Predicting long-term multicategory cause of death in patients with prostate cancer: random forest versus multinomial model

Jianwei Wang, MD, PhD;[1] Fei Deng, PhD;[2] Fuqing Zeng, MD;[3] Andrew J. Shanahan, MD, FACC;[4] Lanjing Zhang, MD, FRCPath[5-8]

[1]Department of Urology, Beijing Jishuitan Hospital, the Fourth Medical College of Peking University, Beijing, China; [2]School of Electrical and Electronic Engineering, Shanghai Institute of Technology, Shanghai, China; [3]Department of Urology, Wuhan Union Hospital of Tongji Medical Collage, Huazhong University of Science and Technology, Wuhan, China; [4]Department of Medicine, Princeton Medical Center, Plainsboro, NJ; [5]Department of Pathology, Princeton Medical Center, Plainsboro, NJ; [6]Department of Biological Sciences, Rutgers University, Newark, NJ; [7]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [8]Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ.

Correspondence: Lanjing Zhang, MD, Department of Pathology, Princeton Medical Center, 1 Plainsboro Rd, Plainsboro, NJ 08536, USA. emails: lanjing.zhang@rutgers.edu or ljzhang@hotmail.com

Key words: Prostate cancer, cause-specific mortality, machine learning, prediction, prognosis

Abstract

IMPORTANCE Patients with prostate cancer more likely die of non-cancer cause of death (COD) than prostate cancer. It is thus important to accurately predict COD more precisely in these patients. Random forest, a model of machine learning, was useful for predicting binary cancer-specific deaths. However, its accuracy for predicting multi-category COD in prostate cancer patients is unclear.

OBJECTIVE To develop and tune a machine-learning model for predicting 6-category COD in prostate cancer patients

DESIGN, SETTING, AND PARTICIPANTS We included patients in Surveillance, Epidemiology, and End Results-18 cancer registry-program with prostate cancer diagnosed in 2004 (followed up through 2016). They were randomly and equally divided into training and testing sets. We evaluated the prediction accuracies of random forest and conventional-statistical/multinomial models for 6-category COD in primary and cross validation processes and by data-encoding types.

EXPOSURE Tumor and patient characteristics

MAIN OUTCOMES AND MEASURES 13-year 6-category COD

RESULTS Among 49,864 men with prostate cancer, 29,611 (59.4%) were alive at the end of follow-up, and 5,448 (10.9%) died of cardiovascular disease, 4,607 (9.2%) of prostate cancer, 3,681 (7.4%) of Non-Prostate cancer, 717 (1.4%) of infection, and 5,800 (11.6%) of other causes. We predicted 6-category COD among these patients with a mean accuracy of 59.1% (n=240, 95% CI, 58.7%-59.4%) in the random forest models with one-hot encoding, and 50.4% (95% CI, 49.7%-51.0%) in the multinomial models. Tumor characteristics, prostate-specific antigen level, and diagnosis confirmation-method were important in random forest and multinomial models. In random forest models, no statistical differences were found between accuracies of primary versus cross validation, and those of conventional versus one-hot encoding.

CONCLUSION: For prostate cancer patients, we developed a random forest model that has an accuracy of 59.1% in predicting long-term 6-category COD. It outperforms conventional-statistical/multinomial models with an absolute prediction-accuracy difference of 8.7%.

Introduction:

Prostate cancer is the most prevalent cancer and the second leading-cause of cancer deaths among men in the U.S, accounting for 174,650 new cases and 31,620 deaths in 2019.[1,2] More patients with prostate cancer died of non-cancer causes than prostate cancer.[3,4] It is thus important to understand, predict and prevent non-cancer causes of death (CODs) among these patients, particularly cardiovascular disease (CVD).[5] However, only a handful of studies were focused on multi-category COD in prostate cancer patients, and none of them investigated the prediction of COD.[3,5,6]

Random forests (RF) model, a widely-used machine/statistical learning model, is based on the assumption that all trees have the same distribution in the same forest, whereas each tree links to the values of a random vector.[7] The RF model outperforms several machine learning and conventional statistical (e.g. logistic regression) models in predicting binary cancer-specific or all-cause deaths, [8-12] except in 1 simulation study and 1 biomarker study.[13,14] It was also used for predicting cancer-specific deaths in prostate cancer patients.[15] But few studies have used RF model for predicting multi-category COD in cancer patients, or compared the prediction accuracies of RF versus conventional statistical model (e.g. multinomial model) for multi-category COD.

This population-based observational study was aimed to predict 12-year multi-category COD in prostate cancer patients using RF and multinomial models.

Methods:

Patients

We extracted individual-patient data from the Surveillance, Epidemiology, and End Results-18 (SEER-18) Program (www.seer.cancer.gov) SEER*Stat Database with Treatment Data using SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version <8.3.6>).[16] SEER-18 is the largest SEER database including cases from 18 states and covering near 30% of the U.S. population.[17] The datasets have been widely used and validated for research on breast, and colorectal cancers.[18-20] Since the SEER database is an existing, de-identified, publicly available dataset, this study is exempt from Institutional Review Board (IRB) review under exempt category 4. Any summary data involving fewer than 15 patients were statistically suppressed to protect patient identity.

We included all qualified invasive prostate cancers in SEER-18 diagnosed in 2004 (2019 data-release, followed up through December 2016). The diagnosis year of 2004 was chosen because the 6th edition of the Tumor, Node and Metastasis staging manual (TNM6) of the American Joint Commission on Cancer (AJCC) was started in 2004 and allowed 12 years of follow-up. But, the AJCC 7th edition of the Tumor, Node and Metastasis staging manual (TNM7) was started in 2010, and would allow only up to 6 years of follow-up, which was not long enough in our view. The inclusion criteria were survival time longer than 1 month, aged 20 years and older, with known COD and first primary only.

Outcome and Covariates

The outcome of the statistical models was patient's 6-category COD. The COD were originally classified using SEER's recodes of the causes of death according to the COD definition of the U.S. Mortality Data, which were extracted from underlying cause of death on the death certificates of deceased patients.[21] The underlying COD was the unique and most important etiology of the patient's death, while other causes may link to the death and be recorded as other COD on the death certificate. We simplified the SEER COD into 6 categories based on the prevalence of COD,[3,6,15] including alive, CVD, infection, non-prostate cancer, prostate cancer and others.

The following factors were included in the analysis as covariates in RF or multinomial models: age at diagnosis, race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black, Asian and Pacific Islanders, and others),[22] T, N and M categories of TNM6, AJCC TNM6 clinical staging, prostate specific antigen level (PSA, ng/ml), sum of the Gleason score, chemotherapy, radiotherapy, surgery, and attributes of the county where the patient resided at the time of diagnosis.[23] The PSA levels and Gleason scores

were collected from medical records as site specific factors of prostate cancer since 2010.[24,25] Specifically, sums of the Gleason score were obtained from pathology report of resected specimen when available, or that of biopsy specimen if no surgery done. The 4 census-regions of patient's residence county were defined by the U.S. Census Bureau.[26] We converted continuous variables into 4-category variables based on their quartiles. The chemotherapy and radiotherapy data were obtained after signing a user agreement.[25,27] It is noteworthy that no or unknown status of these treatments should be considered less reliable, while receipt of these treatments was generally confirmed and reliable. [25,27]

Statistical analysis

We compared the accuracies of the RF and multinomial models after tuning the RF models and choosing the model with best accuracy. Using the 1:1 cross-validation approach, the patients were first randomly divided into two sets of similar size (n=25,000 and 24,864, respectively), namely training and testing sets (**Figure 1**). For data-quality assurance, we compared the covariates in the training and testing sets using Chi-square or Student's *t* test. To identify the RF model with best accuracy, which is termed as tuning process in data science, we examined prediction accuracies (i.e. 1 – validation error) of the models with various numbers of iterations (from 50 to 800 by an interval of 50) and variables (from 1 to 15). During the primary tuning process, the training set was used to develop models, and testing set used to predict outcomes using a RF or multinomial model. After the primary tuning process, we then conducted cross validation by developing model in the testing set and predicting outcomes in the training set. The tuning process during cross-validation followed the same protocol (**Figure 1**).

