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ORIGINAL ARTICLE

Short-term postoperative outcomes after liver resection in the elderly patient: a nationwide population-based study

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Abstract

Background: Liver resection is high-risk surgery in particular in elderly patients. The aim of this study was to explore postoperative outcomes after liver resection in elderly patients.

Methods: In this nationwide study, all patients who underwent liver resection for primary and secondary liver tumours in the Netherlands between 2014 and 2019 were included. Age groups were composed as younger than 70 (70-), between 70 and 80 (septuagenarians), and 80 years or older (octogenarians). Proportion of liver resections per age group and 30-day major morbidity and 30-day mortality were assessed.

Results: In total, 6587 patients were included of whom 4023 (58.9%) were younger than 70, 2135 (32.4%) were septuagenarians and 429 (6.5%) were octogenarians. The proportion of septuagenarians increased during the study period (aOR:1.06, CI:1.02−1.09, $p < 0.001$). Thirty-day major morbidity was higher in septuagenarians (11%) and octogenarians (12%) compared to younger patients (9%, $p = 0.049$). Thirty-day mortality was higher in septuagenarians (4%) and octogenarians (4%) compared to younger patients (2%, $p < 0.001$). Cardiopulmonary complications occurred more frequently with higher age, liver-specific complications did not. Higher age was associated with higher 30-day morbidity and 30-day mortality in multivariable logistic regression.

Conclusion: Thirty-day major morbidity and 30-day mortality are higher after liver resection in elderly patients, attributed mainly to non-surgical cardiopulmonary complications.

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Introduction

Aging of the population has been described to be accompanied by a higher incidence of malignancies.[1] As liver resection has become safer over the past decades, more elderly patients undergo liver resection for varying indications such as colorectal liver metastases (CRLM), liver metastases from other origins, hepatocellular carcinoma (HCC) and biliary cancer.[2] In the Netherlands, liver resection is most frequently performed for CRLM followed by hepatocellular carcinoma and biliary cancer.[3]

Postoperative morbidity and mortality after liver resection for primary and secondary liver tumours tend to increase as older patients are accompanied with more comorbidities and frailty as well as aging of the liver.[4–6] During preoperative multidisciplinary treatment meetings, preoperative optimization becomes more important to decrease the negative impact of these comorbidities of patients who face liver resection for primary and secondary liver tumours.[7] To date, age has been seen as a risk factor for complications and mortality in liver surgery but it remains unclear to what extent other patient demographics, disease burden or operative characteristics play a role.

Several international studies show contradictory results with regard to the influence of age on postoperative outcomes after liver surgery.[5,8,9] However, these studies had small sample size or were focused on a specific liver tumour.[5,8,9] Several initiatives have been conducted to address frailty and optimize patients before major oncological surgery, but postoperative outcomes after liver resection for primary and secondary liver tumours in the elderly are yet to be addressed in the Netherlands.[10–12]

The aim of this study was to assess the proportion of patients who were between 70 and 80 years old (septuagenarians) and 80 years or older (octogenarians) who underwent liver resection for primary and secondary liver tumours over the years, to compare postoperative outcomes between older and younger patients and to explore risk factors for 30-day major morbidity and 30-day mortality in patients who undergo liver resection for primary and secondary liver tumours.

Methods

This nationwide population-based study was performed in the Netherlands. A volume requirement of liver resections per hospital per year is required in order to perform liver surgery in the Netherlands. Data were collected from the DHBA, a mandatory audit in which all hospitals in the Netherlands performing liver surgery register all liver resections. Data verification was performed to provide insight in completeness and accuracy of the DHBA when compared to the Dutch Cancer Registry.[2] No ethical approval was needed under Dutch law as the DHBA is part of the Dutch Inspectorate of health care and the dataset is anonymized as described in earlier studies with data from the DHBA.[3,13,14]

Patient selection

All patients who underwent liver resection for primary and secondary liver tumours between the 1st of January 2014 and the 31st of December 2019 in the Netherlands were included if they were registered in the DHBA before the 22nd of March 2020. Patients were excluded if no date of birth, date of surgery or type of tumour could be obtained. Patients who underwent simultaneous resection of the primary tumour and liver metastases or thermal ablation only were excluded from the study.

Tumour types registered in the DHBA include: CRLM, other liver metastases (LM), HCC and biliary cancer. Bile duct cancer types registered in the DHBA are perihilar cholangiocarcinoma (pCC), intrahepatic cholangiocarcinoma (iCC) and gallbladder cancer. Registration of cholangiocarcinoma patients started in 2015 with 2016 as first full registration year. Therefore analysis of this group were included from 2016 onwards.

