Developing prediction models for short-term mortality after surgery for colorectal cancer using a Danish national quality assurance database

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Accepted: 20 June 2022 / Published online: 18 July 2022 © The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

Purpose The majority of colorectal cancer surgeries are performed electively, and treatment is often decided at the multidisciplinary team conference. Although the average 30-day mortality rate is low, there is substantial population heterogeneity from young, healthy patients to frail, elderly patients. The individual risk of surgery can vary widely, and tailoring treatment for colorectal cancer may lead to better outcomes. This requires prediction of risk that is accurate and available prior to surgery.

Methods Data from the Danish Colorectal Cancer Group database was transformed into the Observational Medical Outcomes Partnership Common Data Model. Models were developed to predict the risk of mortality within 30, 90, and 180 days after colorectal cancer surgery using only covariates decided at the multidisciplinary team conference. Several machine-learning models were trained, but due to superior performance, a Least Absolute Shrinkage and Selection Operator logistic regression was used for the final model. Performance was assessed with discrimination (area under the receiver operating characteristic and precision recall curve) and calibration measures (calibration in large, intercept, slope, and Brier score).

Results The cohort contained 65,612 patients operated for colorectal cancer in the period from 2001 to 2019 in Denmark. The Least Absolute Shrinkage and Selection Operator model showed an area under the receiver operating characteristic for 30-, 90-, and 180-day mortality after colorectal cancer surgery of 0.871 (95% CI: 0.86–0.882), 0.874 (95% CI: 0.864–0.882), and 0.876 (95% CI: 0.867–0.883) and calibration in large of 1.01, 0.98, and 1.01, respectively.

Conclusion The postoperative short-term mortality prediction model showed excellent discrimination and calibration using only preoperatively known predictors.

Keywords Colorectal cancer · Machine learning · Prediction model · Mortality · Postoperative

Introduction

Colorectal cancer (CRC) is the third most common malignant neoplastic disease in the world, with an incidence of 1.8 million patients and 935,000 deaths per year [1]. The only definitive cure is surgery; however, exposure to surgery is also related to risk of adverse events related to morbidity, dependency, and ultimately mortality.

The balance between the short- and long-term beneficial effects of surgery and potential harms is at the very core of any decision when scheduling patients for surgery. The correct identification of patients who face a higher risk of surgery-related complications can lead to a more individually optimized treatment plan facilitating shared decision-making and potentially decrease perioperative morbidity and mortality through interventions before surgery [2]. The potential benefit...
of prehabilitation and optimization will most likely be in patients with limited physical resources, who generally have an increased risk of adverse outcomes after surgery [2, 3]. At the same time, in patients with very low risk of complications, a good prediction model that can identify patients with very low risk of mortality can lead to accelerated treatment strategies both before and after surgery.

Although there are many clinical prediction models on short-term mortality, very few are actually used in a clinical context, and even fewer include only preoperative information, which is a prerequisite for them to be used before surgery, e.g., in the multidisciplinary team (MDT) setting [4, 5].

We aimed to develop a prognostic clinical prediction model for short-term postoperative mortality after colorectal cancer surgery, including only predictors known at the MDT conference in order to address the unmet need of risk assessment prior to surgery. These can be either covariates describing previous diseases or scores like American Society of Anesthesiology (ASA) score, or covariates, which are decided at the MDT conference such as surgery type. Our main goal was to assess the performance of this model using calibration and discrimination metrics.

Materials and methods

Data sources

In Denmark, access to register data does not require ethical approval. Processing of health register data was filed under the research inventory of Region Zealand (record number: REG-047–2020). Quality assurance data from the Danish Colorectal Cancer Group’s database (DCCG) were obtained from The Danish Clinical Quality Program. DCCG is a national quality assurance database for diagnosis and treatment of patients with CRC [6]. The registry contains data for all patients diagnosed with CRC, and having a contact at a surgical department in Denmark since May 1st 2001, and has coverage of > 95% of patients [7]. The database contains detailed information of demography, cancer diagnosis, surgery, oncological treatment, and patient outcomes [6] on over 76,000 patients. Data from DCCG was transformed into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) and Danish vocabularies were translated into standard vocabularies [8, 9].