Several sensitivity analyses were performed on RF models. To exclude patients lost to follow-up, we conducted primary training and prediction processes in the patients who died during the follow-up or was alive for >150 months (12.5 years). We also generated training and testing sets with balanced distribution in all tested independent and dependent variables, which were assessed using Chi-square or Student's *t* test by each variable. Primary training and prediction were conducted in the balanced training and testing sets to study the model's prediction accuracy.

One-hot encoding appears to outperform complex encoding systems.[28] It was also used for machine learning on cancer driver genes.[29] We therefore conducted the primary and cross-validation processes using one-hot encoded data. For one-hot encoding, all multicategory variables (i.e. of >1 strata) were transformed into a number of new binary sub-variables (e.g. quartiles of the age would become 4 binary variables of corresponding age-quartile).

For multinomial model, which is a conventional-statistical model, we first generated the model using training set and predicted 6-category COD using testing set (**Figure 1**). If the predicted probability of a given COD was higher than 0.5, the COD would be assigned to the COD of the patient. Ideally, only one COD had a predicted probability >0.5 and was allowed for each case, thus any patient with 0 or >1 predicted COD was considered unsuccessfully predicted using multinomial model.

We used the RF package and multinomial logistic models of the Stata (version 16, College Station, TX) for statistical analyses.[30-32] The 95% confidence intervals (CI) of prediction accuracies were estimated using both binomial and Poisson models, that produced very similar results. All *P* values were two-tailed, and the *P* value <0.05 was considered statistically significant.

Results:

Patients

We identified and analyzed 49,864 men with qualified prostate cancer diagnosed in 2004 in the SEER-18 (**Table 1**), including 29,611 (59.4%) alive, 5,448 (10.9) died of CVD, 4,607 (9.2%) of prostate cancer, 3,681 (7.4%) of non-prostate cancer, 717 (1.4%) of infection, and 5,800 (11.6%) of other causes. The mean survival time was 117 months, while there were 31,273 patients who died during followup or was alive for >150 months. Majority of the cancers were of AJCC 6 stage 2 (80.9%) and not treated with prostatectomy (61.6%). We randomly divided the cases into training and testing sets (**STable 1**), and found the outcome and all covariates were similarly distributed in these sets, except radiotherapy status (P=0.047). We then sorted the data by outcome and radiotherapy, randomized the

cases again, and achieved similar distributions of the outcome and on covariates in the two sets (**STable 2**). For the sensitivity analyses on the patients who died during followup or was alive >150 months, CODs were similarly distributed in the training and testing sets (**Stable 3**).

Predicting multi-category causes of death with random forests model

There were 17 variables with conventional encoding and 61 variables with one-hot encoding, and 240 models in each tuning process. Our tuning processes showed that the prediction accuracy increased with the iteration number in either conventionally or one-hot encoded data (**Figure 2**), as shown before.[30] The mean prediction-accuracy for 6-category COD were 58.6% (95% CI, 58.2%-59.1%) in the RF models with conventional encoding and 59.1% (95% CI, 58.7%-59.4%) in those with one-hot encoding. The best accuracy was reached in the model of 3 variables and 800 iterations for conventional encoding (59.2%, 95% CI [58.6%-59.8%], **Table 2** and **Figure 3**) and that of 1 variable and 700 iterations for one-hot encoding (59.6%, 95% CI [58.9%-60.2%], **STable 4** and **Figure 3**). The best RF model with one-hot encoding appeared to outperform that with conventional encoding, but no statistical difference was found. Alive was the COD that all RF models could predict with the best accuracy, while cancer pathological staging and age at diagnosis were top-important factors in the RF models (**Figure 3**).

The sensitivity analyses revealed that the prediction accuracies were statistically similar in the primary-validation models, cross-validation models and the models with balanced sets, but statistically lower in the models in patients who died during follow-up or was alive for >150 months (**Figure 3**).

Predicting multi-category causes of death with multinomial model

As RF models, multinomial models with one-hot encoding seemed to have better goodness of fit than with conventional encoding (Pseudo R= 0.1707 versus 0.1416, Likelihood Ratio [Chi-square]= 10854.51 vs 9009.2, respectively). Because multinomial models used a ranking approach to determine the best-fit outcome, it is possible that more than one outcome (i.e. COD) had a probability> .05. However, the predicted COD in multinomial model was only unique in being alive among the 6-category COD and all other categories were of < 0.5 probability (**Table 2** and **STable 4**). The mean prediction-accuracy was 50.4% (95% CI, 49.7%-51.0%) in the multinomial models, and lower than RF models, except the RF model on the patients who died during followup or was alive for >150 months (**Figure 3**). Age at diagnosis, AJCC6 staging, confirmation method of diagnosis, surgery and PSA level were associated with all 6-category COD in multinomial model, while other factors were only linked to some of the 6-category COD (**STable 5**).

Discussion

In the patients with prostate cancer diagnosed in 2004, 59.4% were alive at the end of 12-year follow-up, while the top-3 CODs were CVD, prostate cancer and non-prostate cancer. We predicted 6-category COD among these patients with a mean accuracy of 59.1% (95% CI, 58.7%-59.4%) in the tuned RF model with one-hot encoding, and 50.4% (95% CI, 49.7%-51.0%) in the multinomial model, suggesting RF models outperformed multinomial model. Tumor characteristics, PSA level, diagnosis confirmation-method, and radiotherapy status were the top-ranked variables in RF model, but only age, surgery, diagnosis confirmation-method, PSA level and AJCC6 stages as the factors were linked to all of the COD (versus alive) in multinomial models.

The proportions of various COD in our study are similar to those in prior reports.[4] Given the increasing proportion of deaths from COD other than prostate cancer, it is critical to accurately predict or identify the factors linked to these COD among prostate cancer patients. Several studies have attempted to predict cancer-specific or all-cause deaths in prostate cancer patients using clinical pathological and genomic/genetic factors.[15,33-36] However, few studies to our knowledge predict the causes of death in 6 categories. Multinomial logistic regression is suitable for analyzing categorical/multi-category outcomes.[31,32] In this study, multinomial logistic regression seems only able to predict alive status of the 6-category COD if any unique COD successfully identified. In the meantime, a tuned RF

model outperformed multinomial logistic regression in predicting 6-category COD by 17.2% higher prediction accuracy (8.7% absolute accuracy-difference). This finding supports that RF's accuracy is similar to or better than support vector machines, artificial neural network and logistic regression in predicting various clinical outcomes,[9-11,37] but contrasts to that its accuracy is inferior to that of logistic regression.[38] It is plausible, but needs additional validation, that RF could also be useful in predicting multi-category COD or outcomes of other diseases. Despite the slightly better accuracy linked to data with one-hot encoding than standard encoding, we found no statistical differences between the two methods. This finding is inconsistent with prior reports,[28,29] and needs further validation. We also noticed that the minimal depths of trees in our best-fit RF models were usually 1 to 3. Those observations may help develop and improve machine learning models for predicting multi-category COD in cancer or other patients.