Groups for analysis were based on age and were stratified as: patients of 70 years or younger, septuagenarian patients (between 70 and 80 years old) and octogenarian patients (80 years or older).

Variables

Variables used were sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores classified according to the Charlson Comorbidity Score (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue, previous liver surgery and diameter of the largest tumour before the initiation of tumour-specific treatment.[15] Treatment characteristics included use of preoperative chemotherapy, minor or major liver resection, and type of hospital where treatment took place which was either a tertiary referral center or regional hospital. Major liver resection was defined as resection of three or more Couinaud segments.[16] As a sensitivity analysis, hospital volume was included in multivariable models.[3] Annual overall volume was calculated as total number of liver resections per hospital per year and was categorized <20, 20–39, 40–59, 60–79, and >80 procedures.[3]

Main outcomes

The main outcomes in this study were proportion of septuagenarians and proportion of octogenarians who underwent liver resection for primary and secondary liver tumours every year during the study period and short-term postoperative outcomes in these patients.

Short-term postoperative outcomes consisted of length of stay (shown as median, with interquartile ranges (IQR)), 30-day overall morbidity, 30-day major morbidity and 30-day mortality after liver resection for primary and secondary liver tumours. Major morbidity was defined as a complication grade 3a or higher according the Clavien-Dindo classification, within 30 days of the surgical procedure.[17] Mortality was defined as death during hospitalization in the primary admission or within 30 days of the surgical procedure. Specific surgical complications (bile leakage, postoperative haemorrhage, liver failure defined according the International Study Group of Liver Surgery, deep and superficial surgical site infections) and cardiopulmonary complications were secondary outcomes.[18]

Statistical analysis

Baseline characteristics were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. Continuous variables were compared using independent one-way ANOVA or Kruskal Wallis test as appropriate.

Trends in proportion of septuagenarians and octogenarians who underwent liver resection for primary and secondary liver tumours over the years was assessed using univariable logistic regression. This proportion analysis was performed from 2014 to 2019 for CRLM, other LM and HCC. The proportion analysis was performed from 2016 to 2019 for biliary cancer patients.

The association of variables with 30-day major morbidity and 30-day mortality was assessed using univariable and multivariable logistic regression.

For all multivariable analyses a two-step method was undertaken. All variables were tested in a univariable models per outcome variable. If a significant association was observed ($P < 0.1$, Wald test) the variable was entered in the multivariable model. Statistical significance was defined as a two-sided p-value <0.05 in the multivariable model. Outcomes were adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Multicollinearity was assessed using the Variance Inflation Factor (VIF). A VIF of 2 or lower indicated that there was no multicollinearity. All analyses were performed in R version 3.2.2® (R Core Team (2018): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 6587 patients were included of whom 4023 (58.9%) were 70 years or younger, 2135 (32.4%) were septuagenarians and 429 (6.5%) were octogenarians. Of the 6587 patients, 4759 (72.2%) underwent liver resection for CRLM, 479 (6.5%) for other liver metastases, 738 (11.2%) for HCC and 611 (9.3%) for biliary cancer.

Overall 30-day major morbidity was 10.0% and 30-day mortality was 2.5%. After CRLM resection, overall 30-day major morbidity was 7.8% and 30-day mortality was 1.6%. After other LM resection, overall 30-day major morbidity was 9.2% and 30-day mortality was 1.7%. After HCC resection, overall 30-day major morbidity was 14.1% and 30-day mortality was 5.1%. After bile duct and gallbladder carcinoma, overall 30-day major morbidity was 22.3% and 30-day mortality was 7.4%. Subgroup analysis for perihilar cholangiocarcinoma resection showed overall 30-day major morbidity was 32.4% and 30-day mortality was 11.1%. Subgroup analysis for intrahepatic cholangiocarcinoma resection showed overall 30-day major morbidity was 19.6% and 30-day mortality was 6.5%. Subgroup analysis for gallbladder carcinoma resection showed overall 30-day major morbidity was 16.0% and 30-day mortality was 4.7%.

Population characteristics

Septuagenarians and octogenarians were more often male, had more often CCI of 2 or higher, more often ASA classification 3 or higher and had lower BMI (Table 1). Also, older patients received preoperative chemotherapy less frequently, underwent minor liver resection and laparoscopic liver resection more often and were less frequently treated in a tertiary referral centre. After subgroup analysis for CRLM, other liver metastases, HCC and bile duct and gallbladder carcinoma comparable differences between age groups were observed (supplementary table 1a,1b,1c,1d).

