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## Value of outcomes research in colorectal cancer care

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## Chapter 2

### **DIFFERENCES IN EFFECT OF CASEMIX VARIABLES BETWEEN REFERRAL AND NON-REFERRAL HOSPITALS IN THE NETHERLANDS AND RELEVANCE FOR HOSPITAL COMPARISONS.**

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Michel W.J.M. Wouters, on behalf of the Dutch Surgical Colorectal  
Cancer Audit Group.

Submitted

## ABSTRACT

**Background:** Hospital comparisons based on outcome need to be adjusted for casemix. As there is a trend towards centralisation in oncology, patient population in specialized hospitals might differ from other hospitals to such an extent that the impact of casemix variables may be different for referral hospitals thereby affecting fair hospital comparisons. In addition, referral hospitals treat patients with paradoxical risk profiles e.g. young patients with advanced disease not adequately captured if no interactions are added. Therefore, our aim was to analyse whether the effect of variables used in the Dutch ColoRectal Audit (DCRA) casemix model are different between the referral and non-referral hospital population. Furthermore we added clinically relevant interactions to the standard model and evaluated their effect and added value on model performance.

**Methods:** Patients who underwent a surgical resection for colon cancer between 2009 and 2015 (n=39,604) were selected from the DCRA. 10 hospitals function as tertiary referral hospitals in the Netherlands and were selected as 'referral hospitals'. We analysed differences in effect of variables between referral versus non-referral hospitals in the currently used multivariate regression model for postoperative complicated course and tested the added value of added interactions between age and Charlson comorbidity index, pT4 tumor and metastatic disease (M1). Model performance was assessed by a C-statistic based on an ROC curve.

**Results:** Mean age of patients treated in referral hospitals is 3 years lower ( $p < 0.001$ ) than in non-referral hospitals. Patients treated in referral hospitals more often have pT4 disease or a Charlson comorbidity index of 2+ ( $p < 0.001$ ). The variables age, ASA score, tumor location, M1 disease, preoperative tumor complications, additional resection due to local tumor invasion or metastasis and pT classification have a significantly different effect (all  $p \leq 0.001$ ) on postoperative complicated course in referral hospitals. Added interactions had no significant effect on outcomes for the referral population. A separate model for referral hospitals showed the best model fit.

**Conclusion:** This study shows that referral hospitals treat a different patient population and that the effect of variables on postoperative complicated course is different in the casemix model. A specifically fitted casemix model to the referral population shows best model performance for referral hospitals.

## INTRODUCTION

Patient populations treated for a specific condition significantly differ across hospitals.<sup>1</sup> Because patient and disease characteristics affect outcome, casemix is a confounder in between-hospital comparisons based on outcome. Therefore, casemix adjustment needs to be applied when comparing outcomes across hospitals with the aim to judge quality of hospital care. The most efficient way to execute risk adjustment is with a logistic regression model - in case of a binary outcome - that contains the most important predictors of the outcome parameter.

In oncology, there is a trend towards centralisation of treatment of specific patient subgroups particularly in case of rare disease or high complexity of treatment.<sup>1,2</sup> Although colorectal cancer is one of the cancers with the highest incidence worldwide, specific patient groups with advanced stage of disease may benefit from treatment and thus cluster in expert centres. The patient population in such specialized hospitals might differ from the other hospitals to such an extent that the impact of different casemix variables (and thus also risk adjustment) may be different for referral hospitals.<sup>1,2</sup>

The models for casemix adjustment in the DCRA are implicitly weighted more due to the majority of high volume non-specialised care hospitals, with a smaller contribution of the few referral hospitals. Furthermore, the models only contain main effects for casemix adjustment, and no interaction terms. In this way, the assumption is made that there are no interactions between the variables (e.g. comorbidities have the same effect on outcome across all ages), and it is uncertain whether these assumptions are actually met, especially in the case of paradoxical risk profiles – i.e. young patients with advanced disease - in some (referral) hospitals. Therefore, our aim was to analyse whether the effect of variables used in the DCRA casemix model is different within the referral versus non-referral hospital population and to evaluate the added value of a priori defined and clinically relevant interactions to the standard model.

