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ABSTRACT

Background: Differences in patient demographics and disease burden can influence comparison of hospital performances. This study aimed to provide a case-mix model to compare short-term post-operative outcomes for patients undergoing liver resection for colorectal liver metastases (CRLM).
Methods: This retrospective, population-based study included all patients who underwent liver resection for CRLM between 2014 and 2018 in the Netherlands. Variation in case-mix variables between hospitals and influence on postoperative outcomes was assessed using multivariable logistic regression. Primary outcomes were 30-day major morbidity and 30-day mortality. Validation of results was performed on the data from 2019.
Results: In total, 4639 patients were included in 28 hospitals. Major morbidity was 6.2% and mortality was 1.4%. Uncorrected major morbidity ranged from 3.3% to 13.7% and mortality ranged from 0.0% to 5.0%. between hospitals. Significant differences between hospitals were observed for age higher than 80

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(0.0%–17.1%, $p < 0.001$), ASA 3 or higher (3.3%–36.3%, $p < 0.001$), histopathological parenchymal liver disease (0.0%–47.1%, $p < 0.001$), history of liver resection (8.1%–36.3%, $p < 0.001$), major liver resection (6.7%–38.0%, $p < 0.001$) and synchronous metastases (35.5%–62.1%, $p < 0.001$). Expected 30-day major morbidity between hospitals ranged from 6.4% to 11.9% and expected 30-day mortality ranged from 0.6% to 2.9%. After case-mix correction no significant outliers concerning major morbidity and mortality remained. Validation on patients who underwent liver resection for CRLM in 2019 affirmed these outcomes.

Conclusion: Case-mix adjustment is a prerequisite to allow for institutional comparison of short-term postoperative outcomes after liver resection for CRLM.

Introduction

Colorectal liver metastases occur in 25–50% of patients with colorectal cancer [1,2]. Resection is still the cornerstone of curative treatment of CRLM but is accompanied by considerable morbidity and mortality [3–6]. Strategies to further improve postoperative outcomes after liver resection are therefore still needed.

Clinical auditing of surgical procedures has been described as a powerful tool to assess and improve quality of care [7]. In clinical auditing, the first step is to determine endpoints such as postoperative outcomes. After data collection on the endpoints one is able to reflect on these in order to improve them afterwards [8–10]. The Dutch HepatoBiliary Audit (DHBA) was founded by the board of the Dutch Liver Study Group, representing more than 75% of all Dutch liver surgeons in 2013. From 2013 a minimal required annual volume of 20 liver resections per hospital was mandatory in order to pursue liver surgery, which resulted from new insights during centralization of liver surgery in the Netherlands between 2005 and 2013 [11]. From 2014 onwards, registration of all liver resections in the DHBA was mandatory for all hospitals performing liver surgery. The DHBA was explicitly designed to monitor and compare quality of care between hospitals performing liver surgery in the Netherlands [12].

Quality of care in the DHBA is monitored and compared using several quality indicators [13], which can cover structure of care, process of care or (short-term) postoperative outcomes. Patient- and tumour characteristics that may influence outcomes are often referred to as case-mix factors. Together they show the population treated in a hospital. The case-mix of a hospital can positively or negatively impact the comparison of outcomes as observed in other fields of surgery [14–16]. Case-mix adjustment therefore seems obligatory to produce a reliable and valid comparison of outcomes between hospitals. Contrasting other oncological surgical procedures which are straight forward, for CRLM numerous types of liver resection can be performed [17]. All these anatomical variations of liver resection have their own technical difficulty and associated postoperative outcomes [18,19]. This makes that case-mix adjustment for liver resection is heterogeneous and has not been described earlier.

The aim of this study was to address variation in patient demographics and disease burden between hospitals and to develop and validate a case-mix adjustment model to compare the differences in 30-day major morbidity and 30-day mortality after liver resection for CRLM between hospitals in the Netherlands.

Methods

This was a population-based study performed in the Netherlands. Data were retrieved from the DHBA, a mandatory nationwide audit in which all Dutch hospitals performing liver surgery register all liver resections. The DHBA is an opt-out registry. Data verification was performed to provide insight in completeness and accuracy of the DHBA when compared to the Dutch Cancer Registry [12,20]. No ethical approval was needed under Dutch law as the DHBA is part of the Dutch Inspectorate of health care and research is carried out with an anonymized dataset.

Patient selection

All patients who underwent liver resection for CRLM between the January 1, 2014 and December 31, 2018 in the Netherlands and who were registered in the DHBA before March 22, 2019 were included in this study. Patients were excluded if date of birth, date of surgery type of tumour, type of surgical intervention, and occurrence of major morbidity or mortality was missing. All patients who only underwent thermal ablation without resection for CRLM were excluded.

As a sensitivity analysis, the variation in case-mix factors and final case-mix correction model in the 2014 to 2018 study period was validated on the complete 2019 cohort of the DHBA. Inclusion of patients and analysis were the same for the core set of 2014–2018 and for the validation on the 2019 cohort.

Main outcomes

Main outcomes were major morbidity and mortality after liver resection. Both are existing quality indicators in the DHBA calculated per hospital for the last two consecutive years of full registration in the DHBA. Major morbidity was defined as a complication grade 3a or higher according to Clavien-Dindo classification, within 30 days of the liver resection [21]. Mortality was defined as death during hospitalization or within 30 days of the liver resection. Both quality indicators are public for all hospitals registering in the DHBA both for all resections and stratified for minor and major liver resection. Case-mix corrected funnelplots are calculated for both quality indicators over two consecutive years in the DHBA its daily practice and were calculated over 2018 and 2019 for the validation.