Study population

We included patients over the age of 18 from the DCCG database who have undergone CRC surgery from May 1st 2001 to December 31st 2019.

Outcomes

We assessed all-cause mortality during the times at risk (TAR), 30, 90, and 180 days after surgery.

Included covariates

For development of the model, all concepts in DCCG [6, 10] were mapped to OMOP-CDM standard concepts. Covariates from DCCG include demographic, diagnostic, pathological, and perioperative data. Categorical covariates were converted using one-hot-encoding that meant they all were considered binary. All covariates that contributed to the models are reported in Supplementary Table 1, including description of the original source covariate.

Statistical analysis

The open-source tool ATLAS, provided by the Observational Health Data Science and Informatics (OHDSI) community [9], was used for model development. Data were randomly split into a training set used for model development, containing 75% of patients, and a test set used for internal validation containing 25% of patients. As such, models were trained using a random 75% and 25% training and tested using threefold cross-validation to optimize hyperparameter settings [9]. The ATLAS version used was 2.9.0, and models were trained using R v. 4.0.0 with the “PatientLevelPrediction” package v. 4.3.7 and Anaconda3 v. 4.4.0 with Python v. 3.6.10. We trained Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression, decision tree, random forest, gradient boosting machine, K-nearest neighbor, multilayer perception neural network, and AdaBoost models. We assessed the performance of the best-performing model using area under the receiver operating characteristic (AUROC) [11] and area under the precision-recall curve (AUPRC) and calibration using calibration-in-large, calibration slope, calibration intercept, and Brier score [12].

We trained and tested the models, using both a simple model containing only sex and age as predictors and a more complex model containing all preoperative covariates and covariates, which are decided at the MDT conference, available in DCCG to assess whether or not adding more clinical granularity improved performance. The models are not able to differentiate between a missing or negative value of a covariate which means that there is a risk of misclassification of patients with missing data. However, age and sex are mandatory fields in OMOP-CDM and will therefore never be missing.
The study adheres to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [13].

Results

Participants

A total of 65,612 patients underwent surgery for colorectal cancer from 2001 to 2019, consisting of 53.4% female patients with a median age of 71 years. Most of the patients (86.9%) underwent elective surgery. The incidence of 30-day mortality was 5.42%, 90-day mortality was 8.53%, and 180-day mortality was 11.42%. Patient characteristics can be viewed in Table 1.

Model development

Out of the models tested, the LASSO logistic regression performed best in the three times at risk with excellent discrimination (Figs. 1 and 2a–c) and good calibration (Fig. 3a–c).