## **METHODS**

### **Patients**

Data were derived from the DCRA, a disease specific national audit.<sup>3</sup> This audit collects information on patient, tumor and treatment characteristics of all patients undergoing a resection for primary colorectal cancer in the Netherlands and their postoperative outcomes. All Dutch hospitals participate, with approximately 97 percent completeness in 2012 based on comparison with the Netherlands Cancer Registry (NCR). Details of the DCRA regarding data collection and methodology have been published previously.<sup>1,3,4</sup> All patients with colon cancer registered from 1<sup>st</sup> of January 2009 until the 1<sup>st</sup> of September 2015 were included in this study. For the clarity of this study we excluded patients with rectal cancer, due to the different variables that influence postoperative outcomes in these two populations.<sup>3</sup>

### **Hospitals**

In the Dutch healthcare system, there are 8 university hospitals and 2 non-university hospitals that function as tertiary referral hospitals for high-complex colorectal cancer care and therefore treat a selected patient group, of the total of 92 hospitals. These hospitals will be named 'referral hospitals' throughout the continuation of this manuscript. The population of all referral hospitals combined is referred to as "referral population", the population of all non-referral hospitals combined is referred to as "non-referral population".

### **Outcome Measures**

We used the short-term postoperative outcome of complicated postoperative course for our analyses. Complicated postoperative course was defined as any complication leading to a reintervention (radiological/surgical), prolonged hospital stay (>14 days) or death, within 30 days from surgery.<sup>1,4-6</sup>

### *Casemix correction model and interactions*

#### **Standard casemix correction model**

We used the standard casemix correction model for colon cancer as currently used in the DCRA as reference model.<sup>7</sup> In short, this

multivariate regression model for outcomes after a resection for colon cancer includes several patient and tumor characteristics: age, gender, American Society of Anaesthesiologists (ASA) score, Charlson comorbidity index, Body Mass Index (BMI), tumor location, metastatic disease (M1), preoperative tumor complications, emergency surgery, additional resection due to local tumor invasion or metastasis and TNM classification (pT and c/pM classification). The 5<sup>th</sup> edition of the TNM classification is reported in the DCRA.

### **Interactions**

Clinically relevant interactions were derived from expert opinion. Interactions between the variables age and Charlson comorbidity index, age and pT4 tumor, and age and metastatic disease were considered as potentially different in the referral versus non-referral population and therefore used in our analysis.

### **Statistical analysis**

We first calculated differences between the referral and non-referral population for all variables included in the DCRA casemix model. Differences in casemix between patients treated in referral versus non-referral hospitals were tested using chi-square tests for categorical variables and t-tests for continuous variables. Hospital outcomes adjusted for casemix on postoperative complicated course per hospital in 2013-2014 were presented in a funnel plot using the standard casemix model, showing the overall average outcome with its 95% confidence limits, based on a Poisson distribution, varying in relation to the population size and indicating referral versus non-referral hospitals.

Then we estimated a casemix model separately for referral hospitals and non-referral hospitals, by including the same casemix variables as above in the model but only selecting the referral or non-referral population. In this way we show whether casemix variables have different effects on the outcome of postoperative complicated course in referral versus non-referral hospitals. In order to test whether casemix variables have a significantly different effect in the referral population compared to the non-referral population we added an interaction of each variable with the variable "referral hospital (yes/no) to the standard model. A significant interaction in this analysis indicates a significantly different



effect of the variable on the outcome of postoperative complicated course in the referral versus non-referral hospitals. To test the added value of interactions we extended the standard casemix model (for the total, non-referral and referral population) for the outcome of postoperative complicated course with clinically relevant interactions.

Model performance was assessed using a C-statistic based on a Receiving Operator Characteristic Curve (ROC curve), both for the standard model and for the models fitted for referral and non-referral hospitals separately and with or without clinically relevant interactions for the outcome of postoperative complicated course. We also analysed the model performance of the standard casemix model applied to referral hospitals; by saving the predicted values of the standard casemix model for the referral population and then calculate a c-statistic as above.

