Original article

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Propensity-matched analysis of the influence of perioperative statin therapy on outcomes after liver resection

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Background: **Perioperative use of statins is reported to improve postoperative outcomes after cardiac and non-cardiovascular surgery. The aim of this study was to investigate the influence of statins on postoperative outcomes including complications of grade IIIa and above, posthepatectomy liver failure (PHLF), and 90-day mortality rates after liver resection.**

Methods: **Patients who underwent hepatectomy between 2013 and 2017 were reviewed to identify statin users and non-users (controls). Propensity matching was conducted for age, BMI, type of surgery and pre-operative co-morbidities to compare subgroups. Univariable and multivariable analyses were performed for the following outcomes: 90-day mortality, significant postoperative complications and PHLF.**

Results: **Of 890 patients who had liver resection during the study period, 162 (18·2 per cent) were taking perioperative statins. Propensity analysis selected two matched groups, each comprising 154 patients. Overall, 81 patients (9·1 per cent) developed complications of grade IIIa or above, and the 90-day mortality rate was 3·4 per cent (30 patients), with no statistically significant difference when the groups were compared before and after matching. The rate of PHLF was significantly lower in patients on perioperative statins than in those not taking statins (10·5 *versus* 17·3 per cent respectively; $P = 0·033$); similar results were found after propensity matching (10·4 *versus* 20·8 per cent respectively; $P = 0·026$).**

Conclusion: **The rate of PHLF was significantly lower in patients taking perioperative statins, but there was no statistically significant difference in severe complications and mortality rates.**

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Introduction

Postoperative outcomes following liver resection have improved significantly over the past decade, with postoperative mortality rates falling from 20 to 1–5 per cent[1]. Better outcomes resulted from improved perioperative management and anaesthetic techniques, dedicated high-volume centres and enhanced recovery programmes[2,3]. In addition, prehabilitation programmes were reported to improve cardiopulmonary performance and quality of life[4], and preoperative dietary therapy was recognized to reduce postoperative hospital stay[5].

The use of statins across the perioperative period was reported[6–8] to benefit patients undergoing various types of surgery. In a meta-analysis of more than 30 000 patients undergoing cardiac surgery, statin therapy reduced the absolute and odds risks for all-cause mortality[6]. In non-cardiac vascular surgery, statin use was also associated with increased patency and overall survival[7]. In a retrospective study of colorectal surgery, patients on statins had a significant reduction in postoperative sepsis and anastomotic leak after elective rectal resections[8].

The use of statins in low doses improved liver regeneration and angiogenesis after partial hepatectomy in animal

models[9]. A previous report[10] documented that statins were associated with significantly increased recurrence-free survival in patients undergoing curative resection for hepatocellular carcinoma not due to chronic viral hepatitis. In a small cohort of patients with non-alcoholic steatohepatitis treated with rosuvastatin and lifestyle changes, steatohepatitis was shown to have improved on histological examination of liver biopsies after 12 months[11].

The aim of the present study was to evaluate postoperative outcomes, including posthepatectomy liver failure (PHLF), in a cohort of patients who underwent liver resection, comparing statin users and controls.

Methods

A retrospective analysis was performed using the departmental electronic database. All patients who had liver resection between January 2013 and January 2017 at the Department of Hepatobiliary and Pancreatic Surgery, Queen Elizabeth Hospital, Birmingham, a tertiary referral centre, were included.

Patients under the age of 18 years and those who had multivisceral resection were excluded. All patients had clinical history and physical examination recorded before surgery by a surgeon and an anaesthetist, and radiological findings were reviewed at a multidisciplinary team meeting. Parenchymal transection was performed with low central venous pressure (5 mmHg) and reverse Trendelenburg position. Intermittent inflow vascular control was obtained based on the extent of resection and surgeon preference. Abdominal drains were used after most resections, but were removed according to an enhanced recovery protocol (in use in the department since 2014)[12]. Anatomical remnant liver volumes were measured selectively in patients requiring extended hepatectomy. Energy devices (Cavitron Ultrasonic Aspirator® (CUSA) dissection device, Integra Life Sciences, Plainsboro, New Jersey, USA; and various types of ultrasonic shears) were used according to the surgeon's preference. The extent of resection was categorized as: minor (fewer than 3 segments), major (Brisbane classification[13] – right or left hepatectomy) or extra-major (extended resections, right or left hepatectomy with additional non-anatomical resections in patients with bilobar disease, or hepatectomy with vascular reconstruction). According to department's protocol, all patients who received chemotherapy before liver surgery have an interval of 6–8 weeks between the completion of chemotherapy and liver resection.