### Table 1 Demographic and clinical parameters for patients included in the cohort

| Characteristic                                      | Count (\(n = 65,629\)) | %    |
|-----------------------------------------------------|--------------------------|------|
| 30-day mortality incidence                         | 3557                     | 5.4  |
| 90-day mortality incidence                         | 5596                     | 8.5  |
| 180-day mortality incidence                        | 7496                     | 11.4 |
| Male                                                | 35,073                   | 53.4 |
| Age Mean (SD*)                                      | 70.54 (11.2)             |      |
| Median (IQR*)                                       | 71 (64.75)               |      |
| ASA* score                                          |                         |      |
| 1                                                    | 13,850                   | 21.1 |
| 2                                                    | 15,478                   | 23.6 |
| ≥ 3                                                  | 2703                     | 4.1  |
| Missing                                             |                         |      |
| WHO* performance status                             |                         |      |
| 0                                                    | 14,655                   | 22.3 |
| 1                                                    | 5,519                    | 8.4  |
| 2                                                    | 2,380                    | 3.7  |
| ≥ 2                                                  | 43,075                   | 65.6 |
| Missing                                             |                         |      |
| Charlson’s comorbidity index                        | 41,567                   | 63.3 |
| 0                                                    | 10,872                   | 16.6 |
| 1                                                    | 6,514                    | 9.9  |
| 2                                                    | 6,674                    | 10.2 |
| ≥ 3                                                  | 2703                     | 4.1  |
| Missing                                             |                         |      |
| Alcohol consumption per week                        |                         |      |
| 0 units                                             | 29,503                   | 45   |
| 1–14 units                                          | 3,874                    | 5.9  |
| 15–21 units                                         | 3,602                    | 5.5  |
| ≥ 22 units                                          | 16,752                   | 25.5 |
| Missing                                             |                         |      |
| Body mass index                                     | 1,891                    | 2.9  |
| ≤ 18.5                                              | 23,815                   | 36.3 |
| 18.5–25                                             | 18,815                   | 28.7 |
| 25–30                                               | 6,279                    | 9.6  |
| 30–35                                               | 2,122                    | 3.2  |
| ≥ 35                                                | 12,707                   | 19.3 |
| Missing                                             |                         |      |
| Smoking status                                      | 10,518                   | 16   |
| Smoker                                              | 21,143                   | 32.2 |
| Previous smoker                                     | 19,298                   | 29.4 |
| Never smoked                                        | 14,670                   | 22.4 |
| Missing                                             |                         |      |
| Colon cancer                                        | 44,550                   | 67.9 |
| Rectum cancer                                       | 20,850                   | 31.8 |
| Missing                                             | 229                      | 0.3  |
| T stage*                                            | 445                      | 0.7  |
| T0                                                  | 4629                     | 7.1  |
| T1                                                  | 3,650                    | 5.6  |
| T2                                                  | 8,765                    | 13.4 |
| T3                                                  | 2,644                    | 4    |
| T4                                                  | 3,054                    | 4.7  |
| Tx                                                  | 42,442                   | 64.5 |
| Missing                                             |                         |      |
| N stage*                                            | 7,272                    | 11.1 |
| N0                                                  | 3,411                    | 5.2  |
| N1                                                  | 2,400                    | 3.7  |
| N2                                                  | 3,467                    | 5.3  |
| Nx                                                  | 49,079                   | 74.8 |
| Missing                                             |                         |      |

*SD Standard Deviation, IQR Interquartile Range, ASA American Society of Anesthesiology Score, WHO World Health Organization, T Tumor Category, N Node Category, M Metastasis Category, pMMR Proficient Mismatch Repair, dMMR deficient Mismatch Repair, EMR Endoscopic Mucosal Resection, RFA Radio Frequency Ablation
Model performance

Discrimination of the LASSO regression model is presented as AUROC and AUPRC in Table 4 and Fig. 2a–c, and calibration is shown in Table 4 and Fig. 3a–c, and top 15 positive and negative weighted covariates from the 30-day mortality model are seen in Tables 2 and 3. For all three LASSO mortality models, we found excellent discrimination with AUROC of 0.871, 0.874, and 0.876, respectively. The AUPRC of 0.35, 0.44, and 0.54, respectively, should be considered good as a AUPRC and should be larger than the incidence of the outcome, and AUPRC here is 7-, 5-, and fivefold higher (Table 1). Calibration was also excellent seen by calibration-in-large from 0.98 to 1.02, and calibration slope very close to 1 and calibration intercept and Brier score near 0 for all times at risk can be seen in Table 4 and through assessment of weak calibration plots in Fig. 3a–c.

When comparing the complex models with the models using only age and sex as covariates, we saw markedly better performance in the complex models, which was excellent in terms of discrimination (AUROC > 0.8) and good in terms of calibration, whereas the simple model only showed moderate to fair discrimination (AUROC > 0.6 and > 0.7) and although still a higher AUPRC than the event incidence, markedly lower. Calibration measures were more similar than discrimination, as seen in Table 4.

Discussion and conclusion

We trained prediction models for short-term mortality after colorectal cancer surgery based solely on covariates available at the MDT conference with excellent discrimination and good calibration. Discrimination in terms of AUROC ranged from 0.871 to 0.876 and AUPRC from 0.35 to 0.54 and calibration ranging
from calibration-in-large 0.98 to 1.01, calibration slope 1.001 to 1.02, calibration intercept −0.06 to 0.05, and Brier score 0.04 to 0.07, and with solid calibration plots as seen in Fig. 3a–c. Compared to models based on only age and sex as predictors, the data-driven prediction models showed vastly better performance. Based on the calibration plots, the model slightly underpredicts risks for patients with more than 50% risk of mortality.

