Short-term mortality in patients undergoing colorectal cancer surgery: A prediction study

*Karoline Bendix Bräuner, Mikail Gögenur, Viviane Annabelle Lin, Andreas Weinberger Rosen, Johan Stub Rønø Clausen, Eldar Allakhverdiiev, Rasmus Peuliche Vogelsang, Ismail Gögenur*

**Background**

The past 20 years has been a period of giant leaps in knowledge and quality of health care world-wide. A vast majority of clinical guidelines within the large disease groups including cancer are now based on solid evidence gathered over years. Still clinicians may be shocked by unexpected outcomes, which can seem random and unfortunate. For instance every sixth acute colon cancer surgery and every third rectal cancer surgery in Denmark in 2017 lead to death within 30 days (1), and though short-term mortality after elective surgery decreased impressively from 7,3 % in 2001 to 2,8 % in 2011 (2), improvements can still be made.

Using the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) (3) and the ATLAS patient-level prediction-package (4) we developed a short-term mortality prediction model for 30 and 90 days after colorectal cancer surgery based on only preoperative covariates from the Danish Colorectal Cancer Group database (DCCG) (5) containing 76.849 colorectal patient courses over the course of 18 years.

The treatment plan for colorectal cancer patients in Denmark is decided on a multidisciplinary team (MDT) conference (6,7) in the presence of surgeons, oncologist, radiologist and pathologist. The MDT decision is in a large extent based on the MDT referral note. This can vary greatly in quality and amount of provided information. Using the short-term mortality prediction model in combination with our other prediction-models for long-term mortality, complications, readmission and recurrence may provide a better base of decision making for the team and thus better treatment for the patient. The use of only preoperative covariates means that the model is ready to use at the MDT-conference.

The model provides a risk estimate between 0 and 1, but no threshold of when the risk of short-term mortality is too high. Inn a clinical setting, this will depend on many different factors. Using the combined knowledge of our prediction models may lead to a better understanding of why the predicted risk seems high. We recommend that if the risk exceeds the average of operated colorectal cancer patients, the multidisciplinary team should considers why the risk is so high, and what can be done to reduce it. For short-term mortality an increased risk may be a result of poor performance status (8), many comorbidities (9), anemia (10) or old age. Some of these factors can be attended to by:

* Prehabilitation for patients with poor performance status (11)
* Pre-operative iron transfusions for anemic patients (10)
* Referral to medical experts in the patient’s individual comorbidities in order to optimize treatment before surgery

Some factors are not modifiable such as cancer stage and topography, old age and gender, but if the patient in spite of optimization of modifiable predicators still has a high risk of death within 30 and 90 days after surgery, it can be planned to have an intensified follow-up. This may be through the patient going to the intensive care unit (ICU) for the first night after surgery, a slightly prolonged admission or through an increased number of follow-up outpatient consultation, for instance once a week for the first month. Some hospitals also provide open admissions 7 days after surgery, where the patient can just come in, if they are feeling bad or nervous after surgery.

**Methods**

Using ATLAS patient-level prediction (PLP)-package provided by OHDSI, we developed a 30- and 90-day mortality prediction model. The target cohort was patients, who had undergone colorectal cancer surgery, while the outcome cohort was patients, who died. The time at risk was set to from 0 to 30 days after surgery and 0 to 90 days after surgery. We used the PLP-package in R in order to supplement the standard concepts with custom covariates matching the Danish health care data. Examples of this was categorical grouping of ASA and WHO Performance status scores. We used LASSO logistic regression (12), however ran models with all options in ATLAS. We chose this model due to superior performance (calibration and discrimination) as well as it being a simple model for clinicians to understand compared with more advanced machine learning models. We trained the machine-learning (ML) algorithm on 75 % of the population and tested on 25 %. From the test results, we got a ROC-curve, precision recall curve and calibration plot.

**Results**

Out of the almost 77.000 patients in DCCG, 65.612 patients (85,3 %) were operated for colorectal cancer. We found that 30-day mortality had an incidence of 5,42 % and the model predicted this outcome with an AUROC of 0,868 (0,857-0,88). The primary discrimination parameters are found in table 1. The calibration plot for the test cohort in the 30-day model is in figure 1 and the covariates with the highest magnitude can be seen in figure 2. The Brier score for the calibration plot was 0,06 demonstrating good calibration.