Statistical analyses were carried out with the statistical software packages SPSS version 18.0 (SPSS, Chicago, IL, USA). A p-value of 0.05 was considered significant in all analyses.

## **RESULTS**

### **Patients and hospitals**

Table 1 shows the percentages of patient and tumor characteristics for referral and non-referral hospitals. Referral hospitals more often treat younger patients and more often patients with comorbidity and advanced disease (i.e. pT4 tumor and metastasis). However, there is variance in patient characteristics among the referral hospitals, e.g. mean age for colon cancer varies from 62.8 to 71.2 years per hospital and the percentage of patients with a pT4 colon tumor from 13.0 to 26.0% (data not shown).

Figure 1 shows a funnel plot with the adjusted percentage of postoperative complicated course for colon cancer per hospital in 2013-2014, using the standard casemix model. None of the referral hospitals had significantly worse results compared to the other Dutch hospitals.

### **Casemix correction model and interactions**

Table 2a shows the effect of the different casemix variables on postoperative complicated course after colon cancer resections fitted to respectively the total (general), non-referral and referral population. Overall, the estimated effects in the general model show most resemblance to the non-referral population (descriptive). The variables age, ASA score, tumor location, metastatic disease, preoperative tumor complications, additional resection due to local tumor invasion or metastasis and pT classification have a significantly different effect (all  $p \leq 0.001$ ) on the outcome postoperative complicated course in referral hospitals compared to non-referral hospitals.

In table 2b the clinically relevant interactions are added to the casemix correction models for postoperative complicated course. The interaction effect of age with Charlson score and age with T4 tumor are significant in the total and non-referral population. None of these interactions were significant in the referral population. In the non-referral population, the age-T4 interaction and age-Charlson interaction were significantly associated with postoperative complication outcome. By adding the interactions, T4 was no longer independently associated with postoperative complications, whereas the independent effect of age remained. So T4 is only a significant predictor of the outcome in combination with age. The same was true for the interaction of age with Charlson comorbidity index.

Table 3 shows the C-statistic for each casemix correction model. The addition of interaction terms did not improve model performance. However, a separate model for referral hospitals showed better model fit for referral hospitals than the standard casemix correction model applied to referral hospitals (with saved predicted values) (C-statistic of 0.707 rather than 0.688 for postoperative complicated course). A separate model for non-referral hospitals did not improve model fit for non-referral hospitals compared with the standard model applied to non-referral hospitals (C-statistic of 0.674 for postoperative complicated course in both models).

## DISCUSSION

The present study has shown that multiple casemix variables have a different effect on postoperative complicated course in referral hospitals than in non-referral hospitals. The currently used casemix model (general model) that is fitted in the total population performs equally well in the non-referral population as a casemix model specifically fitted in non-referral hospitals only. In contrast, the general model performs worse in the referral population when compared to a model specifically fitted in referral hospitals only. As hypothesized, casemix correction models based on the total population showed most resemblance to the non-referral population. However, the interactions that were added to the model were only significantly associated with the postoperative complication outcome in the non-referral population but not in the referral population. None of the added interactions resulted in better model performance.

The DRCA provides risk-adjusted benchmarks as feedback to evaluate hospital quality of care by comparing hospitals with their peers. It gives surgeons information about their performance and aims to thereby stimulate processes that need to be developed or improved.<sup>8</sup> In order to have the intended effect, healthcare providers need to trust their feedback and casemix correction should therefore be as adequate as possible. As this paper shows, referral hospitals seem to treat a different patient population. If casemix variables (e.g. age) would have the same effect on the outcome in both referral and non-referral hospitals, but only the distribution would differ (e.g. have more young patients), then performing casemix adjustment in one model will be adequate. However, if the effect of casemix variables differs as shown in this study, then casemix adjustment is likely to be inadequate and particularly in referral hospitals as the effect in the total model closely resembled that in the non-referral population. In addition, important information determining the caseload of this patient population may be lacking, i.e. detailed information about previous surgery, index surgery, intra-abdominal adhesions, multimodality treatments, and medication use (e.g. steroids) and thus cannot be taken into account in hospital comparisons. The addition of such variables would lead to fairer comparison but would increase the registration burden and these variables are often difficult to register unambiguously. A separate