Preoperative variables analysed included patient demographics, diagnoses, co-morbid medical conditions and preoperative laboratory values. Co-morbidities recorded included hypertension (HTN), ischaemic heart disease (IHD), diabetes mellitus (DM), respiratory co-morbidity, chronic kidney disease (CKD), stroke and deep vein thrombosis (DVT). Patients' medication history was reviewed to identify those who were taking statins. These data were verified using electronic medical records, to check whether patients continued these medications after surgery.

Outcomes measured

The primary outcome was 90-day mortality. Secondary outcomes were the development of PHLF (as defined by the International Study Group of Liver Surgery[14]) and complications of grade IIIa or above according to the Clavien–Dindo[15] classification.

Statistical analysis

Comparisons were made between patients who were taking statins and those who were not (control group). The distributions of continuous variables were tested for normality by examining the mean and standard error of skewness and the Shapiro–Wilk test. Normally distributed continuous variables were reported as mean(s.d.) values and compared between groups using independent-samples *t* tests. Other continuous variables were reported as the median (i.q.r.) values, and compared with the Mann–Whitney *U* test. Fisher's exact test was used for categorical variables.

Multivariable binary logistic regression analyses were performed to identify independent preoperative predictors of the outcomes, after accounting for potentially confounding factors. Before the analysis, continuous variables were assessed with Hosmer–Lemeshow tests to ensure a good model fit. When a poor fit was detected, the factors were divided into categories or $\log_2$-transformed, as applicable, to improve the model fit. Factors were then entered into the model, with a backwards-stepwise approach used for outcomes that occurred infrequently, to minimize the potential for overfitting.

Propensity matching was performed to negate the impact of confounding factors on comparisons between statin and control groups. The propensity score was produced from a binary logistic regression model, including patient age, BMI, type of surgery and preoperative co-morbidities including DM, DVT, HTN, IHD, CKD, respiratory co-morbidity and stroke as co-variables. Cases (statins) and controls (no statins) were then matched in a 1 : 1 ratio, without replacement, using a caliper of 5 per cent. Outcome rates were then compared between the propensity-matched groups using McNemar tests. In addition, a multivariable analysis of the propensity-matched

Table 1 Comparison of preoperative variables by statin use before and after propensity matching

	Total cohort			Propensity-matched cohort		
	Statin use			Statin use		
	No ($n = 728$)	Yes ($n = 162$)	P‡	No ($n = 154$)	Yes ($n = 154$)	P‡
Age (years)*	64·0 (54·0–72·1)	70·1 (62·4–74·9)	< 0·001§	67·0 (60·3–74·1)	70·4 (62·2–74·9)	0·012§
Sex ratio (M : F)	408 : 320	99 : 63	0·255	71 : 83	61 : 93	0·300
BMI (kg/m^2)*†	27·7 (24·5–31·6)	28·6 (25·6–32·1)	0·043§	28·6 (24·6–32·6)	28·5 (25·6–32·0)	0·917§
Type of surgery†			0·019			0·321
Minor	380 (79·8)	96 (20·2)		81 (47·4)	90 (52·6)	
Major	163 (79·9)	41 (20·1)		40 (49)	41 (51)	
Extra-major	181 (88·3)	24 (11·7)		33 (59)	23 (41)	
Diabetes mellitus			< 0·001			0·422
Yes	64 (60·4)	42 (39·6)		121 (51·5)	114 (48·5)	
No	664 (84·7)	120 (15·3)		33 (45)	40 (55)	
DVT			0·335			0·623
Yes	26 (90)	3 (10)		153 (50·3)	151 (49·7)	
No	702 (81·5)	159 (18·5)		1 (25)	3 (75)	
Hypertension			< 0·001			0·905
Yes	140 (70·4)	59 (29·6)		101 (50·5)	99 (49·5)	
No	588 (85·1)	103 (14·9)		53 (49·1)	55 (50·9)	
IHD			< 0·001			1·000
Yes	47 (65)	25 (35)		133 (50·0)	133 (50·0)	
No	681 (83·3)	137 (16·7)		21 (50)	21 (50)	
CKD			0·401			1·000
Yes	7 (70)	3 (30)		150 (49·8)	151 (50·2)	
No	721 (81·9)	159 (18·1)		4 (57)	3 (43)	
Stroke			0·002			0·750
Yes	11 (52)	10 (48)		150 (50·3)	148 (49·7)	
No	717 (82·5)	152 (17·5)		4 (40)	6 (60)	
Respiratory co-morbidity			0·389			1·000
Yes	76 (85)	13 (15)		143 (50·2)	142 (49·8)	
No	652 (81·4)	149 (18·6)		11 (48)	12 (52)	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.) †For the total cohort, data for BMI were available for only 863 patients, and for type of surgery only 885. DVT, deep vein thrombosis; IHD, ischaemic heart disease; CKD, chronic kidney disease. ‡Fisher's exact test, except §Mann–Whitney *U* test.