Some of this study's strengths are noteworthy. First, this population-based study provides early evidence on the frequencies of various COD among the prostate cancer patients who were followed up for 12 years. Second, we tuned RF models for predicting 6-category COD in prostate cancer patients, while prior RF models on prostate cancer only predicted binary cancer-specific death,[15,33] all-cause death,[33,39] or cancer recurrence.[40] Compared with binary death-outcomes, multiple-category COD are more informative, but more difficult to predict. This is supported by the low success rate of multinomial models in predicting unique COD. Third, the tuned RF models in this study outperformed multinomial models in predicting 6-category COD. Indeed, the multinomial model was only able to predict alive as a unique COD, and missed other COD. Fourth, we characterized RF models and identified the model with best accuracy, while few of the prior works tuned their models.[15,33,40] Fifth, the large sample-size and cross-validation design increased the statistical power and scientific rigor of this study, respectively.[41] Some of prior studies using machine learning/RF model had either large sample size[15] or cross validation,[42-44] but few combined both. Small sample size was indeed reported as the most common limitation of machine learning studies on cancer prognosis and prediction.[41] Finally, we identified several factors linked to long-term 6-category COD in prostate cancer patients, including age, PSA level and tumor characteristics, as shown by both RF and multinomial models.

This study has the following limitations. The prediction accuracy for 6-category COD in this study is not yet as good as prediction for binary outcomes, such as all-cause deaths.[33] Moreover, despite some shared linked-factors, RF models did not completely agree with multinomial models on the factors linked to 6-category COD. However, RF and other machine learning models are known for their limitations in identifying associated factors.[45] In addition, an outside validation dataset might be needed, but unavailable, largely due to the lack of registry-data. SEER18 is the largest population cancer dataset in the North America.[16] Thus, it is very challenging to obtain another population dataset of similar size for validation. However, we prospectively used the cross-validation approach to validate our findings, as recommended.[41,45] Finally, Gleason scores were available in a very small proportion of the patients, but might otherwise improve prediction accuracy.[46]

Conclusions

In this population-based study, CVD, prostate cancer and non-prostate cancer were the most common long-term COD among prostate cancer patients. RF and multinomial models could predict 6-category COD among these patients with acceptable prediction accuracy, which needs improvement. Those models enable clinicians to gain more granular prognostic information on prostate cancer patients, and target at relevant COD to improve survival. We also show that a tuned RF model outperforms multinomial models by 8.7% (absolute difference), or 15,195 person-case for the cases diagnosed in 2019 alone in the U.S. Additional works are needed to better predict multiple-category COD of other cancers.

Statement

Authors' contributions: JW, FZ, AJS and LZ designed the study, JW, FD and LZ extracted and analyzed the data, JW and LZ wrote the first draft of the manuscript and all authors edited the manuscript. The final manuscript was approved by all authors

except FZ, who unfortunately passed away on Oct. 1, 2018.

No conflict of interest is declared by any of the authors. No funding sources are reported.

Bibliography

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34. doi:10.3322/caac.21551.
2. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin.* 2019;69(5):363-385. doi:10.3322/caac.21565.
3. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. *Ann Oncol.* 2017;28(2):400-407. doi:10.1093/annonc/mdw604.
4. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. *J Natl Cancer Inst.* 2012;104(17):1335-1342. doi:10.1093/jnci/djs299.
5. Walter SD, de Koning HJ, Hugosson J, et al. Impact of cause of death adjudication on the results of the European prostate cancer screening trial. *Br J Cancer.* 2017;116(1):141-148. doi:10.1038/bjc.2016.378.
6. Nguyen-Nielsen M, Moller H, Tjonneland A, Borre M. Causes of death in men with prostate cancer: Results from the Danish Prostate Cancer Registry (DAPROCAdata). *Cancer Epidemiol.* 2019;59:249-257. doi:10.1016/j.canep.2019.02.017.
7. Breiman L. Random Forests. *Machine Learning.* 2001;45(1):5-32. doi:10.1023/A:1010933404324.
8. Sakr S, Elshawi R, Ahmed AM, et al. Comparison of machine learning techniques to predict all-cause mortality using fitness data: the Henry ford exercIse testing (FIT) project. *BMC Med Inform Decis Mak.* 2017;17(1):174. doi:10.1186/s12911-017-0566-6.
9. Peng SY, Chuang YC, Kang TW, Tseng KH. Random forest can predict 30-day mortality of spontaneous intracerebral hemorrhage with remarkable discrimination. *Eur J Neurol.* 2010;17(7):945-950. doi:10.1111/j.1468-1331.2010.02955.x.
10. Shi M, He J. SNRFCB: sub-network based random forest classifier for predicting chemotherapy benefit on survival for cancer treatment. *Mol Biosyst.* 2016;12(4):1214-1223. doi:10.1039/c5mb00399g.
11. Montazeri M, Montazeri M, Montazeri M, Beigzadeh A. Machine learning models in breast cancer survival prediction. *Technol Health Care.* 2016;24(1):31-42. doi:10.3233/thc-151071.
12. Bartholomai JA, Frieboes HB. Lung Cancer Survival Prediction via Machine Learning Regression, Classification, and Statistical Techniques. *Proc IEEE Int Symp Signal Proc Inf Tech.* 2018;2018:632-637. doi:10.1109/isspit.2018.8642753.
13. van der Ploeg T, Austin PC, Steyerberg EW. Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. *BMC Med Res Methodol.* 2014;14:137. doi:10.1186/1471-2288-14-137.
14. Kim S, Park T, Kon M. Cancer survival classification using integrated data sets and intermediate information. *Artif Intell Med.* 2014;62(1):23-31. doi:10.1016/j.artmed.2014.06.003.
15. Hanson HA, Martin C, O'Neil B, et al. The Relative Importance of Race Compared to Health Care and Social Factors in Predicting Prostate Cancer Mortality: A Random Forest Approach. *J Urol.* 2019:101097ju0000000000000416. doi:10.1097/ju.0000000000000416.
16. Surveillance E, and End Results (SEER) Program (www.seer.cancer.gov). SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2018 Sub (1975-2016) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, based on the November 2018 submission. In:2019
17. SEER. Number of Persons by Race and Hispanic Ethnicity for SEER Participants (2010 Census Data). https://web.archive.org/web/20191028021627/https://seer.cancer.gov/registries/data.html. Accessed Oct 27, 2019.