model for referral centres might solve the before mentioned problem by creating a comparison with similar hospitals ('hospitals like mine') but might induce new questions. That is whether we are sure that any difference in average performance between these 2 groups of hospitals is based on the complexity of patients and not on a difference in quality of care and whether a hospital treats sufficient referral patients to be classified as a referral hospital.

In 2015 Walker et al. published a paper on casemix correction models in the field of hospital comparisons.<sup>9</sup> On the basis of previous literature they concluded that most publications described suboptimal methods for casemix model development, i.e. by the usage of significance testing for the selection of risk factors, a small sample size, categorizing continuous risk factors and ignoring potential interactions between risk factors. They then developed a casemix correction model with casemix variables that were selected on clinical grounds and complemented the model with interaction terms. The only stable interaction - with a bootstrap method - was the interaction between age and metastases and was added to the casemix correction model. In our study we added interactions based on clinical relevance in accordance with the selection of the risk factors in the casemix correction model, but only age-T4 and age-comorbidity were found to be significantly associated and only in non-referral hospitals. Given that model fit also did not improve, it is not clear whether adding these interactions will be of added value for our hospital comparisons.

Our study has some limitations. The division into referral and non-referral hospitals was based on expert consensus. Over time, hospitals may be in one or the other group e.g. if hospitals merge with other hospitals. Furthermore it remains unclear whether referral hospitals have been insufficiently adjusted with the current casemix model, as the effect of some variables was higher in the referral population than in the general model but also lower for other variables so that the net effect remains unclear. Within the general model, none of the referral hospitals performed significantly worse compared to other hospitals on postoperative complicated course in the years 2013-2014. Nevertheless this study clarifies that some variables have a different effect on postoperative outcome in the referral population, and model performance does improve when the casemix model is specifically fitted to the referral population.

In conclusion, this study showed that referral hospitals treat a different population in which the effect of casemix variables on postoperative complicated course is different after a resection for colon cancer. Adding clinically relevant interactions did not improve model performance in referral hospitals as these were not significantly associated with the outcome. A casemix model which was specifically fitted to the referral population showed the best model performance for referral hospitals.

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**TABLES AND FIGURES****Table 1.** Patient and tumor characteristics of colon cancer patients in referral hospitals and non-referral hospitals.

	<b>Non-referral</b>		<b>Referral</b>		<b>P-value</b>
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	
Total	36284		3320		
Age <= 60	5780	15.9	768	23.1	<0.001
Age (mean)	71		68		<0.001
Charlson 2+	9252	25.5	1069	32.2	<0.001
pT4	5920	16.4	683	20.8	<0.001
M1	4277	11.8	711	21.4	<0.001

**Table 2a:** Casemix correction models for postoperative complicated course after resection for colon cancer fitted to all hospitals, non-referral hospitals and referral hospitals. The interaction of each variable with the variable “referral hospital (yes/no) added to the standard model; the p-value of this interaction is displayed in the last column.