Proportion of elderly patients over the years

Overall number of liver resections for primary and secondary liver tumours performed in the Netherlands did not change over the study period with 997 resections in 2014 and 1023 resections in 2019 (supplementary table 4). For biliary cancer, HCC, CRLM and other liver metastases, 35.4%, 32.8%, 33.0% and 22.3% of the patients respectively were septuagenarians (Fig. 1). These groups consisted of octogenarians for 4.7%, 6.1%, 7.1% and 3.1%, respectively.

For all tumour types combined, the proportion of patients who were younger than 70 years old decreased over time (aOR 0.95, CI: 0.92–0.98, $p < 0.001$). The proportion of septuagenarians for all tumour types combined increased (aOR 1.06, CI: 1.02–1.09, $p < 0.001$) while the proportion of octogenarians did not change (aOR 1.02, CI: 0.96–1.08, $p = 0.571$) (supplementary table 3, supplementary figure 1, 2 &3).

The proportion of patients younger than 70 years old who underwent liver resection for CRLM decreased (aOR 0.96, CI: 0.93–1.00, $p = 0.033$). The proportion of septuagenarians who were resected for CRLM increased (aOR 1.04, CI: 1.01–1.08, $p = 0.025$) while the proportion of octogenarians did not change (aOR 1.00, CI: 0.94–1.07, $p = 0.953$).

The proportion of patients who were younger than 70 years old who underwent liver resection for HCC decreased (aOR 0.87, CI: 0.80–0.94, $p = 0.001$). The proportion of septuagenarians who underwent liver resection for HCC increased (aOR 1.11, CI: 1.01–1.21, $p = 0.024$) and the proportion of octogenarians also increased (aOR 1.18, CI: 0.01–1.40, $p = 0.049$).

For other liver metastases and bile duct and gallbladder carcinoma, no statistically significant differences were observed regarding the proportion of patients in the different age groups.

Postoperative outcomes

Length of stay was longer in octogenarians (median 7.00 days, IQR 4.00–9.00) as compared with septuagenarians (median 6.00 days, IQR 4.00–8.00) and patients younger than 70 (median 6.00 days, IQR 5.00–10.00, $p < 0.001$) (Table 2). Overall 30-day morbidity more frequently occurred in septuagenarians (36.8%) and octogenarians (37.1%) as compared with patients younger than 70 (28.1%, $p < 0.001$). Thirty-day major morbidity more frequently occurred in septuagenarians (11.0%) and octogenarians (11.7%) as compared with patients younger than 70 (9.2%). Thirty-day mortality was significantly higher in septuagenarians (3.5%) and octogenarians (4.1%) as compared to patients younger than 70 (1.9%, $p < 0.001$).

Table 1 Baseline characteristics stratified for age in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands

Factor	Age <70 N = 4023	Age 70-80 N = 2135	Age ≥80 N = 429	p-value
Sex				**<0.001**
Male	2319 (58)	1413 (66)	280 (65)	
Female	1696 (42)	716 (34)	146 (34)	
Missing[a]	8	6	3	
Charlson Comorbidity Index (CCI)				**<0.001**
0/1	3124 (78)	1338 (63)	263 (61)	
2+	899 (22)	797 (37)	166 (39)	
American Society of Anesthesiology (ASA) classification				**<0.001**
I/II	3229 (81)	1452 (69)	263 (63)	
III+	738 (19)	646 (31)	156 (37)	
Missing[a]	56	37	10	
Body Mass Index (BMI)				**0.002**
Mean (sd)	26.3 (4.8)	26.4 (4.2)	25.5 (3.5)	
Liver resection in the past				0.313
No	3267 (82)	1754 (84)	364 (86)	
Yes	691 (18)	342 (16)	58 (14)	
Missing[a]	65	39	7	
Histological diagnosis of liver parenchyma				0.167
Normal	2348 (71)	1260 (72)	283 (79)	
Steatosis	666 (20)	334 (19)	58 (16)	
Steato-hepatitis	89 (3)	52 (3)	6 (2)	
Cirrhosis	152 (5)	74 (4)	11 (3)	
Sinusoidal dilatation	50 (2)	24 (1)	1 (1)	
Missing[a]	718	391	70	
Type of tumour				**<0.001**
CRLM	2849 (71)	1570 (74)	340 (79)	
Other liver metastases	357 (9)	107 (5)	15 (4)	
HCC	451 (11)	242 (11)	45 (11)	
Biliary cancer	366 (9)	216 (10)	29 (7)	
Preoperative chemotherapy				**<0.001**
No	2557 (70)	1537 (80)	364 (90)	
Yes	1073 (30)	394 (20)	41 (10)	
Missing[a]	393	204	24	
Maximum diameter of largest tumour (mm)				**0.027**
< 20	913 (29)	502 (29)	79 (21)	
20–34	1108 (35)	591 (34)	141 (38)	
35–54	634 (20)	353 (20)	96 (26)	
> 55	539 (17)	287 (17)	58 (16)	
Missing[a]	829	402	55	
Major liver resection				**0.001**
No	2731 (71)	1480 (73)	334 (80)	
Yes	1126 (29)	560 (28)	83 (20)	
Missing[a]	166	95	12	