Case-mix factors

Several categories of variables were assessed to represent the case-mix in the DHBA. Variables were selected on the basis of expert opinion. The DHBA scientific committee, consisting of 23 liver surgeons and interventional radiologists from the Netherlands, acted as experts. Patient characteristics included sex, age, American Society of Anesthesiologist (ASA) classification, Body Mass Index (BMI), comorbidity scores according the Charlson Comorbidity Score (CCI), histopathological classification of liver parenchyma adjacent to tumour tissue and previous liver surgery. Tumour characteristics included number of CRLM, diameter of the largest CRLM before the initiation of tumour-specific treatment

such as preoperative chemotherapy and synchronous (within 6 months of detection of the primary tumour) or metachronous diagnosis of the CRLM. Treatment characteristics included use of preoperative chemotherapy, use of thermal ablation in combination with resection, minor or major liver resection, and type of hospital where resection was performed. Latter was either a regional hospital or a tertiary referral center. Major liver resection was defined as resection of three or more adjacent Couinaud segments.

Statistical analysis

The mean percentage accompanied by the minimum and maximum percentage for every variable in every hospital was calculated to assess between hospital variation regarding possible case-mix factors. These percentages and ranges were displayed in a violin graph. Using univariable logistic regression models with case-mix factors as dependent variable and hospitals as independent variable the significance of this variation between hospitals was calculated.

The association of case-mix factors with major morbidity and mortality was investigated using two separate multivariable logistic regression models. For this multivariable model, all possible case-mix factors were selected. Case-mix factors were included through univariable logistic regression ($p < 0.10$) after checking for multicollinearity when a restriction of the multivariable logistic regression model was needed due to the number of degrees of freedom. For major morbidity, all possible case-mix factors were included as no restriction was needed because of high number of events. For mortality restriction of case-mix factors was performed, due to low number of events.

Based on the case-mix of all patients, the expected morbidity and mortality was calculated per patient using a multivariable logistic regression model. As a result of all patients operated on in a hospital, the expected morbidity and mortality per hospital was calculated. To visualize the difference in quality indicators between hospitals, the observed/expected ratio (O/E ratio) was used. By dividing the observed morbidity of every hospital by the expected morbidity of that same hospital, the O/E ratio was calculated. This is the case-mix adjusted ratio indicating the performance of a hospital. An O/E ratio above 1 indicated that a hospital performed worse than expected, an O/E ratio below 1 indicated that a hospital performed better than expected. The 95% confidence intervals (CI) were calculated to indicate whether the O/E ratio of a hospital was statistically different from the other hospitals.

Multicollinearity was tested through the Variance Inflation Factor (VIF). A VIF of 3 or more was the cut-off value indicating multicollinearity. Patients with missing values were analysed as a separate group in multivariable logistic regression if these exceeded 5% of the total included number of patients. If the missing values in a variable was below 5%, the missing patients were excluded from the analysis.

As a sensitivity analysis, the association of annual hospital volume (<20, 20–39, 40–59, 60–79, and >80) with postoperative major morbidity and mortality was assessed. This variable was added in both multivariable logistic regression models (not shown).

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

Population characteristics

In total 4776 patients who underwent liver resection for CRLM were included during the study period (Table 1). One hundred and thirty-seven patients were excluded because of missing information regarding critical variables. In the remaining 4639 patients, 30-day major morbidity was 6.2% and 30-day mortality was 1.4%.

Between-hospital variation in case-mix factors

Considerable differences in the case-mix variables between hospitals were observed (Fig. 1, Supplementary Table 1). Differences between hospitals in the range of mean percentages were observed in age higher than 80 (0.0%–17.1%, $p < 0.001$), ASA 3 or higher (3.3%–36.3%, $p < 0.001$), a CCI of 2 or higher (19.7%–63.3%, $p < 0.001$), histopathological parenchymal liver disease (0.0%–47.1%, $p < 0.001$), history of liver resection (8.1%–36.3%, $p < 0.001$), preoperative chemotherapy (1.5%–55.1%, $p < 0.001$), resection of more than 3 CRLM in one surgical session (7.0%–36.9%, $p < 0.001$), resection of largest CRLM with a diameter of 55 mm or larger (0.0%–26.4%, $p < 0.001$), major liver resection (6.7%–38.0%, $p < 0.001$), bilobar disease (5.0%–60.6%, $p < 0.001$), synchronous metastases (35.5%–62.1%, $p < 0.001$) and rectal primary tumour (20.4%–46.6%, $p < 0.001$) and extra-hepatic disease (3.9%–38.5%, $p < 0.001$). The proportion of female patients did not differ between hospitals (25.0%–47.0%, $p = 0.232$).

Case-mix factors for 30-day major morbidity and 30-day mortality

Several case-mix factors were associated with the occurrence of 30-day major morbidity. The factors male sex, age above 65, ASA classification 3 or higher, histopathological steato-hepatitis or sinusoidal dilatation, major liver resection, synchronous diagnosis of metastases, extra-hepatic disease and treatment in a tertiary referral center were all statistically significant case-mix factors for 30-day major morbidity (Table 2a). Rectal primary tumour was associated with lower 30-day major morbidity. Based on Table 2a we observe that age, ASA classification and major liver resection were most important to correct for concerning 30-day morbidity.

Charlson Comorbidity index, Body Mass Index, histopathological steatosis or cirrhosis, history of liver resection, history of preoperative chemotherapy, number of CRLM, diameter of largest CRLM and bilobar disease were also included in the 30-day morbidity case-mix model but were not significant case-mix factors. No restriction in the case-mix model was needed due to the high number of events ($n = 286$).

Several case-mix factors were significantly associated with 30-day mortality. These case-mix factors included age above 80, ASA classification 3 or higher, histopathological steato-hepatitis or sinusoidal dilatation, history of liver resection, and major liver resection (Table 2b). Based on Table 2b we observe that age above 80, ASA classification 3 or higher, history of liver resection and major liver resection were most important to correct for concerning 30-day mortality.

Sex, BMI, preoperative chemotherapy, number of CRLM and type of hospital were all non-significant case-mix factors for 30-day mortality. Due to the low number of events ($n = 66$), Body Mass Index, Charlson comorbidity index, maximum diameter of largest CRLM, bilobar disease, location of primary tumour, synchronous or metachronous diagnosis of the metastases and extra-hepatic

Table 1
Baseline characteristics of patients diagnosed with colorectal liver metastases (CRLM) between 2014 and 2018 in the Netherlands.