All predictors used in the prediction model could be available at a pre-operative MDT-conference. The risk factors for short-term postoperative mortality are aligned with the current literature, namely, that high age, high ASA score, exploratory procedures, and poor tumor differentiation were risk factors for mortality [14]. We found that predictors such as young age, low World Health Organization Performance Status (WHO PS), low ASA score, and slightly overweight body mass index (BMI) were associated with a lower risk of death during the time at risk.

We found the incidence of postoperative mortality to be 5.42%, 8.53%, and 11.42% for 30-day, 90-day, and 180-day time at risk, respectively. Although this may be considered high in today’s context, it is important to emphasize that the model is based on data from 2001 to late 2019. During this time in Denmark, 30-day mortality for elective colorectal cancer surgery has decreased from 7.3 (2001) [14] to 1.4% (2018) [15]. Similar studies in France, England, and the Netherlands have shown a 30-day mortality in the time of 2006–2008 of 5–5.8% [16–18] and a subsequent decrease in 30-day mortality to 1.2% and 90-day mortality to 4.6% in 2017 [18], which is similar to the development in Denmark during the same time. This is likely due to changes in surgical approach from primarily open to primarily laparoscopic surgery [19] and implementation of (ERAS) regimens [20]. The model includes both elective and emergency surgery, and it is well-known that the mortality rate for emergency surgery is considerably higher with an incidence of 15.8% in 2018 [15].

Designing prediction models targeted for clinical use is not a new phenomenon. The most well-known surgical risk assessment tool is the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator. Discriminative accuracy for 30-day mortality showed an AUROC of 0.944 and a Brier score of 0.011 [21]; however, in validation for colorectal cancer patients, performance was somewhat lower with AUROC of 0.86 and a Brier score of 0.018. Comparably, Fazio et al. designed a 30-day mortality model after colorectal surgery with an AUROC of 0.801 [22], van der Sluis et al. created the Identification of Risk in Colorectal Surgery score with an AUROC
of 0.83 [23], and van den Bosch et al. designed a 30-day mortality model with an AUROC of 0.82 [24]. Generally, most previous studies do not include as many performance metrics, and a majority show no calibration measures such as calibration-in-large, intercept, and calibration slope. Brier score has previously been criticized for not being an optimal measure of performance and calibration in clinical models [25], and other parameters such as calibration-in-large are considered essential for external validation [26]. Therefore, we decided to report all performance measures in order to provide full transparency and optimal interpretation of model performance. All of the four studies above defined the covariates of the model

Table 2  Top 15 covariates associated with increased risk for 30-day mortality according to the LASSO model (for full covariate table, see Supplementary Table 1). In total, 114, 124, and 142 preoperative covariates were used in the 30-, 90-, and 180-day mortality models, respectively

| Covariate name                                           | Covariate value | Covariate count | Covariate mean | Covariate standard deviation |
|----------------------------------------------------------|-----------------|-----------------|----------------|-----------------------------|
| Age group: 95–99                                         | 1.173           | 190             | 0.003          | 0.054                       |
| Age group: 90–94                                         | 1.021           | 1317            | 0.02           | 0.14                        |
| Age group: 85–89                                         | 0.884           | 4622            | 0.07           | 0.256                       |
| Age group: 80–84                                         | 0.594           | 8373            | 0.128          | 0.334                       |
| ASA score 4*                                             | 1.098           | 1300            | 0.02           | 0.139                       |
| ASA score 3*                                             | 0.391           | 14,118          | 0.215          | 0.411                       |
| Primary malignant neoplasm of splenic flexure of colon   | 0.335           | 1939            | 0.03           | 0.169                       |
| MX category*                                            | 0.479           | 8961            | 0.137          | 0.343                       |
| Emergency operation                                      | 0.484           | 7584            | 0.116          | 0.32                        |
| Only exploratory surgery, diagnostic laparoscopy, or     | 0.932           | 300             | 0.005          | 0.067                       |
| exploratory laparotomy                                   |                |                 |                |                             |
| Endoscopic insertion of permanent colonic stent          | 0.488           | 862             | 0.013          | 0.114                       |
| Ileocolic resection                                      | 0.346           | 130             | 0.002          | 0.044                       |
| Defunctioning stoma                                      | 0.559           | 2394            | 0.036          | 0.187                       |
| Tumor perforation, open perforation                      | 0.555           | 1442            | 0.022          | 0.147                       |
| Gastrointestinal perforation                             | 0.471           | 945             | 0.014          | 0.119                       |