(*continued on next page*)

Table 1 (*continued*)

Factor	Age <70 N = 4023	Age 70-80 N = 2135	Age ≥80 N = 429	p-value
Surgical approach				**0.006**
Open	2911 (76)	1473 (73)	293 (70)	
Laparoscopic	940 (24)	558 (28)	124 (30)	
Missing	172	104	12	
Type of hospital[b]				**<0.001**
Regional hospitals	1659 (41)	1039 (49)	262 (61)	
Tertiary referral center	2354 (59)	1096 (51)	167 (39)	
Year of surgery				0.058
2014	651 (16)	282 (13)	64 (15)	
2015	670 (17)	320 (15)	69 (16)	
2016	714 (18)	387 (18)	69 (16)	
2017	689 (17)	409 (19)	81 (19)	
2018	702 (17)	387 (18)	70 (16)	
2019	597 (15)	350 (16)	76 (18)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.
[a] Missing not included in the analysis.
[b] Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery.

In minor liver resection, overall 30-day morbidity more frequently occurred in septuagenarians (29.0%) and octogenarians (32.9%) as compared with patients younger than 70 (21.1%, $p < 0.001$). Thirty-day major morbidity was not different in septuagenarians (6.4%) and octogenarians (8.7%) as compared with patients younger than 70 (6.2%, $p = 0.212$). Thirty-day mortality was not different in septuagenarians (1.2%) and octogenarians (1.5%) as compared to patients younger than 70 (0.6%, $p = 0.065$).

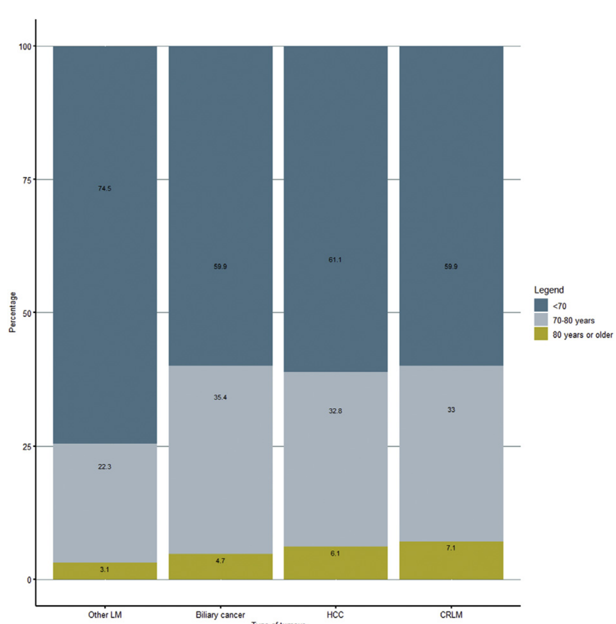

Figure 1 Percentage of patients of 70–80 years old and 80 years or older stratified for tumour type who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands

In major liver resection, overall 30-day morbidity more frequently occurred in septuagenarians (57.0%) and octogenarians (48.2%) as compared with patients younger than 70 (44.8%, $p < 0.001$). Thirty-day major morbidity more frequently occurred in septuagenarians (22.7%) and octogenarians (24.1%) as compared with patients younger than 70 (16.8%), $p = 0.007$. Thirty-day mortality was significantly higher in septuagenarians (9.5%) and octogenarians (10.8%) as compared to patients younger than 70 (5.0%, $p = 0.001$).

Rates of liver-specific complications such as bile leakage, postoperative haemorraghe and liver failure were not statistically different between age groups. Pneumonia more frequently occurred in septuagenarians (7.7%) and octogenarians (9.3%) as compared with patients younger than 70 (4.6%, $p < 0.001$). Cardiac complications more often occurred in septuagenarians (4.7%) and octogenarians (7.7%) as compared with patients younger than 70 (2.1%, $p < 0.001$).