Factor		N (%)
Total		**4639**
Patient characteristics		
Sex		
	Male	2926 (63)
	Female	1713 (37)
Age (years)		
	<50	329 (7)
	50–64	1593 (34)
	65–79	2375 (51)
	≥80	333 (7)
	Missing	9 (0)
Charlson Comorbidity Index (CCI)		
	0/1	3393 (73)
	≥2	1113 (24)
	Missing	133 (3)
Body Mass Index (BMI)	Mean (sd)	26.3 (4.4)
American Society of Anesthesiology (ASA) classification		
	ASA I/II	3638 (78)
	ASA III+	870 (19)
	Missing	131 (3)
History of liver resection		
	No	3713 (80)
	Yes	815 (18)
	Missing	111 (2)
Histopathology liver parenchyma[a]		
	Normal liver	2907 (63)
	Steatosis	720 (16)
	Steato-hepatitis	76 (2)
	Cirrhosis	35 (1)
	Sinusoidal dilatation	51 (1)
	Missing	850 (18)
Preoperative chemotherapy		
	No	3009 (70)
	Yes	1314 (30)
Tumour characteristics		
Number of lesions		
	1	1978 (43)
	2	969 (21)
	3	512 (11)
	4	316 (6)
	≥5	668 (15)
	Missing	196 (4)
Maximum diameter of largest CRLM (mm[b])		
	<20	1230 (27)
	20–34	1508 (33)
	35–54	746 (16)
	≥55	456 (9)
	Missing	699 (15)
Location primary tumour		
	Colon	2966 (64)
	Rectal	1657 (46)
	Missing	16 (0)
Major liver resection		
	No	3620 (78)
	Yes	1019 (22)
Bilobar disease		
	No	2472 (53)
	Yes	2015 (44)
	Missing	152 (3)
Timing of metastases		
	Metachronous	2361 (51)
	Synchronous	2064 (45)
	Missing	214 (4)
Extra-hepatic disease		
	No	3799 (82)
	Yes	543 (12)
	Missing	297 (6)
Type of hospital[c]		
	Regional hospitals	2557 (55)
	Tertiary referral centers	2082 (45)
Year of surgery		
	2014	854 (19)
	2015	896 (19)
	2016	984 (21)
	2017	986 (21)
	2018	919 (20)

[a] Histopathology of the liver on the basis of pathological examination.
[b] Millimeter.
[c] Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery

disease were not included in the case-mix model for 30-day mortality.

The sensitivity analysis concerning inclusion of annual hospital volume (<20, 20–39, 40–59, 60–79, >80) did not reveal significant differences concerning 30-day major morbidity and 30-day mortality and was therefore not reported here.

Also, multicollinearity was assessed in all models and was ruled out as the VIF was below 2.0 in all models for all variables.

Hospital comparison of 30-day major morbidity and 30-day mortality

Uncorrected 30-day major morbidity between hospitals ranged from 3.3% to 13.7% (Supplementary Fig. 1a). Uncorrected 30-day mortality between hospitals ranged from 0.0% to 5.0% (Supplementary Fig. 1b). Expected 30-day major morbidity between hospitals ranged from 6.4% to 11.9% (Fig. 2a). Expected 30-day mortality between hospitals ranged from 0.6% to 2.9% (Fig. 2b).

After adjustment for case-mix factors, O/E ratios for 30-day morbidity ranged from 0.41 to 1.42 (Table 2a). None of the hospitals performing liver surgery had a significantly higher 30-day major morbidity rate than expected (Fig. 3a). Two hospitals had significantly lower 30-day major morbidity rates than expected.

After correction for case-mix factors, O/E ratios for 30-day mortality ranged from 0.0 to 5.18 (Table 2b). None of the hospitals performing liver surgery had a significantly higher 30-day mortality rate than expected (Fig. 3b). In four hospitals a significantly lower 30-day mortality rate than expected was observed.

Validation on patients who underwent liver resection for CRLM in 2019 in the Netherlands

778 patients who underwent liver resection for CRLM in the Netherlands in 2019 were included from all 23 hospitals still performing liver surgery (Supplementary Table 2). Significant differences between hospitals in the range of mean percentages were observed in ASA 3 or higher (11.9%–86.1%, $p < 0.001$), a CCI of 2 or higher (6.7%–100%, $p < 0.001$), histopathological parenchymal liver disease (0.0%–100%, $p < 0.001$), preoperative chemotherapy (0.0%–72.2%, $p < 0.001$), resection of more than 3 CRLM in one surgical session (0.0%–57.1%, $p < 0.001$), major liver resection (0.0%–40.3%, $p < 0.001$), bilobar disease (6.7%–65.0%, $p < 0.001$), synchronous metastases (20.4%–80.0%, $p < 0.001$) and rectal primary tumour (12.5%–58.2%, $p < 0.001$). No differences in sex, age higher than 80, history of liver resection, resection of largest diameter CRLM with a diameter of 55 mm and extra-hepatic disease were observed in this validation cohort. Uncorrected 30-day morbidity ranged from 0.0% to 28.6% uncorrected 30-day mortality ranged from 0.0%% to 8.6% in 2019. Expected 30-day morbidity ranged from 2.9% to 13.3%