18. Chavali LB, Llanos AAM, Yun JP, Hill SM, Tan XL, Zhang L. Radiotherapy for Patients With Resected Tumor Deposit-Positive Colorectal Cancer: A Surveillance, Epidemiology, and End Results-Based Population Study. *Arch Pathol Lab Med.* 2018;142(6):721-729. doi:10.5858/arpa.2017-0099-OA.
19. Yang M, Bao W, Zhang X, Kang Y, Haffty B, Zhang L. Short-term and long-term clinical outcomes of uncommon types of invasive breast cancer. *Histopathology.* 2017;71(6):874-886. doi:10.1111/his.13328.
20. Mayo E, Llanos AA, Yi X, Duan SZ, Zhang L. Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. *Histopathology.* 2016;69(2):230-238. doi:10.1111/his.12936.
21. SEER. SEER Cause of Death Recode 1969+ (03/01/2018). https://web.archive.org/web/20191028030412/https://seer.cancer.gov/codrecode/1969_d03012018/index.html. Accessed Oct. 28, 2019.
22. SEER. Race Recode Changes: For the 1973-2005 SEER Research Data (November 2007 Submission) and Later Releases. https://web.archive.org/web/20191028023614/https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity/. Accessed Oct. 28, 2019.
23. SEER. County attributes. 2019; https://web.archive.org/web/20191028025023/https://seer.cancer.gov/seerstat/variables/countyattribs/. Accessed Oct. 27, 2019.
24. SEER. Collaborative Stage Data Set: Prostate. 2013; https://web.archive.org/web/20190517115038/http://web2.facs.org/cstage0205/prostate/Prostateschema.html. Accessed May 3, 2019.
25. Guo Y, Mao S, Zhang A, et al. Survival Significance of Patients With Low Prostate-Specific Antigen and High-Grade Prostate Cancer After Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy. *Front Oncol.* 2019;9:638. doi:10.3389/fonc.2019.00638.
26. Bureau UC. Geographic Terms and Concepts - Census Divisions and Census Regions. https://www.census.gov/geo/reference/gtc/gtc_census_divreg.html. Accessed Dec. 19, 2018.
27. SEER. Radiation/Chemotherapy Databases (1975-2016). https://web.archive.org/save/https://seer.cancer.gov/data/treatment.html. Accessed May 3, 2019.
28. Waldmann P. Approximate Bayesian neural networks in genomic prediction. *Genet Sel Evol.* 2018;50(1):70. doi:10.1186/s12711-018-0439-1.
29. Agajanian S, Oluyemi O, Verkhivker GM. Integration of Random Forest Classifiers and Deep Convolutional Neural Networks for Classification and Biomolecular Modeling of Cancer Driver Mutations. *Front Mol Biosci.* 2019;6:44. doi:10.3389/fmolb.2019.00044.
30. Zou R, Schonlau M. Applications of Random Forest Algorithm. 2018; https://web.archive.org/web/20191014125205/https://www.stata.com/meeting/canada18/slides/canada18_Zou.pdf. Accessed Oct. 15, 2019.
31. Long JS, Freese J. *Regression models for categorical dependent variables using Stata.* Stata press; 2006
32. Multinomial Logistic Regression Stata data analysis examples. https://web.archive.org/web/20181010004634/https://stats.idre.ucla.edu/stata/dae/multinomiallogistic-regression/. Accessed Oct. 31, 2019.
33. Lin YT, Lee MT, Huang YC, Liu CK, Li YT, Chen M. Prediction of Recurrence-associated Death from Localized Prostate Cancer with a Charlson Comorbidity Index-reinforced Machine Learning Model. *Open Med (Wars).* 2019;14:593-606. doi:10.1515/med-2019-0067.
34. Kleppe A, Albregtsen F, Vlatkovic L, et al. Chromatin organisation and cancer prognosis: a pan-cancer study. *Lancet Oncol.* 2018;19(3):356-369. doi:10.1016/s1470-2045(17)30899-9.
35. Cruz JA, Wishart DS. Applications of machine learning in cancer prediction and prognosis. *Cancer Inform.* 2007;2:59-77.
36. Carmona R, Zakeri K, Green G, et al. Improved Method to Stratify Elderly Patients With Cancer at Risk for Competing Events. *J Clin Oncol.* 2016;34(11):1270-1277. doi:10.1200/JCO.2015.65.0739.

37. Song Y, Gao S, Tan W, Qiu Z, Zhou H, Zhao Y. Multiple Machine Learnings Revealed Similar Predictive Accuracy for Prognosis of PNETs from the Surveillance, Epidemiology, and End Result Database. *J Cancer.* 2018;9(21):3971-3978. doi:10.7150/jca.26649.
38. van der Ploeg T, Nieboer D, Steyerberg EW. Modern modeling techniques had limited external validity in predicting mortality from traumatic brain injury. *J Clin Epidemiol.* 2016;78:83-89. doi:10.1016/j.jclinepi.2016.03.002.
39. Zhang Y, Yan L, Zeng J, et al. Pan-cancer analysis of clinical relevance of alternative splicing events in 31 human cancers. *Oncogene.* 2019;38(40):6678-6695. doi:10.1038/s41388-019-0910-7.
40. Shen J, Wang L, Taylor JMG. Estimation of the optimal regime in treatment of prostate cancer recurrence from observational data using flexible weighting models. *Biometrics.* 2017;73(2):635-645. doi:10.1111/biom.12621.
41. Kourou K, Exarchos TP, Exarchos KP, Karamouzis MV, Fotiadis DI. Machine learning applications in cancer prognosis and prediction. *Comput Struct Biotechnol J.* 2015;13:8-17. doi:10.1016/j.csbj.2014.11.005.
42. Fa B, Luo C, Tang Z, Yan Y, Zhang Y, Yu Z. Pathway-based biomarker identification with crosstalk analysis for robust prognosis prediction in hepatocellular carcinoma. *EBioMedicine.* 2019;44:250-260. doi:10.1016/j.ebiom.2019.05.010.
43. Hussain L, Ahmed A, Saeed S, et al. Prostate cancer detection using machine learning techniques by employing combination of features extracting strategies. *Cancer Biomark.* 2018;21(2):393-413. doi:10.3233/cbm-170643.
44. Agranoff D, Fernandez-Reyes D, Papadopoulos MC, et al. Identification of diagnostic markers for tuberculosis by proteomic fingerprinting of serum. *Lancet.* 2006;368(9540):1012-1021. doi:10.1016/s0140-6736(06)69342-2.
45. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart.* 2018;104(14):1156-1164. doi:10.1136/heartjnl-2017-311198.
46. Rodrigues G, Warde P, Pickles T, et al. Pre-treatment risk stratification of prostate cancer patients: A critical review. *Can Urol Assoc J.* 2012;6(2):121-127. doi:10.5489/cuaj.11085.

Figure Legends

Figure 1. Study flow.

(**1**) We randomized the patients into training and testing sets with similar sample-size in each group, and performed quality assurance to ensure similar distribution of covariates in the two sets. (**2**) We then tuned the random forest (RF) model, chose the best-fit RF model, and developed multinomial (NM) model using training set (bold dash line). Using the NM and chosen RF models, we predicted 6-category causes of death among the patients in testing set (dash line). (**3**) The model building and outcome prediction were repeated in cross validation process, but using testing set for model building (bold solid line) and training set for prediction (solid line).

Figure 2. Characteristics of random forest models.

During primary validation process, prediction accuracies of random forest models varied by the corresponding numbers of variable and iteration (Contour graphs: **A**. conventional data encoding; **B**. One-hot data encoding). The random forest models provided computed relative importance-values for all included variables (**C**. and **D**. Relative-importance values of the top 10 variables in the chosen random forest models using conventional data encoding and one-hot data encoding, respectively). Note: *, Continuous variables were converted to 4-category variables by their respective quartiles; Dx, diagnosis; PSA, Prostate specific antigen; Education attainment defined as percent of residents with less than high-school graduate in the county; Person in poverty defined as percent of residents with income below 200% of poverty in the county.

Figure 3. Summary of prediction accuracies by model and data type.