	Postoperative complicated course								INTERACTION WITH REFERRAL	p-value
	ALL HOSPITALS		NON-REFERRAL		REFERRAL		OR	95%CI		
	OR	95%CI	OR	95%CI	OR	95%CI				
<b>Female (ref male)</b>	0.688	0.651	0.727	0.703	0.664	0.745	0.543	0.452	0.653	0.652
<b>BMI</b>										0.087
unknown	1.243	1.138	1.358	1.254	1.145	1.373	1.423	0.913	2.216	0.429
<18.5	1.498	1.239	1.811	1.489	1.216	1.825	1.600	0.911	2.812	0.532
18.5-25 (ref)										
25-29	1.026	0.963	1.094	1.034	0.967	1.105	1.015	0.826	1.247	<b>0.065</b>
30+	1.151	1.060	1.249	1.150	1.055	1.254	1.173	0.907	1.516	0.052
<b>Age (continuous)</b>	1.016	1.013	1.019	1.017	1.014	1.020	1.010	1.002	1.019	<b>0.001</b>
<b>Charlson score (continuous)</b>	1.099	1.078	1.120	1.101	1.079	1.125	1.071	1.013	1.132	0.133
<b>ASA score</b>										<b>&lt;0.001</b>
I - II (ref)										
III	1.711	1.608	1.822	1.665	1.559	1.778	2.214	1.797	2.728	<b>&lt;0.001</b>
IV - V	3.253	2.795	3.785	3.346	2.856	3.921	2.232	1.296	3.844	0.162





Continuation of Table 2a

	Postoperative complicated course									
	ALL HOSPITALS		NON-REFERRAL		REFERRAL		INTERACTION WITH REFERRAL			
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI		
<b>Pathological T classification</b>										
(y)pTX/unknown	1.572	1.175	2.103	1.599	1.164	2.197	1.141	0.532	2.449	0.666
(y)pT0-1 (ref)										<0.001
(y)pT2	1.118	0.980	1.275	1.111	0.966	1.277	1.213	0.808	1.821	0.017
(y)pT3	1.194	1.062	1.344	1.218	1.075	1.381	1.020	0.714	1.459	0.411
(y)pT4	1.380	1.208	1.576	1.383	1.201	1.594	1.418	0.950	2.117	<0.001
<b>Metastatic disease</b>	0.966	0.888	1.052	0.945	0.863	1.034	1.115	0.870	1.428	<0.001

**Table 2b:** Casemix correction models with added interactions for postoperative complicated course after resection for colon cancer fitted to all hospitals, non-referral hospitals and referral hospitals.

	Postoperative complicated course								
	ALL HOSPITALS			NON-REFERRAL			REFERRAL		
	AUC= 0.675	OR	95%CI	AUC= 0.797	OR	95%CI	AUC= 0.797	OR	95%CI
<b>Female (ref male)</b>	0.688	0.651	0.727	0.704	0.664	0.745	0.544	0.452	0.654
<b>BMI</b>									
unknown	1.245	1.139	1.360	1.255	1.146	1.375	1.422	0.912	2.216
<18.5	1.503	1.243	1.818	1.493	1.219	1.830	1.610	0.917	2.827
18.5-25 (ref)									
25-29	1.027	0.963	1.094	1.034	0.966	1.105	1.018	0.828	1.252
30+	1.156	1.065	1.255	1.155	1.059	1.259	1.181	0.913	1.528
<b>Age (continuous)</b>	1.013	1.009	1.016	1.013	1.010	1.017	1.005	0.993	1.016
<b>Charlson score (continuous)</b>	0.919	0.796	1.062	0.921	0.785	1.080	0.859	0.604	1.221
<b>ASA score</b>									
I - II (ref)									
III	1.713	1.609	1823	1.668	1.562	1.781	2.214	1.795	2.729
IV - V	3.242	2.785	3774	3.341	2.850	3.916	2.186	1.262	3.786