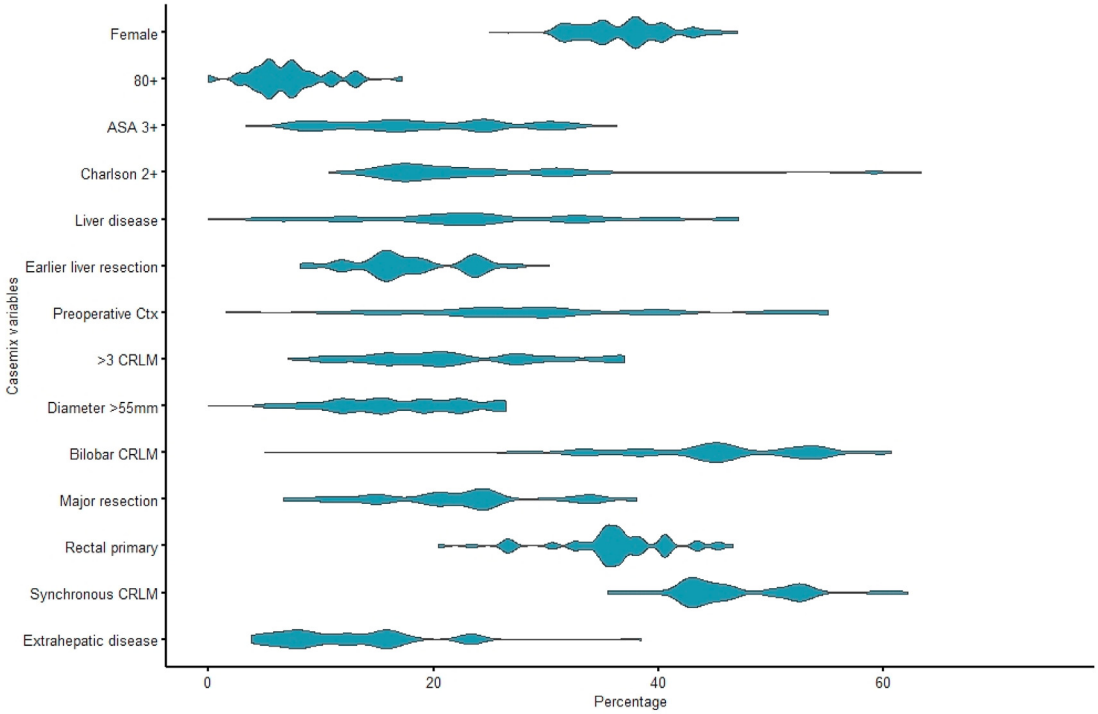

Fig. 1. a Violin graph showing the distribution of mean percentages (range) of case-mix variables per hospital in the Netherlands in patients who underwent liver resection for colorectal liver metastases between 2014 and 2018.

between hospitals. Expected 30-day mortality ranged from 0.1% to 2.6% between hospitals.

Case-mix corrected funnelplots based on data from 2018 to 2019 combined showed that one hospital performed significantly worse than expected and one hospital performed significantly better than expected concerning 30-day major morbidity (Supplementary Fig. 2a). No significant outliers were observed regarding 30-day mortality in after case-mix correction (Supplementary Fig. 2b). However, validation of the case-mix corrected funnelplot concerning 30-day mortality was performed on a underpowered cohort with only 29 events.

Discussion

This study confirms that adjustment for several patient demographics and disease burden in hospitals (i.e. case-mix factors) is required when comparing postoperative outcomes between hospitals after liver resection for CRLM. Significant differences observed in the distribution of mean percentages of case-mix factors between hospitals in the Netherlands result in expected 30-day major morbidity which ranged between hospitals 6.4%–11.9% and expected 30-day mortality which ranged from 0.6% to 2.9% respectively. After adjustment for case-mix factors, no significant outliers were observed. Moreover, uncorrected 30-day mortality ranged between hospitals from 0% to 5% and no significant outliers were observed after case-mix correction. Validation on the 2019 cohort in the Netherlands confirmed significant variation in case-mix, variation in expected outcomes and need for case-mix correction to compare postoperative outcomes between hospitals. Age above 80, high ASA classification, presence of steato-hepatitis or sinusoidal dilatation, previous history of liver resection and major liver resection were the most important case-mix factors for 30-day major morbidity and for 30-day mortality.

Oncological liver resection is heterogeneous compared to other oncological resections. This is due the large variety in localization of tumours within the liver and different surgical approaches that exist each having their own technical difficulty. As a result, daily practice of case-mix correction for liver surgery has not been described to date. However, risk factors for adverse postoperative outcomes have been described earlier. One study on major liver surgery in the USA that focused on case-mix correction for major morbidity and mortality showed that cardiac and renal comorbidities negatively impacted postoperative outcomes, which is concordant with results in this study [22]. Several studies observed comparable case-mix factors such as higher number of CRLM, synchronous detection of CRLM, and major resection being risk factors for major morbidity and mortality [23,24]. Recently, an Italian study showed that complexity of the resection, earlier liver resection and concomitant liver disease influenced postoperative outcomes in benchmarking laparoscopic liver resections [25]. The current study shows that variation in major morbidity from 3.3% to 13.7% and variation in mortality from 0% to 5% between hospitals in the Netherlands was deemed non-significant after case-mix correction. This underlines the importance of case-mix adjustment when comparing outcomes after resection of CRLM.

The observed variation in distribution of percentages of patient demographics and disease burden between hospitals found in this study is not unexpected given the referral patterns in oncological networks that have been established in the Netherlands over the last years. There are seven oncological networks. Each consists of one or two tertiary referral centers which perform liver surgery and several regionals hospitals of which a few perform liver surgery [26]. This structure of oncological care can be a reason for the variation in case-mix between hospitals and this variation in case-mix is in concordance with earlier studies on colorectal cancer and thoracic surgery in the Netherlands [15,27].

The primary objective of this study was to create a case-mix model to perform a valid comparison of hospital performances

Table 2a
Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day morbidity in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014 and 2018.