In the tuning process and sensitivity analyses, we computed the validation accuracy of each random forest model by the numbers of variable and iteration (n=240), and chose the one with the best accuracy as the final model. The error bars show 95% confidence intervals of prediction accuracies in those models and data types during tuning process, except 3 models, whose 95% confidence intervals were calculated for the accuracy of a single model using binomial model (indicated by *). One-hot indicates one-hot encoding of the data; balanced set refers to the sensitivity analysis with training and testing sets that had balanced distribution of all variables.

Table 1. Baseline characteristics of included subjects

	Alive, n=29,611	CVD, n=5,448	Infection, n=717	Non-Prostate cancer, n=3,681	Other cause, n=5,800	Prostate cancer, n=4,607	Total, n=49,864
Age (yr)¶	63 (50-77)	74 (59-87)	75 (58-88)	70 (56-83)	73 (58-86)	72 (54-88)	67 (51-83)
Survival time (mo)¶	146 (131-155)	77 (7-143)	78 (6-141)	78 (12-141)	82 (11-143)	59 (4-137)	117 (16-154)
Race							
API	1,453	210	43	172	268	195	2,341
(%)	(4.9)	(3.9)	(6.0)	(4.7)	(4.6)	(4.2)	(4.7)
Hispanic	2,662	412	68	249	497	423	4,311
(%)	(9.0)	(7.6)	(9.5)	(6.8)	(8.6)	(9.2)	(8.7)
NH Black	3,830	865	143	553	807	812	7,010
(%)	(12.9)	(15.9)	(19.9)	(15.0)	(13.9)	(17.6)	(14.1)
NH White	21,093	3,920	461	2,690	4,189	3,147	35,500
(%)	(71.2)	(72.0)	(64.3)	(73.1)	(72.2)	(68.3)	(71.2)
Unknown/Other	573	41	<15*	17	39	30	702
(%)	(1.9)	(0.8)		(0.5)	(0.7)	(0.7)	(1.4)
TNM6 T category							
T1/2	26,641	4,873	635	3,245	5,201	2,917	43,512
(%)	(90.0)	(89.5)	(88.6)	(88.2)	(89.7)	(63.3)	(87.3)
T3/4	2,543	278	40	281	329	890	4,361
(%)	(8.6)	(5.1)	(5.6)	(7.6)	(5.7)	(19.3)	(8.8)
Unknown/Other	427	297	42	155	270	800	1,991
(%)	(1.4)	(5.5)	(5.9)	(4.2)	(4.7)	(17.4)	(4.0)
TNM6 N category							
0	28,140	4,850	631	3,354	5,226	3,057	45,258
(%)	(94.7)	(88.3)	(87.2)	(90.6)	(89.4)	(65.2)	(90.2)
1	283	64	<15*	60	55	357	830
(%)	(1.0)	(1.2)		(1.6)	(0.9)	(7.6)	(1.7)
Unknown/Other	1,307	579	82	289	566	1,272	4,095
(%)	(4.4)	(10.5)	(11.3)	(7.8)	(9.7)	(27.1)	(8.2)

TNM6 M category							
0	28,615	4,911	648	3,389	5,291	2,794	45,648
(%)	(96.3)	(89.4)	(89.5)	(91.5)	(90.5)	(59.6)	(91.0)
1	160	182	25	120	174	1,363	2,024
(%)	(0.5)	(3.3)	(3.5)	(3.2)	(3.0)	(29.1)	(4.0)
Unknown/Other	955	400	51	194	382	529	2,511
(%)	(3.2)	(7.3)	(7.0)	(5.2)	(6.5)	(11.3)	(5.0)
AJCC6 staging							
1	47	21	<15*	<15*	26	<15*	110
(%)	(0.2)	(0.4)			(0.5)		(0.2)
2	25476	4459	574	3013	4785	2054	40361
(%)	(86.0)	(81.9)	(80.1)	(81.9)	(82.5)	(44.6)	(80.9)
3	2110	173	19	200	216	328	3046
(%)	(7.1)	(3.2)	(2.7)	(5.4)	(3.7)	(7.1)	(6.1)
4	607	252	38	200	240	1595	2932
(%)	(2.1)	(4.6)	(5.3)	(5.4)	(4.1)	(34.6)	(5.9)
Unknown/Other	1371	543	81	258	533	629	3415
(%)	(4.6)	(10.0)	(11.3)	(7.0)	(9.2)	(13.7)	(6.9)
Chemotherapy							
None/Unknown	29,617	5,472	720	3,671	5,821	4,516	49,817
(%)	(99.6)	(99.6)	(99.5)	(99.1)	(99.6)	(96.4)	(99.3)
Received	113	21	<15*	32	26	170	366
(%)	(0.4)	(0.4)		(0.9)	(0.4)	(3.6)	(0.7)
Radiotherapy							
None/Unknown	18,450	3,364	446	2,094	3,537	3,257	31,148
(%)	(62.1)	(61.2)	(61.6)	(56.6)	(60.5)	(69.5)	(62.1)
Received	11,280	2,129	278	1,609	2,310	1,429	19,035
(%)	(37.9)	(38.8)	(38.4)	(43.5)	(39.5)	(30.5)	(37.9)
Surgery							
Local Excision	1,093	599	72	270	657	483	3,174
(%)	(3.7)	(11.0)	(10.0)	(7.3)	(11.3)	(10.5)	(6.4)
No surgery	15,142	4,261	578	2,649	4,413	3,666	30,709
(%)	(51.1)	(78.2)	(80.6)	(72.0)	(76.1)	(79.6)	(61.6)
Prostatectomy	13,376	588	67	762	730	458	15,981
(%)	(45.2)	(10.8)	(9.3)	(20.7)	(12.6)	(9.9)	(32.1)
Rural-urban continuum 2003§							
Metro	26,709	4,758	635	3,178	4,958	4,039	44,277
(%)	(89.8)	(86.6)	(87.7)	(85.8)	(84.8)	(86.2)	(88.2)
Non-Metro	3,021	735	89	525	889	647	5,906
(%)	(10.2)	(13.4)	(12.3)	(14.2)	(15.2)	(13.8)	(11.8)
Census region							
Midwest	2,946	658	77	399	613	429	5,122
(%)	(10.0)	(12.1)	(10.7)	(10.8)	(10.6)	(9.3)	(10.3)
Northeast	4,797	882	123	631	874	721	8,028