In a subgroup analysis for tumour type, 30-day major morbidity ($p < 0.001$) and 30-day mortality ($p = 0.001$) after CRLM resection were 7.3% and 1.0% respectively in patients younger than 70, 8.3% and 2.3% in septuagenarians and 9.7% and 2.6% in octogenarians (supplementary table 2a). In patients younger than 70, the pneumonia rate was 4.3%, this was 7.0% in septuagenarians and 9.6% in octogenarians ($p < 0.001$). In patients younger than 70, cardiac

Table 2 Postoperative outcomes stratified for age in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands

Factor	Age <70 N = 4023	Age 70-79 N = 2135	Age ≥80 N = 429	P-value
Bile leakage				0.816
No	3831 (96)	2025 (95)	407 (95)	
Yes	170 (4)	95 (5)	20 (5)	
Missing[a]	22	15	2	
Postoperative haemorraghe				0.513
No	3630 (99)	1831 (99)	370 (99)	
Yes	31 (1)	20 (1)	5 (1)	
Missing[a]	362	284	54	
Postoperative liver failure				0.587
No	3906 (98)	2077 (98)	420 (98)	
Yes	95 (2)	46 (2)	7 (2)	
Missing[a]	22	12	2	
Intra-abdominal infection				0.110
No	3566 (93)	1809 (92)	375 (94)	
Yes	246 (7)	154 (8)	24 (6)	
Missing[a]	211	172	30	
Surgical site infection				0.327
No	3692 (97)	1888 (96)	384 (96)	
Yes	119 (3)	76 (4)	14 (4)	
Missing[a]	212	171	31	
Pneumonia				**<0.001**
No	3637 (95)	1813 (92)	362 (91)	
Yes	177 (5)	152 (8)	37 (9)	
Missing[a]	209	170	30	
Cardiac complication				**<0.001**
No	3914 (98)	2020 (95)	395 (92)	
Yes	85 (2)	100 (5)	33 (8)	
Missing[a]	24	15	1	
Thromboembolic complication				**0.015**
No	3913 (98)	2051 (97)	418 (98)	
Yes	85 (2)	71 (3)	10 (2)	
Missing[a]	24	15	1	
Length of stay (median + IQR)				**<0.001**
	6.00 (4.00–8.00)	6.00 (4.00–9.00)	7.00 (5.00–10.0)	
Overall 30-day morbidity				**<0.001**
No	2892 (82)	1349 (63)	270 (63)	
Yes	1131 (28)	786 (37)	159 (37)	
30-day major morbidity				**0.049**
No	3651 (91)	1901 (89)	379 (88)	
Yes	372 (9)	234 (11)	50 (12)	

(*continued on next page*)

Table 2 (*continued*)

Factor	Age <70 N = 4023	Age 70-79 N = 2135	Age ≥80 N = 429	P-value
30-day mortality				**<0.001**
No	3947 (98)	2061 (96)	414 (96)	
Yes	76 (2)	74 (4)	15 (4)	

Percentages are shown in brackets and are rounded to the nearest full number. Therefore, they may not add to 100.
Synchronous additional resection was defined as any extra procedure including vascular resection or reconstruction or as additional intra-abdominal resection as a result of in-growth in other structures.
Major liver resection was defined as resection of at least 3 liver segments.
Postoperative complicated course was defined as a complication after surgery resulting in prolonged hospitalization (>14 days), or reintervention or death as a result of a complication.
Major morbidity was defined as a Clavien Dindo Grade 3 or higher complication.
[a] Missing are not included in the analysis.

complications occurred in 1.6%, this was 4.1% in septuagenarians and 7.6% in octogenarians ($p < 0.001$).

In a subgroup analysis for non-colorectal liver metastases, 30-day major morbidity ($p = 0.200$) and 30-day mortality ($p = 0.263$) were 8.4% and 1.4% respectively in patients younger than 70, 10.3% and 2.8% in septuagenarians and 20.0% and 0.0% in octogenarians (supplementary table 2b). In patients younger than 70, cardiac complications occurred in 1.4%, this was 6.5% in septuagenarians and 7.1% in octogenarians ($p = 0.010$).

In a subgroup analysis for HCC, 30-day major morbidity ($p = 0.348$) and 30-day mortality ($p = 0.203$) were 12.6% and 4.0% respectively in patients younger than 70, 16.1% and 7.0% in septuagenarians and 17.8% and 6.7% in octogenarians (supplementary table 2c).