			Univariable analysis			Multivariable analysis		
Factor		N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex					0.001			**<0.001**
	Male	2926	1			1		
	Female	1713	0.69	0.55–0.86		0.63	0.49–0.81	
Age (years)					0.030			**0.049**
	<50	329	1			1		
	50 - 64	1593	1.56	0.96–2.68	0.085	1.68	0.91–3.25	0.083
	65 - 79	2375	1.76	1.11–2.99	0.025	1.73	1.02–3.37	**0.048**
	≥80	333	2.23	1.26–4.07	0.007	2.27	1.21–4.97	**0.015**
	Missing*	9						
Charlson Comorbidity Index (CCI)					0.015			0.315
	0/1	3393	1			1		
	≥2	1113	1.32	1.05–1.65		1.15	0.88–1.48	
	Missing*	133						
Body Mass Index			1.01	0.98–1.03	0.545	1.00	0.97–1.03	0.813
American Society of Anesthesiology (ASA) classification					<0.001			**<0.001**
	I/II	3638	1			1		
	III +	870	1.80	1.42–2.26		1.76	1.36–2.31	
	Missing*	131						
Histopathology liver parenchyma§					<0.001			0.134
	Normal liver	2907	1			1		
	Steatosis	720	1.35	1.02–1.75	0.028	1.19	0.88–1.62	0.300
	Steato-hepatitis	76	1.80	0.89–3.31	0.078	2.02	1.02–3.94	**0.042**
	Cirrhosis	35	1.00	0.24–2.80	1.000	0.51	0.03–2.37	0.479
	Sinusoidal dilatation	51	2.59	1.21–5.03	0.008	2.35	1.00–4.67	**0.050**
	Missing	850	0.71	0.52–0.95	0.027	0.91	0.60–1.30	0.581
History of liver resection					0.495			0.804
	No	3713	1			1		
	Yes	815	1.10	0.84–1.41		1.03	0.75–1.52	
	Missing*	111						
Preoperative chemotherapy					0.124			0.672
	No	3009	1			1		
	Yes	1315	1.19	0.95–1.49		1.03	0.71–1.25	
	Missing*	316						
Number of lesions					0.312			0.702
	1	1978	1			1		
	2	969	0.97	0.73–1.29	0.857	0.92	0.62–1.23	0.458
	3	512	1.30	0.93–1.80	0.112	1.28	0.80–1.76	0.385
	4	316	1.23	0.81–1.81	0.320	1.31	0.63–1.66	0.872
	≥5	668	1.24	0.91–1.66	0.165	1.09	0.65–1.50	0.965
	Missing*	196						
Maximum diameter largest CRLM (mm)*					<0.001			0.233
	<20	1230	1			1		
	20 - 34	1508	1.13	0.85–1.50	0.420	1.05	0.67–1.25	0.566
	35 - 54	746	1.47	1.06–2.03	0.020	1.09	0.78–1.58	0.564
	≥55	465	2.26	1.61–3.17	<0.001	1.41	0.93–2.06	0.105
	Missing	699	1.23	0.87–1.73	0.230	1.22	0.80–1.87	0.343
Major liver resection					<0.001			**<0.001**
	No	3620	1			1		
	Yes	1019	2.20	1.77–2.72		2.04	1.54–2.60	
Bilobar disease					0.344			0.942
	No	2472	1			1		
	Yes	2015	1.10	0.90–1.36		1.11	0.75–1.31	
	Missing*	152						
Location primary tumour					<0.001			**<0.001**
	Colon	2966	1			1		
	Rectal	1657	0.63	0.50–0.77		0.64	0.50–0.83	
	Missing*	16						
Timing of metastasis					0.001			**0.002**
	Metachronous	2361	1			1		
	Synchronous	2064	1.41	1.15–1.73		1.50	1.16–1.94	
	Missing*	214						
Extra-hepatic disease					0.083			**0.023**
	No	3799	1			1		
	Yes	543	1.29	0.96–1.72		1.46	1.05–2.00	
	Missing	297						
Type of hospital∞					0.030			**0.041**
	Regional centers	2557	1			1		
	Tertiary referral centers	2082	1.25	1.02–1.54		1.29	1.02–1.64	

*Missing not included in analyses based on relatively small group.
§History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
Mm = millimeter.
∞ Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery
$Unclear why percentage missing is so high.

Table 2b
Univariable and multivariable logistic regression model to assess the association of patient and tumour characteristics with 30-day mortality in patients with colorectal liver metastasis (CRLM) in the Netherlands between 2014 and 2018.

			Univariable analysis			Multivariable analysis		
Factor		N	OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex					0.034			0.200
	Male	2926	1			1		
	Female	1713	0.54	0.30–0.93		0.68	0.37–1.20	
Age (years)					0.044			0.122
	<50	329	1			1		
	50 - 64	1593	3.54	0.72–63.9	0.220	3.11	0.62–57.4	0.280
	65 - 79	2375	5.90	1.28–105	0.080	4.81	0.97–87.8	0.131
	≥80	333	6.02	1.02–114	0.010	6.73	1.03–133	**0.049**
	Missing*	9						
Charlson Comorbidity Index (CCI)					0.179			
	0/1	3393	1					
	≥2	1113	1.43	0.83–2.38				
	Missing*	133						
Body Mass Index			1.05	1.00–1.10	0.046	1.03	0.97–1.09	0.264
American Society of Anesthesiology (ASA) classification					<0.001			**<0.001**
	I/II	3638	1			1		
	III +	870	4.58	2.81–7.50		4.30	2.51–7.40	
	Missing*	131						
Histopathology liver parenchyma§					0.011			0.078
	Normal liver	2907	1			1		
	Steatosis	720	1.73	0.89–3.18	0.089	1.62	0.84–3.10	0.161
	Steato-hepatitis	76	4.84	1.42–12.6	0.004	4.93	1.46–14.1	**0.007**
	Cirrhosis	35	5.28	0.83–18.4	0.026	2.77	0.14–16.8	0.361
	Sinusoidal dilatation	51	5.44	1.28–15.9	0.006	4.29	1.13–14.2	**0.041**
	Missing	850	1.04	0.48–2.04	0.921	1.39	0.63–2.82	0.382
History of liver resection					0.004			**0.022**
	No	3713	1			1		
	Yes	815	2.16	1.25–3.59		1.96	1.18–3.72	
	Missing*	111						
History of preoperative chemotherapy					0.156			0.873
	No	3009	1			1		
	Yes	1315	1.44	0.86–2.37		1.05	0.57–1.91	
	Missing*	316						
Number of CRLM					0.072			0.231
	1	1978	1			1		
	2	969	1.33	0.64–2.66	0.425	1.29	0.61–2.65	0.487
	3	512	2.35	1.11–4.77	0.021	2.26	1.03–4.77	0.071
	4	316	0.94	0.22–2.76	0.919	0.74	0.18–2.26	0.639
	≥5	668	2.26	1.13–4.40	0.019	1.54	0.73–3.16	0.245
	Missing*	196						
Maximum diameter largest CRLM (mm)*					0.103			
	<20	1230	1					
	20 - 34	1508	1.64	0.78–3.67	0.204			
	35 - 54	746	2.33	1.04–5.44	0.042			
	≥55	465	3.02	1.26–7.29	0.012			
	Missing	699	1.95	0.82–4.70	0.129			
Major liver resection					<0.001			**<0.001**
	No	3620	1			1		
	Yes	1019	6.03	3.67–10.1		6.08	3.56–10.6	
Bilobar disease					0.115			
	No	2472	1					
	Yes	2015	1.49	0.91–2.46				
	Missing*	152						
Location primary tumour					0.146			
	Colon	2966	1					
	Rectal	1657	0.67	0.38–1.13				
	Missing*	16						
Timing of metastasis					0.814			
	Metachronous	2361	1					
	Synchronous	2064	0.94	0.57–1.56				
	Missing*	214						
Extra-hepatic disease					0.593			
	No	3799	1					
	Yes	543	1.21	0.56–2.36				
	Missing	297						
Type of hospital∞					0.068			0.219
	Regional	2557	1			1		
	Tertiary referral centers	2082	1.58	0.97–2.59		1.39	0.82–2.37	