(%)	(16.2)	(16.2)	(17.2)	(17.1)	(15.1)	(15.7)	(16.1)
South	5,573	1,140	176	843	1,393	1,009	10,134
(%)	(18.8)	(20.9)	(24.6)	(22.9)	(24.0)	(21.9)	(20.3)
West	16,295	2,768	341	1,808	2,920	2,448	26,580
(%)	(55.0)	(50.8)	(47.6)	(49.1)	(50.3)	(53.1)	(53.3)
Percent of education attainment, quartile§							
Q1, <15.08	8,001	1,200	140	836	1,339	1,029	12,545
(%)	(26.9)	(21.9)	(19.3)	(22.6)	(22.9)	(22.0)	(25.0)
Q2, 15.09-18.15	7,538	1,287	182	898	1,448	1,193	12,546
(%)	(25.4)	(23.4)	(25.1)	(24.3)	(24.8)	(25.5)	(25.0)
Q3, 18.17-25.79	7,236	1,420	189	997	1,492	1,212	12,546
(%)	(24.3)	(25.9)	(26.1)	(26.9)	(25.5)	(25.9)	(25.0)
Q4, >50.77	6,955	1,586	213	972	1,568	1,252	12,546
(%)	(23.4)	(28.9)	(29.4)	(26.3)	(26.8)	(26.7)	(25.0)
Percent of persons in poverty, quartile§							
Q1, <21.18	8,034	1,210	160	865	1,305	1,044	12,618
(%)	(27.0)	(22.0)	(22.1)	(23.4)	(22.3)	(22.3)	(25.1)
Q2, 21.33-29.81	7,655	1,258	152	929	1,364	1,129	12,487
(%)	(25.8)	(22.9)	(21.0)	(25.1)	(23.3)	(24.1)	(24.9)
Q3, 29.86-37.36	7,276	1,493	220	986	1,662	1,256	12,893
(%)	(24.5)	(27.2)	(30.4)	(26.6)	(28.4)	(26.8)	(25.7)
Q4, >67.40	6,765	1,532	192	923	1,516	1,257	12,185
(%)	(22.8)	(27.9)	(26.5)	(24.9)	(25.9)	(26.8)	(24.3)
Percent of foreign-born residents, quartile§							
Q1, <5.95	6,864	1,467	188	1,041	1,747	1,254	12,561
(%)	(23.1)	(26.7)	(26.0)	(28.1)	(29.9)	(26.8)	(25.0)
Q2, 5.98-15.22	7,739	1,399	172	922	1,498	1,157	12,887
(%)	(26.0)	(25.5)	(23.8)	(24.9)	(25.6)	(24.7)	(25.7)
Q3, 15.45-21.55	7,412	1,257	179	866	1,342	1,171	12,227
(%)	(24.9)	(22.9)	(24.7)	(23.4)	(23.0)	(25.0)	(24.4)
Q4, >38.52	7,715	1,370	185	874	1,260	1,104	12,508
(%)	(26.0)	(24.9)	(25.6)	(23.6)	(21.6)	(23.6)	(24.9)
Confirmation method of diagnosis							
Microscopic	29,628	5,321	697	3,652	5,688	4,223	49,209
(%)	(99.7)	(96.9)	(96.3)	(98.6)	(97.3)	(90.1)	(98.1)
Radiologic and clinic	40	122	21	43	104	285	615
(%)	(0.1)	(2.2)	(2.9)	(1.2)	(1.8)	(6.1)	(1.2)
Unknown/Other	62	50	<15*	<15*	55	178	359
(%)	(0.2)	(0.9)			(0.9)	(3.8)	(0.7)
PSA, quartiles (ng/ml)							
<4.9	8,360	765	88	665	874	367	11,119
(%)	(28.2)	(14.0)	(12.3)	(18.1)	(15.1)	(8.0)	(22.3)
5.0-6.8	7,406	829	108	735	1,023	337	10,438
(%)	(25.0)	(15.2)	(15.1)	(20.0)	(17.6)	(7.3)	(20.9)

6.9-11.3	6,331	1,199	157	804	1,239	580	10,310
(%)	(21.4)	(22.0)	(21.9)	(21.8)	(21.4)	(12.6)	(20.7)
11.3+	4,081	1,487	216	887	1,494	2,331	10,496
(%)	(13.8)	(27.3)	(30.1)	(24.1)	(25.8)	(50.6)	(21.1)
Unknown/Other	3,433	1,168	148	590	1,170	992	7,501
(%)	(11.6)	(21.4)	(20.6)	(16.0)	(20.2)	(21.5)	(15.0)
Gleason score							
5	<15*	<15*	<15*	<15*	<15*	<15*	15
6	264	37	<15*	21	26	19	374
(%)	(0.9)	(0.7)		(0.6)	(0.5)	(0.4)	(0.8)
7	219	29	<15*	22	28	32	335
(%)	(0.7)	(0.5)		(0.6)	(0.5)	(0.7)	(0.7)
8	36	15	<15*	<15*	<15*	20	94
(%)	(0.1)	(0.3)				(0.4)	(0.2)
9	<15*	<15*	<15*	<15*	<15*	<15*	65
(%)							(0.1)
10	<15*	<15*	<15*	<15*	<15*	<15*	<15*
Unknown/Other	29,069	5,358	701	3,624	5,728	4,493	48,973
(%)	(98.2)	(98.4)	(97.8)	(98.5)	(98.8)	(97.5)	(98.2)

Note: AJCC, 6th edition clinical staging of the American Joint Commission on Cancer; TNM6, 6th edition Tumor, node and metastasis staging manual of the American Joint Commission on Cancer; API, Asian Pacific Islanders; NH, Non-Hispanic; CVD, cardiovascular disease; PSA, Prostate specific antigen; *, statistically suppressed; ¶ 95% confidence intervals in parenthesis; §, County attributes of Year 2000; Education attainment defined as percent of residents with less than high-school graduate in the county; Person in poverty defined as percent of residents with income below 200% of poverty in the county.

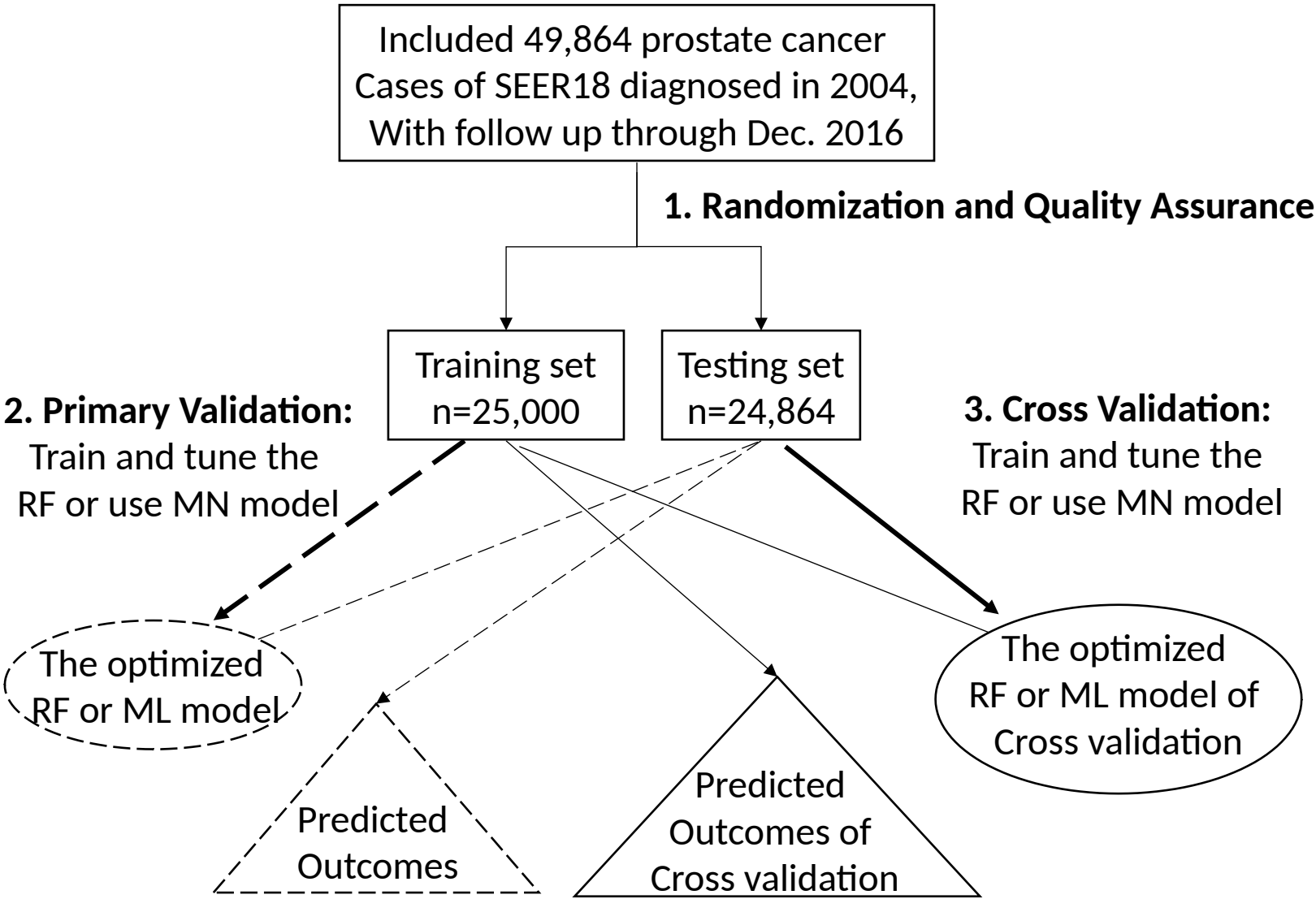
.