Continuation of Table 2b

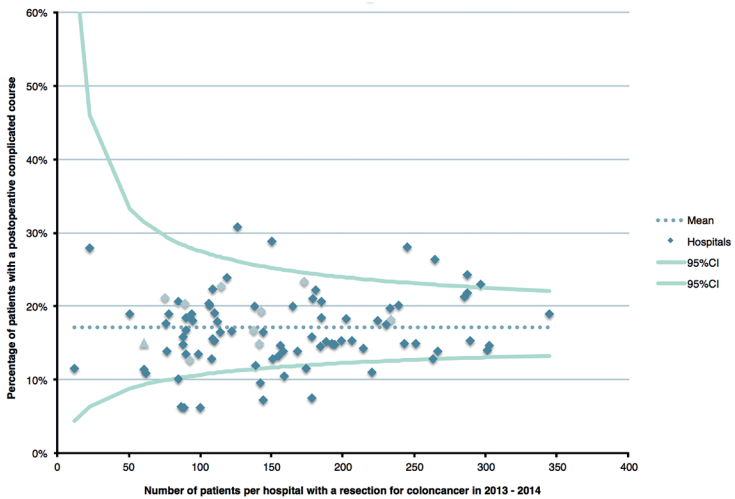
	Postoperative complicated course								
	ALL HOSPITALS			NON-REFERRAL			REFERRAL		
	AUC= 0.675	OR	95%CI	AUC= 0.797	OR	95%CI	AUC= 0.797	OR	95%CI
<b>Location tumor</b>									
Caecum (ref)									
Appendix	1.029	0.729	1.453	0.728	0.459	1.155	1.461	0.808	2.643
Ascendens	1.044	0.956	1.140	1.056	0.963	1.158	0.939	0.697	1.265
Flexura hepatica	1.224	1.086	1.379	1.219	1.076	1.383	1.304	0.879	1.935
Transversum	1.485	1.334	1.652	1.527	1.365	1.708	1.139	0.798	1.626
Flexura splenica	1.462	1.264	1.692	1.586	1.363	1.845	0.609	0.349	1.064
Descendens	1.431	1.272	1.608	1.456	1.288	1.644	1.263	0.818	1.950
Sigmoid	0.968	0.897	1.046	0.966	0.891	1.047	1.013	0.788	1.301
<b>Preoperative tumor complication</b>	1.132	1.063	1.205	1.099	1.028	1.175	1.385	1.137	1.687
<b>Setting</b>									
urgent/emergency	1.655	1.536	1.782	1.703	1.575	1.842	1.512	1.173	1.948

## Continuation of Table 2b

<b>Additional resection</b>									
due to tumor invasion (extensive)	1.858	1.650	2.093	1.667	1.459	1.905	2.351	1.756	3.146
due to tumor invasion (limited)	1.146	1.027	1.279	1.160	1.033	1.302	1.063	0.753	1.501
due to metastatic disease	1.371	1.191	1.578	1.177	0.996	1.392	1.023	0.288	3.631
<b>Pathological T classification</b>									
(y)pTX/unknown	1.561	1.166	2.088	1.589	1.157	2.183	1.121	0.522	2.404
(y)pT0-1 (ref)									
(y)pT2	1.118	0.980	1.276	1.113	0.976	1.280	1.209	0.805	1.815
(y)pT3	1.191	1.059	1.340	1.216	1.073	1.378	1.011	0.707	1.447
(y)pT4	0.835	0.521	1.338	0.763	0.456	1.274	0.812	0.226	2.913
<b>Metastatic disease</b>	1.058	0.628	1.780	0.895	0.500	1.603	1.023	0.288	3.631
<b>Age by Charlson score</b>	1.002	1.000	1.004	1.002	1.000	1.005	1.003	0.998	1.008
<b>Age by pT4 tumor</b>	1.007	1.001	1.013	1.008	1.001	1.015	1.008	0.990	1.026
<b>Age by Metastatic disease</b>	0.999	0.992	1.006	1.001	0.993	1.009	1.001	0.983	1.020

**Table 3:** Model performance of casemix correction models for postoperative complicated course calculated for the total, non-referral and referral population estimated by separate models per population with or without added interactions and estimated per population with saved predicted values.

	<b>Colon</b>	<b>Postoperative complicated course C-statistic</b>
No interactions	Total	0.675
	Non- referral	0.674
	Referral	0.707
With interactions	Total	0.675
	Non- referral	0.674
	Referral	0.707
Fixed model in	Total	0.675
	Non-referral	0.674
	Referral	0.688



**Figure 1:** Funnel plot showing differences in risk-adjusted percentages of postoperative complicated course after resection for colon cancer between hospitals (2013-2014). Light dots are referral hospitals. 95%CI= 95 percent confidence interval.