In a subgroup analysis for bile duct and gallbladder carcinoma, 30-day major morbidity ($p = 0.484$) and 30-day mortality (0.599) were 20.8% and 6.6% respectively in patients younger than 70, 25.0% and 8.3% in septuagenarians and 20.7% and 10.3% in octogenarians (supplementary table 2d). In patients younger than 70, the pneumonia rate was 4.2%, this was 9.6% in septuagenarians and 12.5% in octogenarians ($p = 0.026$).

Association of patient demographics, disease burden and operative characteristics with postoperative outcomes

Age 80 years or older (aOR 1.42, CI: 1.00–2.00, $p = 0.045$), ASA classification 3 or higher (aOR 1.52, CI: 1.25–1.85, $p < 0.001$) histopathological steato-hepatitis (aOR 2.16, CI: 1.33–3.39, $p = 0.001$), resection of biliary cancer (aOR 2.98, CI: 2.21–4.00, $p < 0.001$), and major liver resection (aOR 2.45, CI: 2.01–2.98, $p < 0.001$) were associated with higher 30-day major morbidity (Table 3). Female sex (aOR 0.66, CI 0.55–0.81, $p < 0.001$) and laparoscopic liver resection (aOR 0.61, CI: 0.47–0.78, $p < 0.001$) were associated with lower 30-day major morbidity. No influence of hospital volume on 30-day major morbidity was observed (data not shown).

Table 3 Univariable and multivariable logistic model of patient, tumor and surgical factors associated with 30-day major morbidity in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				<0.001			**<0.001**
Male	4012	1			1		
Female	2558	0.70	0.59–0.83		0.66	0.55–0.81	
Missing[a]	17						
Age in years				0.051			**0.049**
<70	4023	1			1		
70-80	2135	1.21	1.02–1.44	0.032	1.13	0.93–1.37	0.202
>80	429	1.29	0.94–1.76	0.106	1.42	1.00–2.00	**0.045**
Charlson Comorbidity Index (CCI)				0.004			0.169
0/1	4725	1			1		
2+	1862	1.29	1.08–1.53		1.15	0.94–1.39	
Body Mass Index		1.00	0.98–1.02	0.933			

Table 3 (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
American Society of Anesthesiology (ASA) classification				<0.001			**<0.001**
I/II	4944	1			1		
III+	1540	1.66	1.39–1.97		1.52	1.25–1.85	
Missing[a]	103						
History of liver resection				0.711			
No	5385	1					
Yes	1091	1.04	0.84–1.28				
Missing[a]	111						
Histopathological liver disease				0.001			**0.010**
Normal	3891	1			1		
Steatosis	1058	1.25	1.00–1.55	0.050	1.26	0.99–1.58	0.054
Steato-hepatitis	147	2.23	1.42–3.39	<0.001	2.16	1.33–3.39	**0.001**
Cirrhosis	237	1.72	1.16–2.47	0.005	1.39	0.89–2.14	0.140
Sinusoidal dilatation	75	2.08	1.09–3.70	0.018	1.71	0.86–3.15	0.103
Missing	1179	1.00	0.79–1.24	0.938	0.95	0.71–1.25	0.703
Type of tumour				<0.001			**<0.001**
CRLM	4759	1			1		
Other LM	479	1.19	0.85–1.64	0.291	1.27	0.88–1.78	0.186
HCC	738	1.93	1.53–2.42	<0.001	1.22	0.92–1.62	0.169
Biliary cancer	611	3.38	2.71–4.19	<0.001	2.98	2.21–4.00	<**0.001**
Preoperative chemotherapy				0.621			
No	4458	1					
Yes	1508	0.81	0.75–1.11	0.377			
Missing	621	0.92	0.69–1.22	0.585			
Maximum diameter of largest tumour (mm)				<0.001			0.204
< 20	1494	1			1		
20-34	1840	1.08	0.81–1.40	0.572	0.98	0.74–1.29	0.871
35-54	1083	1.5	1.13–1.98	0.050	1.14	0.85–1.54	0.381
> 55	884	2.04	1.55–2.69	<0.001	1.20	0.88–1.63	0.249
Missing	1286	2.13	1.66–2.75	<0.001	1.32	0.99–1.77	0.071
Major liver resection				<0.001			**<0.001**
No	4545	1			1		
Yes	1769	3.42	2.89–4.04	<0.001	2.45	2.01–2.98	<**0.001**
Missing[a]	273	1.66	1.08–2.46	0.015	1.12	0.16–4.75	0.887
Surgical approach				<0.001			**<0.001**
Open	4677	1			1		
Laparoscopic	1622	0.44	0.36–0.55		0.61	0.47–0.78	
Missing[a]	288						
Type of hospital[b]				<0.001			0.217
Regional hospitals	2960	1			1		
Tertiary referral hospital	3627	1.74	1.47–2.07		1.14	0.93–1.39	

[a] Missing not included in analyses based on relatively small group.
[b] Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery.