ASA American Society of Anesthesiology Score, MX Metastasis Category Unknown

Table 3  Top 15 covariates associated with decreased risk for 30-day mortality based on the LASSO model (for full covariate table, see Supplementary Table 1)

| Covariate name                                           | Covariate value | Covariate count | Covariate mean | Covariate standard deviation |
|----------------------------------------------------------|-----------------|-----------------|----------------|-----------------------------|
| Age group: 50–54                                         | −1.034          | 2914            | 0.044          | 0.206                       |
| Age group: 55–59                                         | −0.883          | 4849            | 0.074          | 0.262                       |
| Age group: 60–64                                         | −0.593          | 7508            | 0.114          | 0.318                       |
| ASA score 1*                                             | −0.889          | 13,850          | 0.211          | 0.408                       |
| ASA score 2*                                             | −0.37           | 33,595          | 0.512          | 0.5                          |
| WHO performance status 0*                                 | −0.484          | 14,655          | 0.223          | 0.416                       |
| Body mass index (by algorithm) > 25 ≤ 30                 | −0.581          | 18,811          | 0.287          | 0.452                       |
| Body mass index (by algorithm) > 18.5 ≤ 25               | −0.393          | 23,809          | 0.363          | 0.481                       |
| Never smoked tobacco                                     | −0.433          | 19,297          | 0.294          | 0.456                       |
| Curative—procedure intent                                | −0.355          | 48,435          | 0.738          | 0.44                        |
| Endoscopic procedure                                     | −0.939          | 3874            | 0.059          | 0.236                       |
| Laparoscopy                                              | −0.352          | 26,577          | 0.405          | 0.491                       |
| Abdominoperineal resection                               | −0.373          | 5205            | 0.079          | 0.27                        |
| Other local resection including polypecsection or EMR*    | −0.475          | 2152            | 0.033          | 0.178                       |
| Local macroradical excision of colorectal tumor          | −0.568          | 22,133          | 0.337          | 0.473                       |

ASA American Society of Anesthesiology Score, WHO World Health Organization, EMR Endoscopic Mucosal Resection
initially. However, our approach was to train the LASSO model with all available covariates and let it exclude all irrelevant covariates, in order to use all covariates that affect the prediction. This model requires 38 variables in the shape of 114–142 covariates, which are either positive or negative, and this is a large amount of variables to manually input into the model when predicting the outcome on a new patient. However, this issue could be addressed through automation of the data retrieval through software interfaces that communicate with the electronic health record (EHR). Although having a large number of covariates might be impractical for input purposes, including a large number of variables with a data-driven approach minimized the bias comparing to an inclusion of variables that are only assumed to be important without considering all possible options. On the other hand, including variables without a clinician set boundary may lead to bigger variance of covariates and covariate weights. Fazio et al. had 6 preoperative covariates; van der Sluis et al. used 8 pre-, intra-, and postoperative covariates; and ACS included 21 preoperative covariates. In comparison, we found 38 predictors known at the time of MDT.

We view the use of our model as a tool to estimate mortality risk and tailor different patient treatment trajectories. This is because the current treatment guidelines for colorectal cancer lead some patients to overtreatment and some to undertreatment—both with unnecessarily high risk for the patient. The model should be viewed as a decision-support tool rather than a decision-making tool, where the individual patient risks should be put into context by experienced clinicians and fuel multidisciplinary treatment approaches.