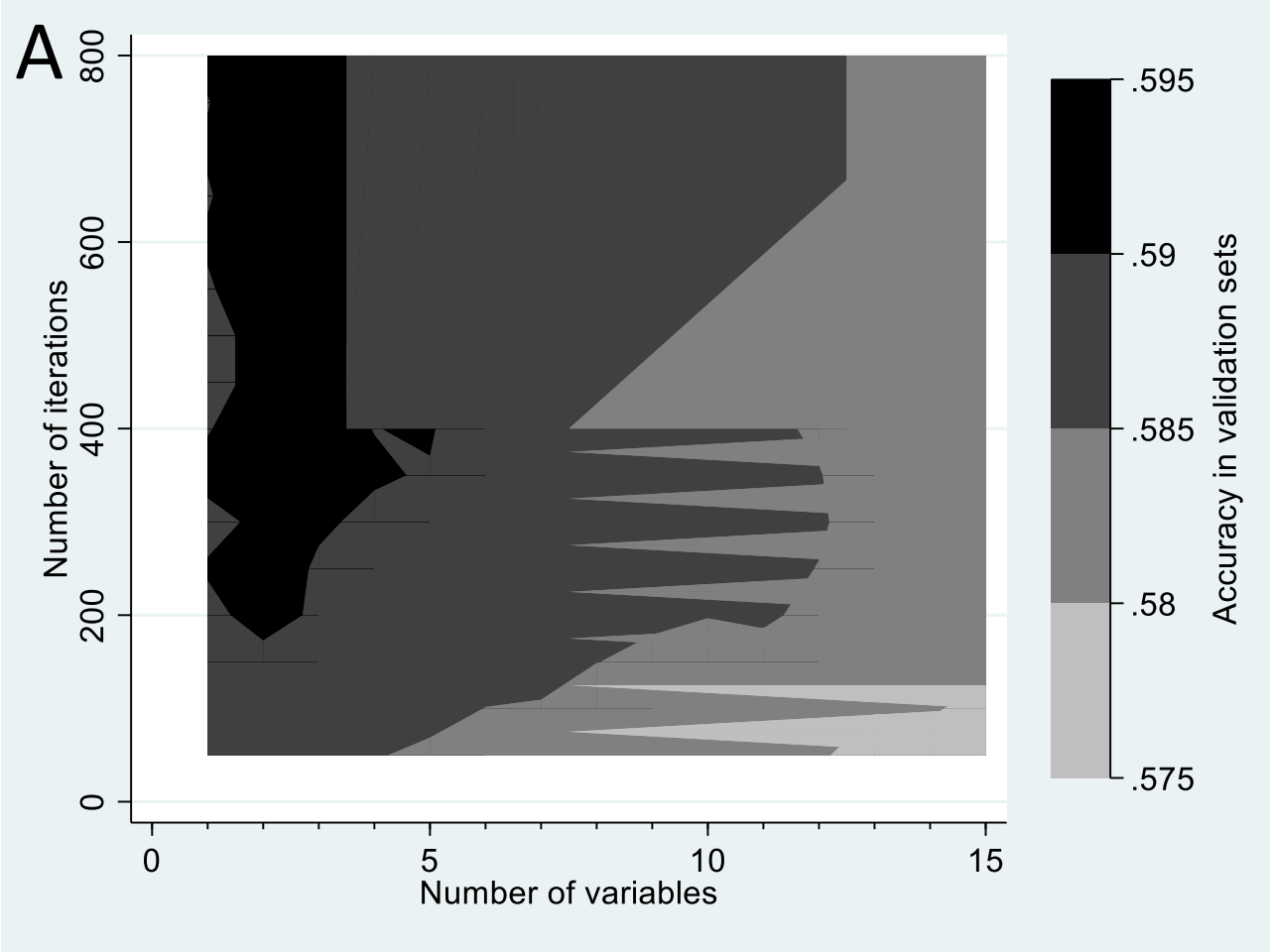
Table 2. Prediction accuracy for long-term 6-category causes of death among the patients with prostate cancer diagnosis in 2004 (follow up through Dec. 2016)