*Missing not included in analyses based on relatively small group.
§ History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis
Mm = millimeter
∞ Type of hospital: tertiary referral centre is defined as hospitals with highest expertise on oncologic surgery
$ Unclear why percentage missing is so high.

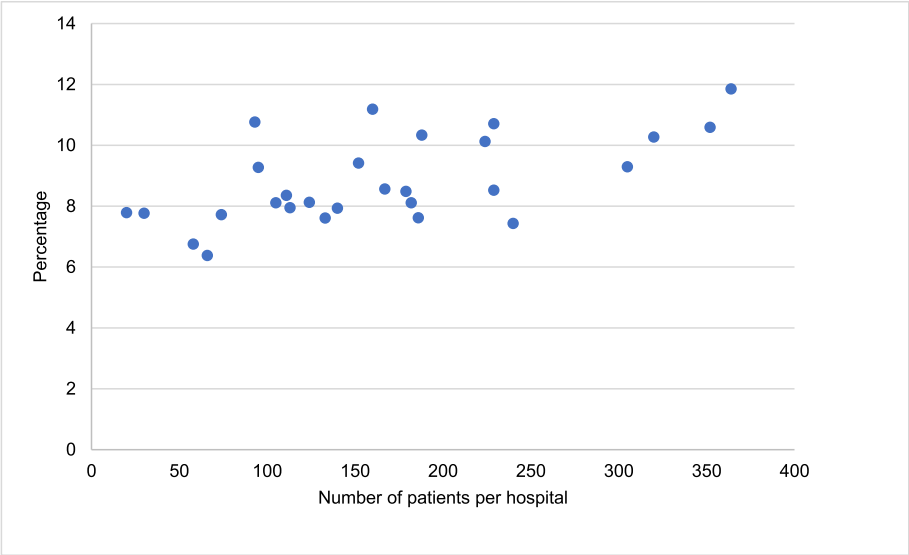

Fig. 2a. Expected percentage of 30-day major morbidity in hospitals in performing liver resection for colorectal liver metastases in the Netherlands between 2014 and 2018.

regarding major morbidity and mortality after CRLM resection. A case-mix model should include only not patient- and tumor characteristics that are not in the preoperative decisional pathway and that cannot be influenced. Including decisions from the treating team that are in the preoperative decisional pathway would distort or nullify the measurement of quality of surgical care in a hospital as one would correct for decisions made by the treating physician or its team [28].

In this study we included tertiary referral centre as a case-mix factor because patient characteristics and disease burden in these centers can be different from regional hospitals due to specific tertiary care. These differences between tertiary and regional hospitals include more patients with abnormalities regarding anatomy or histological liver parenchyma such as liver cirrhosis, centrally located, CRLM located diffuse in the liver and the more frequent use of two-stage procedures which have been proven a risk for worse postoperative outcomes as these procedures are technically more demanding and cannot be easily captured in the existing case-mix variables available in the DHBA [29,30]. In the Netherlands patients are also referred to tertiary centers if a treating physician in a regional hospital is unsure about the capability to perform a certain surgical procedure. However, this type of detailed information is lacking in the DHBA which is the reason for instead including tertiary centre as factor in the case-mix.

Also included in the case-mix model was synchronous diagnosis of the primary colorectal tumour and CRLM. This variable was associated with higher major morbidity but not with mortality. This association was not found in earlier studies [31,32]. The negative effect from synchronous diagnosis of primary colorectal tumour and CRLM is possibly a result of patients in this group who underwent simultaneous resection of both the colorectal primary tumour and CRLM in one surgical session. Earlier studies have shown a negative effect on postoperative outcomes of this treatment regime [33,34].