For the 90-day mortality model, we found an incidence of 8,53 %, which the model predicted with a AUROC of 0,869 (0,859-0,878). The discrimination values can be found in table 1 and the impactful covariates can be found in table 2. The Brier score for the calibration plot was 0,06 demonstration good calibration.

Due to the significant reduction in postoperative mortality in the years of 2001-2011, we compared the model to a 30-day-mortality model on a cohort from 2011 onwards, which using LASSO demonstrated an AUC of 0,878 and thus not significantly improved performance. We opted to present the 2001 and onwards models as these contained more patients and performance was similar.

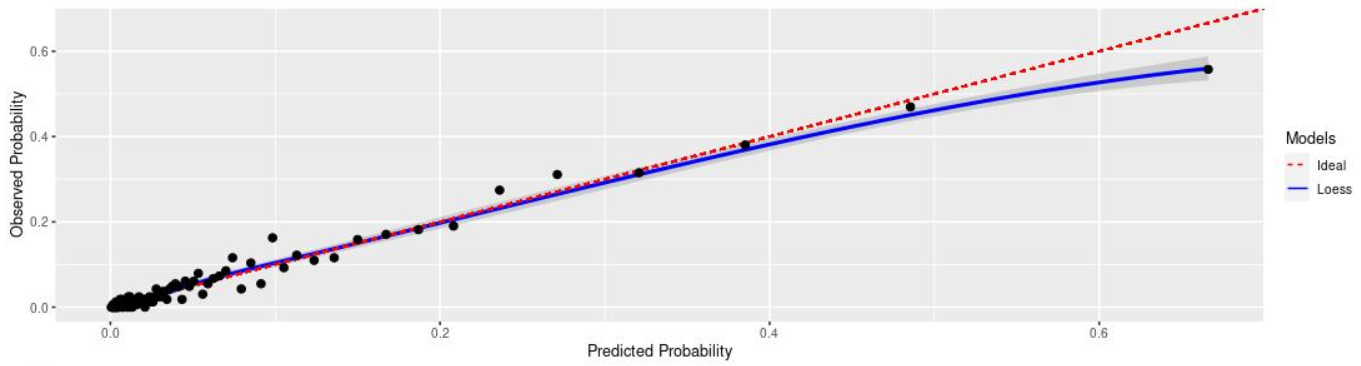
**Conclusion**

Our short-term mortality prediction model may along with the remaining prediction models from Center for Surgical Science be a valid support in multidisciplinary decision-making for cancer patients due to its strong discrimination and usage of multiple clinical covariates.

**Table 1.** Cohort and discrimination value for both prediction models

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Model | Number of patients at risk | Number of patients with outcome | Incidence (%) | AUROC (95% CI) | AUPRC | Brier score |
| 30-day mortality | 65.612 | 3357 | 5,42 % | 0,868 (0,857-0,88) | 0,339 | 0,06 |
| 90-day mortality | 65.612 | 5596 | 8,53 % | 0,869 (0,859-0,878) | 0,429 | 0,06 |