Table 4 Univariable and multivariable logistic model of patient, tumor and surgical factors associated with 30-day mortality in patients who underwent liver resection for primary and secondary liver tumours between 2014 and 2019 in the Netherlands

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.009			**0.023**
Male	4012	1			1		
Female	2558	0.64	0.45–0.89		0.65	0.44–0.94	
Missing[a]	17						
Age in years				<0.001			**0.001**
<70	4023	1			1		
70-80	2135	1.86	1.35–2.58	<0.001	1.78	1.25–2.55	**0.001**
>80	429	1.88	1.03–3.21	0.028	2.19	1.13–4.00	**0.012**
Charlson Comorbidity Index (CCI)				0.349			
0/1	4725	1					
2+	1862	1.17	0.83–1.63				
Body Mass Index		1.01	0.98–1.05	0.404			
American Society of Anesthesiology (ASA) classification				<0.001			**<0.001**
I/II	4944	1			1		
III+	1540	2.90	2.12–3.96		2.39	1.69–3.37	
Missing[a]	103						
History of liver resection				0.500			
No	5385	1					
Yes	1091	1.15	0.76–1.68				
Missing[a]	111						
Histopathological liver disease				<0.001			**0.015**
Normal	3891	1			1		
Steatosis	1058	1.43	0.92–2.16	0.103	1.45	0.91–2.26	0.103
Steato-hepatitis	147	2.81	1.23–5.60	0.007	2.86	1.19–6.07	**0.011**
Cirrhosis	237	3.54	1.97–6.00	<0.001	2.76	1.37–5.34	**0.003**
Sinusoidal dilatation	75	3.49	1.20–8.09	<0.001	2.39	0.75–6.01	0.096
Missing	1179	1.19	0.76–1.82	0.440	1.23	0.71–2.04	0.433
Type of tumour				<0.001			**<0.001**
CRLM	4759	1			1		
Other LM	479	1.07	0.47–2.11	0.847	1.33	0.57–2.75	0.465
HCC	738	3.44	2.28–5.09	<0.001	1.51	0.87–2.49	0.145
Biliary cancer	611	5.04	3.42–7.33	<0.001	3.21	1.85–5.55	**<0.001**
Preoperative chemotherapy				0.029			**0.003**
No	4458	1			1		
Yes	1508	0.75	0.50–1.10	0.154	1.06	0.66–1.67	0.817
Missing	621	0.45	0.20–0.87	0.031	0.10	0.02–0.55	**0.023**
Maximum diameter of largest tumour (mm)				<0.001			0.121
< 20	1494	1			1		
20-34	1840	1.31	0.73–2.42	0.367	1.24	0.67–2.40	0.352
35-54	1083	2.18	1.21–4.02	0.011	1.53	0.81–2.97	0.124
> 55	884	3.18	1.80–5.80	<0.001	1.46	0.77–2.85	0.110
Missing	1286	3.80	2.27–6.68	<0.001	2.12	1.17–4.02	**<0.001**
Major liver resection				<0.001			**<0.001**

Table 4 (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
No	4545	1			1		
Yes	1769	8.05	5.65–11.7	<0.001	5.92	3.97–9.01	<**0.001**
Missing[a]	273	1.12	0.76–1.45	0.567	1.03	0.82–1.35	0.631
Surgical approach				<0.001			0.159
Open	4677	1			1		
Laparoscopic	1622	0.39	0.23–0.61		0.69	0.40–1.15	
Missing[a]	288						
Type of hospital[b]				<0.001			0.847
Regional hospitals	2960	1			1		
Tertiary referral hospital	3627	2.08	1.39–2.96		1.02	0.63–1.36	

[a] Missing not included in analyses based on relatively small group.
[b] Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery.

Age between 70 and 80 (aOR 1.78, CI: 1.25–2.55, p = 0.001), age 80 years or older (aOR 2.19, CI: 1.13–3.00, p = 0.012), ASA classification 3 or higher (aOR 2.39, CI: 1.69–3.37, p < 0.001), histopathological steato-hepatitis (aOR 2.86, CI: 1.19–6.07, p = 0.011), histopathological liver cirrhosis (aOR 2.76, CI: 1.37–5.34, p = 0.003), resection of biliary cancer (aOR 3.21, CI: 1.85–5.55, p < 0.001) and major liver resection (aOR 5.92, CI: 3.97–9.01, p < 0.001) were associated with higher 30-day mortality (Table 4). Female sex (aOR 0.65, CI: 0.44–0.94, p = 0.023) was associated with lower 30-day mortality. No influence of hospital volume on 30-day mortality was observed (data not shown).