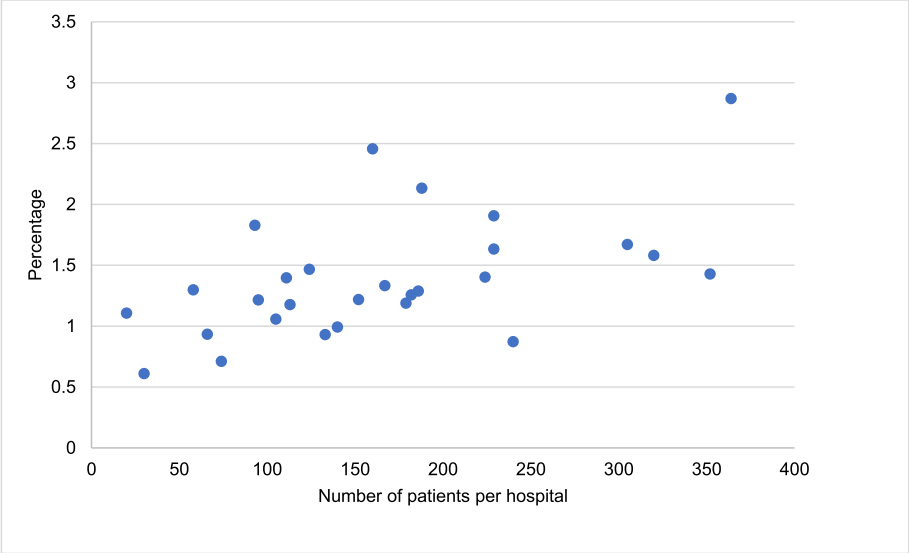

Fig. 2b. Expected percentage of 30-day mortality in hospitals in performing liver resection for colorectal liver metastases in the Netherlands between 2014 and 2018.

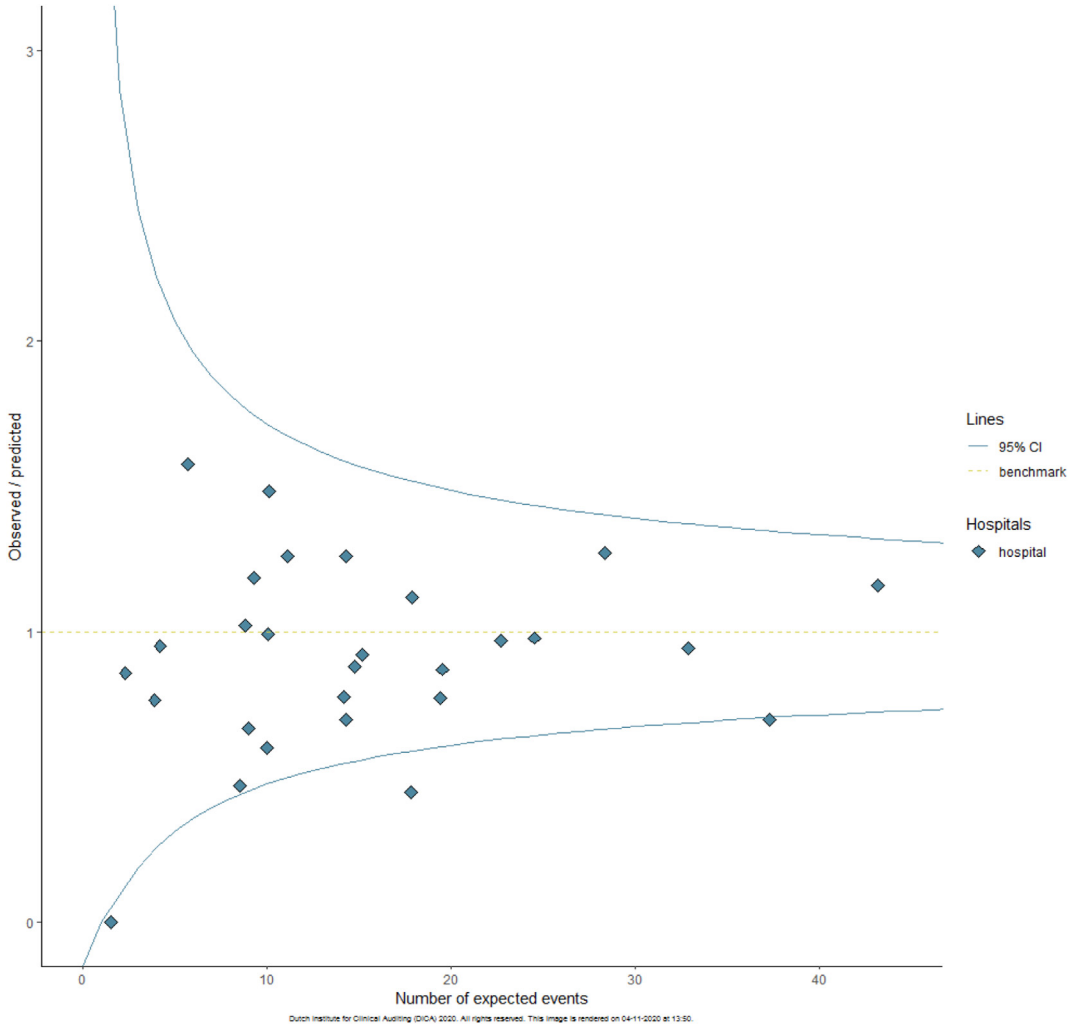

Fig. 3a. Case-mix adjusted funnel-plot of between-hospital variation in 30-day major morbidity in patients with colorectal liver metastases in the Netherlands between 2014 and 2018.
Case-mix adjusted for: sex, age in years, ASA III/IV, Charlson Comorbidity Index, histopathology of liver parenchyma, history of liver resection, preoperative chemotherapy, number of CRLM, maximum diameter of the largest CRLM prior to treatment, major liver resection, location of the primary tumour, Bilobar disease, synchronous metastases, extra-hepatic disease and type of hospital.

Not included in the case-mix model was a minimally invasive approach. Several studies showed less postoperative morbidity after minimally invasive liver resection compared to open liver resection and it is increasingly used [9,35,36]. However, whether a liver resection is performed minimally invasive and is successful depends mainly on patient selection by the surgical team and their technical capability. For this reason, minimally invasive approach finds itself in the decisional pathway and was not included in the case-mix model.