**Figure 1.** Calibration plot for the test set in the 30-day post-operative mortality model



**Table 2.** Most meaningful covariates in 30-day and 90-day mortality models

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 30-day mortality | | | | 90-day mortality | | | |
| Negative valued covariates | | **Positive valued covariates** | | **Negative valued covariates** | | **Positive valued covariates** | |
| Age group  40-44 | -1,63 (n = 4132) | **ASA score 4** | 1,26 (n = 190) | **Excision of liver metastasis** | -1,03 (n = 487) | **Only exploratory surgery (diagnostic laparoscopy or exploratory laparotomy)** | 1,12 (n = 300) |
| Age group  50-54 | -1,12 (n = 2203) | **Only exploratory surgery** | 1,12 (n = 1300) | **Age group 50-54** | -0,97 (n = 2914) | **ASA Score 4** | 1,08 (n = 1300) |
| Age group 45-49 | -1.09 (n = 10515) | **Age group 100-104** | 1,072 (n = 300) | **Age group 40-44** | -0,837 (n = 655) | **Age group 90-94** | 0,961 (n = 1317) |
| Endoscopic procedure before final surgery | -1,01 (n = 10213) | **Age group 90-94** | 1,066 (n = 9) | **ASA Score 1** | -0,783 (n = 13850) | **Primary procedure: Diverting ileostomy** | 0,943 (n = 2394) |
| Age group 55-59 | -0,908 (n = 4351) | **Endoscopic insertion of permanent colonic stent** | 1,01 (n = 1317) | **WHO Performance status 0** | -0,762 (n = 14655) | **Age group 85-89** | 0,829 (n = 4622) |
| ASA Score 1 | -0,896 (n = 8224) | **Age group 85-89** | 0,978 (n = 862) | **Age group 55-59** | -0,627 (n = 4849) | **Endoscopic insertion of permanent colonic stent** | 0,797 (n = 862) |
| Age group 35-39 | -0,814 (n = 100) | **Emergency surgery** | 0,863 (n = 4622) | **Body Mass Index 25-30** | -0,598 (n = 18811) | **Age group 95-99** | 0,699 (n = 190) |
| Performance status 0 | -0,782 (n = 29390) | **Poorly differentiated adenomatous carcinoma** | 0,836 (n = 7584) | **Age group 60-64** | -0,553 (n = 7508) | **Age group 80-84** | 0,582 (n = 8373) |
| Body Mass Index 25-30 | -0,637 (n = 3410) | **Primary procedure: Diverting ileostomy** | 0,828 (n = 266) | **Local macroradical excision of colorectal tumor** | -0,496 (n = 22133) | **Preoperative perforation of large intestine** | 0,524 (n = 526) |
| Age group 60-64 | -0,609 (n =1779) | **Age group 80-84** | 0,609 (n = 2394) | **Age group 45-49** | -0,4529 (n = 1385) | **Emergency operation** | 0,468 (n = 7584) |

**References**

1. Ingeholm P. Landsdækkende database for kræft i tyk- og endetarm (dccg.dk) Klinisk rapport. Dccg [Internet]. 2018;(december). Available from: https://www.sundhed.dk/content/cms/81/4681\_dccg-klinisk-basisrapport-2018.pdf

2. Iversen LH, Ingeholm P, Gögenur I, Laurberg S. Major reduction in 30-day mortality after elective colorectal cancer surgery: A nationwide population-based study in Denmark 2001-2011. Ann Surg Oncol. 2014;21(7):2267–73.

3. Observational Health Data Sciences and Informatics. The Book of OHDSI. 2019;1–470. Available from: https://ohdsi.github.io/TheBookOfOhdsi/TheBookOfOhdsi.pdf

4. Reps J, Schuemie MJ, Ryan PB, Rijnbeek PR. Building patient-level predictive models. 2020;1–45.

5. Ingeholm P, Gögenur I, Iversen LH. Danish colorectal cancer group database. Clin Epidemiol. 2016;8:465–8.

6. Iversen L et al. Den multidisciplinære team-konference (MDT-konferencen). DCCG guideline. Danish Color Cancer Gr [Internet]. 2016;1–2. Available from: https://dccg.dk/wp-content/uploads/2017/08/2016\_11\_MDT.pdf

7. Nielsen KT. Danish Colorectal Cancer Group’s national guidelines for diagnostics and treatment of colorectal cancer - screening [Danish]. 2006;(6). Available from: https://dccg.dk/wp-content/uploads/2017/08/2014\_screening.pdf

8. Bojesen RD, Degett TH, Dalton SO, Gögenur I. High World Heath Organization Performance Status Is Associated With Short And Long-term Outcomes After Colorectal Cancer Surgery. Dis Colon Rectum [Internet]. 2021 Mar 30;Publish Ah(2252):58–66. Available from: http://www.tjyybjb.ac.cn/CN/article/downloadArticleFile.do?attachType=PDF&id=9987

9. Tan KY, Kawamura Y, Mizokami K, Sasaki J, Tsujinaka S, Maeda T, et al. Colorectal surgery in octogenarian patients - Outcomes and predictors of morbidity. Int J Colorectal Dis. 2009;24(2):185–9.

10. Okuyama M, Ikeda K, Shibata T, Tsukahara Y, Kitada M, Shimano T. Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. Surg Today. 2005;35(1):36–40.

11. Bojesen RD, Jørgensen LB, Grube C, Skou ST, Johansen C, Dalton SO, et al. Fit for Surgery – Effects of short-course multimodal individualized prehabilitation in high-risk frail colon cancer patients prior to surgery: A feasibility studyle. Pilot Feasability Stud. :1–15.

12. Williams RD, Markus AF, Yang C, Salles TD, DuVall SL, Falconer T, et al. Seek COVER: Development and validation of a personalized risk calculator for COVID-19 outcomes in an international network. medRxiv. 2020;