Discussion

In this nationwide population-based study postoperative outcomes, including 30-day overall morbidity, 30-day major morbidity, 30-day mortality and length of stay, were all worse in septuagenarians and octogenarians compared to patients who were younger than 70 years old. Not liver-specific complications, but cardiopulmonary complications were mainly responsible. This association remained significant after correction for patient demographics, disease burden and operative characteristics.

Overall number of liver resections for primary and secondary liver tumours did not increase during the study period in the Netherlands and an increase in the proportion of older patients resected 2014 to 2019 was attributed to a decrease in patients who were younger than 70 years. Aging of the Dutch population has been described since 2000 and could induce an increase of primary and secondary liver tumours at older age which has been observed in this study.[19] This is comparable to earlier studies which stated that an increase in patients undergoing liver resection would be observed over time in CRLM, HCC and cholangiocarcinoma patients.[9,20–22] Recent studies showed a significant increase of several types of primary and secondary liver tumours.[23,24] Stabilization of the number of liver resections could have several reasons such as other treatment options for primary and secondary liver tumours such as definitive chemotherapy, thermal ablation, stereotactive radiotherapy or liver transplantation which are not included in the DHBA might be increasingly used. Another explanation might be that colorectal cancer is treated at an earlier stage in our country due to the nationwide screening for colorectal cancer.[25] This could have decreased the incidence of CRLM in the Netherlands and could have attributed to the stabilization of liver resection. Future studies will have to show whether there is a shift from surgery to other definitive treatments in the Netherlands for primary and secondary liver tumours and what this means for postoperative and oncological outcomes.

The more complicated course in elderly patients is concordant with two studies from the UK which addressed postoperative outcomes after CRLM resection in elderly patients, and found comparable overall morbidity of 49% and mortality of 3% in the elderly patient.[6,7] A large cohort from the UK confirmed that age is associated with worse postoperative outcomes.[26] In Australia, a report showed that octogenarians had postoperative major morbidity of 27%.[5] It was described that elderly patients may benefit more from laparoscopic resection of CRLM with better postoperative outcomes.[27,28] In the present study the same beneficial effect of minimally invasive surgery was observed in elderly patients. As expected, cardiopulmonary complications have occurred more often in patients who underwent liver resection in the current study, while no differences were observed regarding liver-specific complications. This implies that patients may benefit from additional perioperative physiotherapy focusing on specifically breathing exercises to decrease cardiopulmonary complications.[29] The UK studies showed that no differences in survival was seen between younger and older patients.[26] However, the current study did not assess oncological outcomes. With respect to short-term postoperative outcomes, resection of primary and secondary liver tumours can be performed in elderly patients and is safe as demonstrated in the current study. Laparoscopic liver resection could improve postoperative outcomes as well as preoperative and postoperative optimization of frail patients. Several options such as comprehensive cardiopulmonary screening and possibilities regarding prehabilitation could be explored to achieve better postoperative outcomes in elderly patients.[30]

In accordance with literature, postoperative outcomes observed after liver resection for HCC and biliary cancer are significantly worse in elderly patients.[8,31–38] Long-term survival after resection of HCC or biliary cancer was not different in elderly patients.[36,38–40] The nationwide data form this study and previous reports show that liver resection of primary and secondary liver tumours in elderly patients can be performed with relatively low mortality. Preoperative patient selection is key, in particular in HCC and biliary cancer patients.

Several characteristics such as preoperative higher age, ASA classification, histopathological liver diseases, biliary cancer and major liver resection were independently associated with 30-day major morbidity and 30-day mortality. These risk factors for major morbidity and mortality can be used by surgeons treating patients with primary and secondary liver tumours. This study may help to counsel and select patients before resection and to discuss aforementioned strategies to reduce complication rates in elderly patients.

This study from a national surgical database has several limitations including the retrospective design which inherently induces selection and indication bias that could have influenced the results. In this kind of auditing data, several important operative and postoperative data such as exact tumour location, peroperative complications and detailed operative characteristics are lacking. Ninety-day postoperative outcomes and oncological outcomes are lacking and could influence the results and conclusions drawn from the present study.

In conclusion, this study shows higher 30-day major morbidity and 30-day mortality in elderly patients mainly due to non-surgical cardiopulmonary complications. Therefore, perioperative patient optimization should be stressed to improve postoperative outcomes in the elderly patient.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.03.002.