Comparing postoperative outcomes is the main purpose of the DHBA and several other clinical audits affiliated to the Dutch Institute of Clinical Auditing. The authors think that it is important to also provide unadjusted outcomes to caregivers as every opportunity should be given to reflect and improve on adverse events. This is important to address possible outliers that have been positively or negatively been affected by case-mix correction independent from patient characteristics and disease burden. Some hospitals 'choose' to operate only patient with certain characteristics. This can reflect on outcomes before and after case-mix correction and is the main reason for showing both uncorrected and corrected outcomes to caregivers. After adjusting for case-mix factors, several hospitals showed to perform better (Fig. 3a and b) than expected on the basis of their case-mix. It is reassuring that none of the centers had higher morbidity and mortality than expected in the overall cohort. It is intriguing that some had significantly lower rates, and other centers should try to learn from their decisional process in order to improve their own process and outcomes.

Limitations of the study include the lack of 90-day morbidity and mortality data as these could be a better estimate of postoperative outcomes as well as the possible heterogeneity in the reporting of complications between hospitals [37–39]. Also, as this study was performed from an auditing database several possible case-mix factors that might influence postoperative outcomes such as technical difficulty of the procedure and patients' muscle mass index could not be included in the case-mix model. It should be noted that the case-mix corrected funnelplots are underpowered mainly for the 30-day mortality, which could cloud the absence of significance of hospitals who suffered higher or lower mortality than expected. Future studies should also evaluate oncological

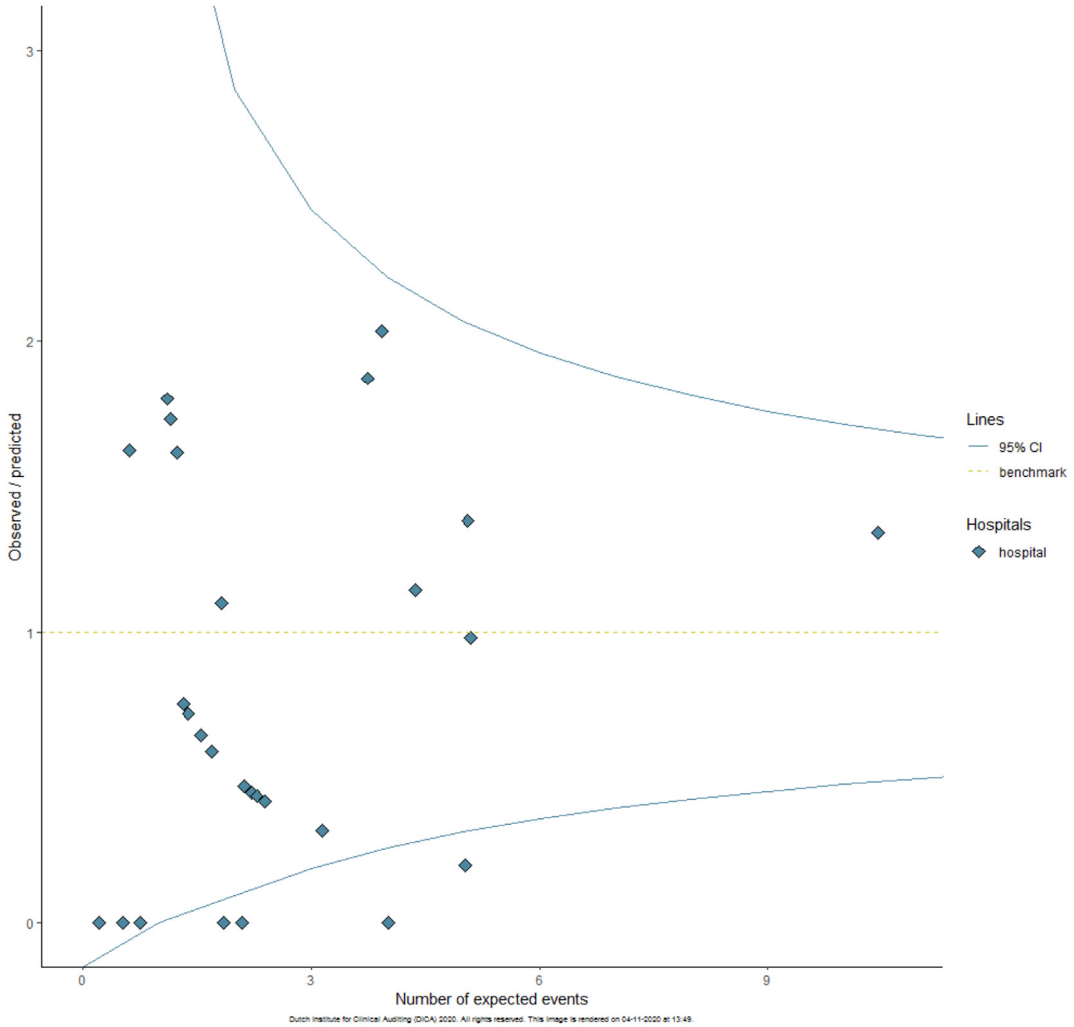

Fig. 3b. Case-mix adjusted funnel-plot of between-hospital variation in 30-day mortality in patients with colorectal liver metastases in the Netherlands between 2014 and 2018. Case-mix adjusted for: sex, age in years, ASA III/IV, histopathology of liver parenchyma, preoperative chemotherapy, history of liver resection, number of CRLM, major liver resection and type of hospital.

long-term outcomes which are not present in our audit. Finally, external validation of the presented case-mix model is lacking. Internal validation proved that this case-mix model based on CRLM patients who underwent surgery between 2014 and 2018 in the Netherlands was valid, but external validation should be performed in another country to establish the model and prove its use in practice.

In conclusion, the large between-hospital variation in population demographics and disease burden of patients who underwent liver resection for CRLM results in a wide range of expected 30-day major morbidity and expected 30-day mortality. This emphasizes the use of a case-mix adjustment model in order to properly compare postoperative outcomes between Dutch hospitals in a national audit.

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Credit author statement

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Declaration of conpeting interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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