Knowledge about individual risks of mortality shortly after surgery can support the MDT-conferences in making individualized treatment plans, which takes individual risk factors into consideration. This personalization of treatment to individual risk profiles may limit both over- and undertreatment and consequences thereof.

A significant limitation of this study is the lack of external validation, which is essential for proving model generalizability and has been shown to improve clinicians’ trust in the model and its predictions [27]. Also, due to the complexity in the treatment of colorectal cancer and the multitude of different variables in DCCG, some variables may be proxy for outcomes or actions in the patient course, which can lead to multicollinearity [28]. However, this is partly addressed using LASSO logistic regression, which considers whether or not multicollinearity seems to occur between variables and downscales their predictive weight [29].

The strengths of this study are the development of a prediction model based on a large national database including more than 95% of all patients with the condition and the model is only including data known prior to surgery, making the model available as a clinical decision support in the preoperative setting. The utilization of OMOP-CDM eases future external validation and enrichment of data from other databases.

In conclusion, we found that designing a short-term postoperative mortality model for outcomes after colorectal surgery using a data-driven approach and utilizing only covariates known prior to surgery is feasible and led to models with excellent discrimination and good calibration.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00384-022-04207-6.

**Acknowledgements** The authors thank The Danish Clinical Quality Program and Danish Colorectal Cancer Group for access to their outstanding data. We also sincerely thank the European Health Data Evidence Network (EHDEN), edenceHealth, and Computerome for contributions and support during the project. Lastly, we thank Peter Rijnbeek and Iannis Drakos for sparring and advice in the process.

**Author contribution** All authors contributed to the study design. Karoline Bendix Brüàner, Julie Sparholt Walbech, and Adamantia Tsouchniki did the statistical analyses. Karoline Bendix Brüàner, Andreas Weinberger Rosen, Viviane Annabell Lin, Mikail Gögenur, and Johan Stub Rønø Clausen defined the research questions and interpreted the results. Karoline Bendix Brüàner and Julie Sparholt Walbech prepared tables and figures. Karoline Bendix Brüàner wrote the main manuscript text. All authors have reviewed the manuscript and given approval for submission to International Journal of Colorectal Disease.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

**Table 4** Cohort, calibration, and discrimination metrics for 30-, 90-, and 180-day post-operative mortality using LASSO logistic regression

| Patients | Number of outcomes | Predictors | AUROC* | AUPRC* | Calibration in large | Calibration-slope | Calibration-intercept | Brier score |
|----------|--------------------|------------|--------|--------|---------------------|------------------|----------------------|------------|
| 30-day mortality | 65,612 | 3557 | 38 | 0.871 (0.86–0.88) | 0.35 | 1.01 | 1.02 | 0.05 | 0.04 |
| 30-day mortality (simple) | 65,612 | 3557 | 2 | 0.728 (0.71–0.75) | 0.13 | 0.99 | 1.049 | 0.13 | 0.05 |
| 90-day mortality | 65,612 | 5596 | 38 | 0.874 (0.87–0.88) | 0.44 | 0.98 | 1.001 | 0.023 | 0.06 |
| 90-day mortality (simple) | 65,612 | 5596 | 2 | 0.689 (0.68–0.70) | 0.18 | 1.00 | 0.97 | −0.06 | 0.07 |
| 180-day mortality | 65,612 | 7496 | 38 | 0.876 (0.87–0.88) | 0.54 | 1.01 | 1.004 | −0.006 | 0.07 |
| 180-day mortality (simple) | 65,612 | 7496 | 2 | 0.693 (0.66–0.71) | 0.23 | 1.01 | 1.08 | 0.14 | 0.10 |

*AUROC Area under the Receiver Operating Characteristic, AUPRC Area Under Precision Recall Curve
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This paper in an earlier format has been presented as a poster at the Observational Health Data Science and Informatics Symposium 2021 (online convention) running from Sunday September 12th 2021 to Wednesday September 15th 2021 and as a lightning talk on the Danish Surgical Society annual meeting in Copenhagen, Denmark, running from Thursday November 18th 2021 to Friday November 19th 2021.