cohort was produced, using binary logistic regression models with a backwards-stepwise approach, to account for any residual demographic differences between the matched groups.

$P < 0·050$ was considered statistically significant. All analyses were performed using IBM SPSS® version 22 (IBM, Armonk, New York, USA). Patients with missing data were included where possible, being excluded only from any analyses that considered those factors with missing data.

Results

Table 1 shows the clinical and surgical features of the 890 patients included. The most common indication for liver surgery was a diagnosis of colorectal liver metastasis (530 patients, 59·6 per cent). Other indications for resection were primary liver malignancy (134 patients, 15·1 per cent), other malignant liver tumours (117, 13·1 per cent) and benign pathology (85, 9·6 per cent).

Some 162 patients (18·2 per cent) were taking statins before surgery, and all continued the treatment throughout the perioperative period. These patients were significantly older (median 70·1 years *versus* 64·0 years for those not taking statins; $P < 0·001$) and had a higher BMI (28·6 *versus* 27·7 kg/m^2 respectively; $P = 0·043$) (*Table 1*). In addition, patients taking statins had significantly higher rates of DM, HTN, IHD and stroke than those not on statins in the perioperative period, and underwent fewer extra-major liver resections. Propensity matching identified matches for 154 statin users, giving a cohort of 308 for analysis.

Table 2 Postoperative outcomes by statin use

	Statin	Control	Odds ratio*	*P*
90-day mortality				
Whole cohort	6 of 162 (3·7)	24 of 728 (3·3)	1·13 (0·45, 2·81)	0·473†
Propensity-matched	6 of 154 (3·9)	13 of 154 (8·4)	0·44 (0·16, 1·19)	0·118‡
PHLF				
Whole cohort	17 of 162 (10·5)	126 of 728 (17·3)	0·56 (0·33, 0·96)	0·033†
Propensity-matched	16 of 154 (10·4)	32 of 154 (20·8)	0·44 (0·23, 0·85)	0·026‡
Clavien–Dindo grade ≥ IIIa				
Whole cohort	14 of 162 (8·6)	67 of 728 (9·2)	0·93 (0·51, 1·71)	1·000†
Propensity-matched	12 of 154 (7·8)	19 of 154 (12·3)	0·60 (0·28, 1·28)	0·230‡

Values in parentheses are percentages unless indicated otherwise; *odds ratio for the statin relative to control with 95 per cent confidence intervals in parentheses. PHLF, posthepatectomy liver failure. †Fisher's exact test; ‡McNemar's test.

