Kingdom Model for End Stage Liver Disease.

Table 5: Cause of death. Data presented as frequency (*n*) and percentage of each study group. ALD, Alcoholic liver disease; NAFLD, Non-alcoholic fatty liver disease; Viral, Viral hepatitis; HCC, Hepatocellular carcinoma. *p <0.05 is significant.

Figure 1: Study flow.

Figure 2: Kaplan-Meier curves for carvedilol and non-carvedilol groups. Carvedilol therapy was associated with lower hazard compared with non-carvedilol group over the follow-up period. Log Rank (Mantel-Cox) *p* value of 0.001; *$p<0.05$ is significant.