Table 3 Multivariable analysis of outcomes in the matched cohort of 308 patients

	90-day mortality		PHLF		Clavien–Dindo grade ≥ IIIa	
	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Statin use	0·37 (0·13, 1·08)	0·068	0·44 (0·21, 0·89)	0·023	0·52 (0·24, 1·14)	0·100
Age at surgery (per year)	n.s.		n.s.		1·04 (1·00, 1·08)	0·082
BMI (per kg/m^2)	n.s.		0·92 (0·85, 0·99)	0·020	n.s.	
Sex	n.s.		n.s.		n.s.	
Diabetes mellitus	5·95 (1·99, 17·79)	0·001	n.s.		n.s.	
DVT	14·41 (1·05, 198·42)	0·046	n.s.		10·03 (1·36, 77·82)	0·024
Hypertension	0·32 (0·10, 1·06)	0·062	n.s.		n.s.	
IHD	n.s.		n.s.		n.s.	
CKD	n.s.		19·85 (2·43, 162·29)	0·005	n.s.	
Stroke	n.s.		n.s.		n.s.	
Respiratory co-morbidity	n.s.		n.s.		n.s.	
Extent of surgery		0·098		< 0·001		
Minor	1·00 (reference)		–		n.s.	
Major	3·53 (1·10, 11·33)	0·034	19·34 (6·90, 54·23)	< 0·001	n.s.	
Extra-major	2·53 (0·68, 9·36)	0·165	11·58 (3·89, 34·46)	< 0·001	n.s.	

Values in parentheses are 95 per cent confidence intervals. PHLF, posthepatectomy liver failure; n.s., not selected for inclusion in the final model by the stepwise procedure; DVT, deep vein thrombosis; IHD, ischaemic heart disease; CKD, chronic kidney disease.

Ninety-day mortality

The overall 90-day mortality rate was 3·4 per cent (30 patients). Statin use was not found to be significantly associated with 90-day mortality in univariable analysis ($P = 0·473$), and was not selected for inclusion in the multivariable model, which identified only DM as a significant independent risk factor for 90-day mortality (odds ratio (OR) 5·00, 95 per cent c.i. 2·23 to 11·10; $P < 0·001$) (*Table S1*, supporting information). After propensity matching, the difference in 90-day mortality rates between the statin and control cohorts remained non-significant, both in univariable analysis (3·9 *versus* 8·4 per cent respectively; $P = 0·118$) (*Table 2*) and after adjustment for confounders in multivariable analysis (OR 0·37, 0·13 to 1·08; $P = 0·068$) (*Table 3*).

Posthepatectomy liver failure

A total of 143 patients (16·1 per cent) developed PHLF. In univariable analysis, a prevalence of male sex ($P = 0·034$) and major/extra-major hepatectomy ($P < 0·001$) was noted among patients with PHLF, whereas the rate of PHLF was lower in those using statins *versus* controls (10·5 *versus* 17·3 per cent; $P = 0·033$) (*Table 2*). After accounting for the effects of confounding factors on multivariable analysis, statin use was found to be a significant independent predictor of reduced PHLF (OR 0·54, 95 per cent c.i. 0·30 to 1·00; $P = 0·049$) (*Table S2*, supporting information). This remained significant after propensity matching (*Table 2*), with an OR of 0·44 (0·21 to 0·89; $P = 0·023$) in multivariable analysis (*Table 3*).

Table 4 Associations between complications, patient outcomes and statin use in the unmatched cohort

		90-day mortality		PHLF		Statin use	
Type of complication	***n***	***n***	***P****	***n***	***P****	***n***	***P****
PHLF			< 0·001				0·033
Yes	143	13 (9·1)				17 (11·9)	
No	747	17 (2·3)				145 (19·4)	
Wound			0·669		0·156		0·562
Yes	47	2 (4)		11 (23)		10 (21)	
No	843	28 (3·3)		132 (15·7)		152 (18·0)	
Respiratory			0·020		0·122		0·140
Yes	86	7 (8)		19 (22)		21 (24)	
No	804	23 (2·9)		124 (15·4)		141 (17·5)	
Cardiac			0·003		0·001		0·843
Yes	45	6 (13)		16 (36)		7 (16)	
No	845	24 (2·8)		127 (15·0)		155 (18·3)	
Renal			< 0·001		0·001		0·138
Yes	12	7 (58)		7 (58)		0 (0)	
No	878	23 (2·6)		136 (15·5)		162 (18·5)	
Bleeding			0·405		1·000		0·495
Yes	15	1 (7)		2 (13)		4 (27)	
No	875	29 (3·3)		141 (16·1)		158 (18·1)	
Intra-abdominal collection			0·060		< 0·001		0·695
Yes	45	4 (9)		17 (38)		9 (20)	
No	845	26 (3·1)		126 (14·9)		153 (18·1)	
Bile leak			0·641		0·003		0·834
Yes	40	2 (5)		14 (35)		8 (20)	
No	850	28 (3·3)		129 (15·2)		154 (18·1)	

Values in parentheses are percentages. PHLF, posthepatectomy liver failure. *Fisher's exact test.

Postoperative complications

A total of 223 patients (25·1 per cent) experienced complications (excluding PHLF); 81 (9·1 per cent) reported complications of grade IIIa or above. Statin use was not significantly associated with the rate of complications of grade IIIa or above in either the unmatched or the propensity-matched cohort (*Tables 2–4*; *Table S3*, supporting information). The median hospital stay was 6 (i.q.r. 5–9) days, and did not differ significantly between the statin and control group ($P = 0·231$).

Discussion

It has previously been reported[16] that, by inhibiting the action of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, statins cause an increase in the expression of low-density lipoprotein receptors, which leads to their antilipid activity. The primary effect of HMG-CoA reductase inhibition is a decrease in mevalonate levels[16]. Mevalonate is an important precursor to several intracellular isoprenoids, and can affect the production of many intracellular signalling proteins[16]. Statins are also known to reduce margination and chemotaxis by exerting an inhibitory effect on intracellular adhesion molecules[17], and to improve microcirculation by preventing the production of microthrombi, increasing the production of thromboxane A2[18]. They also cause an improvement in endothelial function by increasing endothelial nitric oxide synthase gene-mediated nitric oxide synthesis.

In the present study, patients taking statins had a higher prevalence of co-morbidities such as DM, HTN, IHD and previous stroke. Preoperative factors such as DM, cardiac co-morbidity and CKD are reported[19–21] to have a negative influence on the overall outcomes after liver resection. A meta-analysis[19] documented that DM was associated with a significantly higher risk of overall complications, postoperative infections and liver failure. Previous studies[20,21] have documented that the presence of cardiac co-morbidities led to a higher risk of 30-day mortality also in non-cardiac and major liver surgery. In the present analysis, similar effects were reported with

diabetes, IHD and CKD, which all had a negative impact on 90-day mortality (*Table S1*, supporting information).

PHLF is a serious complication following liver resection. It has a multifactorial aetiology, and the extent of liver resection and volumes of future liver remnant are significant prognostic factors[22–25]. Even if the regenerative capacity of the liver could permit the surgical removal of large or multiple liver tumours with curative intent, when the liver remnant is too small the altered blood-to-liver volume ratio results in increased portal venous pressure and sinusoidal endothelial injury[26]. The overall incidence of PHLF in the present series was 16·1 per cent across all three International Study Group of Liver Surgery grades of PHLF. This is consistent with findings in recent publications[27–31], where rates of up to 32 per cent have been reported, depending on the definition of PHLF used. However, several factors were associated with PHLF, such as obesity, DM, malnutrition, hyperbilirubinaemia[24], age, chronic renal insufficiency, cirrhosis and chemotherapy[32–35].

Models of rats treated with low-dose statins have demonstrated increased mitochondrial enzyme activity, improved angiogenesis and regeneration of liver[9]. The use of statins has also proven beneficial in patients with NASH, which is also an independent factor influencing morbidity after liver resection[36]. A previous report[37] on this topic concluded that the use of statins was independently and negatively associated with both NASH and significant fibrosis on histological examination. In the present study, statins were associated with reduced PHLF, with an OR of 0·56 (95 per cent c.i. 0·33 to 0·96) in the unmatched cohort, and after propensity matching with a risk reduction from 20·8 to 10·4 per cent and an OR of 0·44 (0·23 to 0·85).

Limitations of this study include the retrospective design and lack of data on the type, dose and duration of consumption of statins before liver surgery. Thus it was not possible to assess whether this affected the magnitude of the observed effect, or to identify the optimal treatment regimen. A prospective RCT designed to test this effect, based on the present findings, would require a total sample size of 420 patients (210 per arm) to achieve 80 per cent power.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.