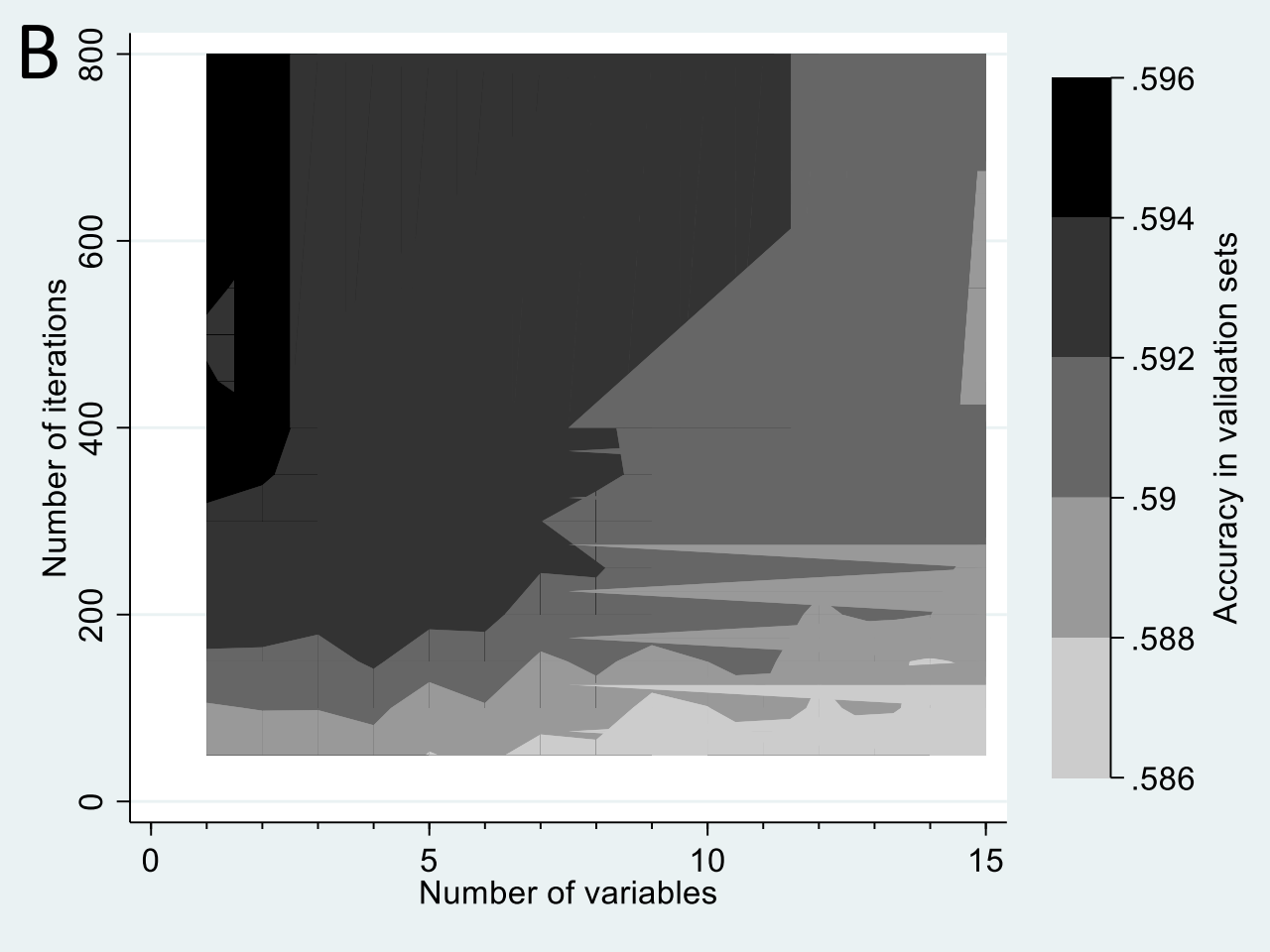
Predicted classes	Alive, n=14,746	CVD, n=2,689	Infection, n=371	Non-Prostate cancer, n=1,873	Other cause, n=2,897	Prostate cancer, n=2,288	Total, n=24,864
Random forest model							
Alive, %	87.70*	52.73	52.29	67.49	55.82	39.9	73.75
CVD, %	3.79	15.88*	15.90	10.04	15.08	8.92	7.54
Infection, %	0.21	0.67	0.27*	0.32	0.69	0.31	0.33
Non-Prostate cancer, %	1.94	3.35	2.96	2.94*	3.11	3.23	2.44
Other cause, %	3.82	17.44	16.44	10.62	15.05*	10.01	7.87
Prostate cancer, %	2.54	9.93	12.13	8.60	10.25	37.63*	8.06
Multinomial model							

Alive, %	82.63*	33.51	31.27	51.84	37.04	32.87	64.34
NA, %	17.37	66.49	68.73	48.16	62.96	67.13	35.66

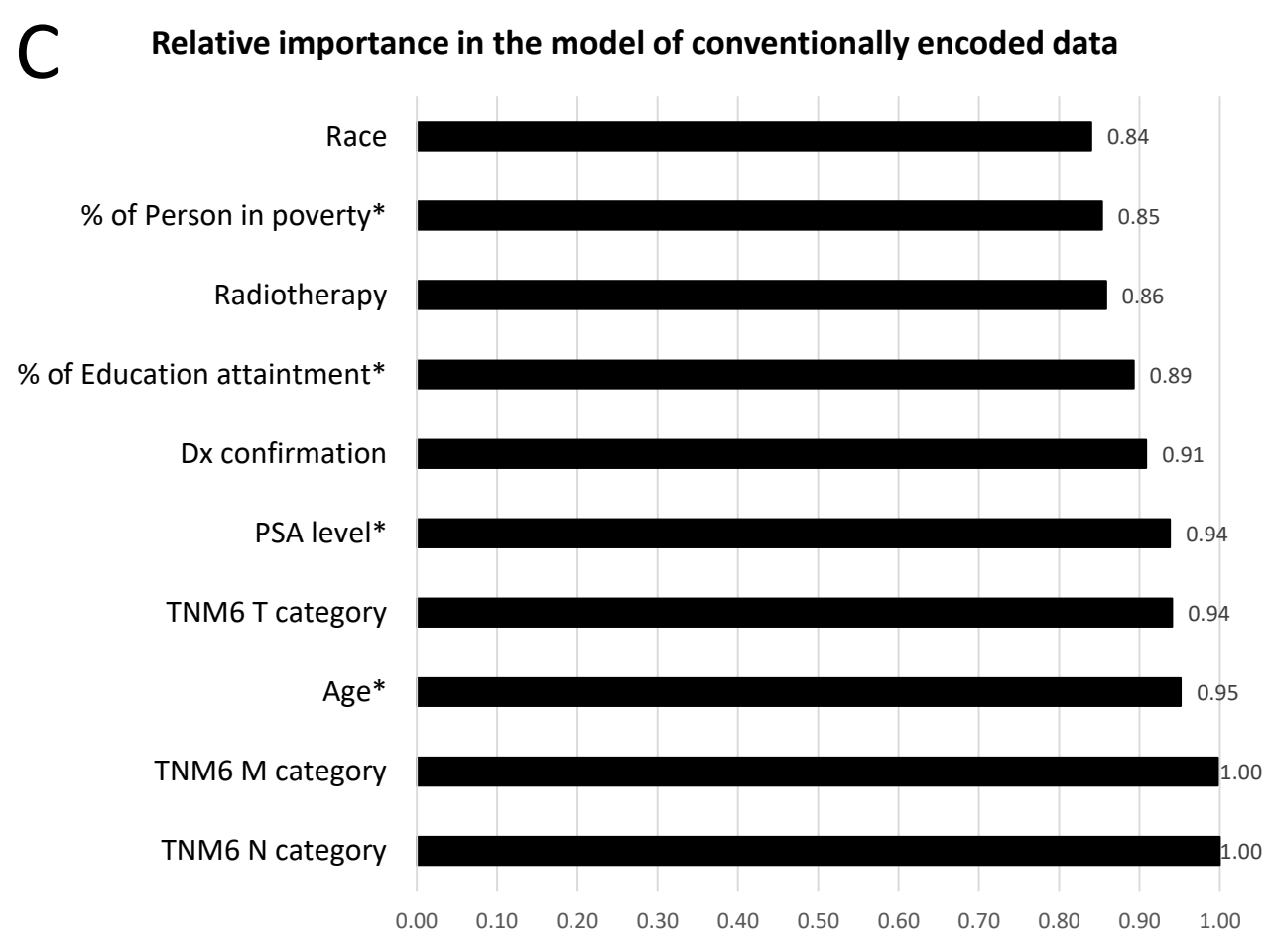
Note: CVD, cardiovascular disease; NA, not available; *, correct prediction.


Included 49,864 prostate cancer
Cases of SEER18 diagnosed in 2004,
With follow up through Dec. 2016
1. Randomization and Quality Assurance
Training set
n=25,000
Testing set
n=24,864
2. Primary Validation:
Train and tune the
RF or use MN model
3. Cross Validation:
Train and tune the
RF or use MN model
The optimized
RF or ML model
The optimized
RF or ML model of
Cross validation
Predicted
Outcomes
Predicted
Outcomes of
Cross validation

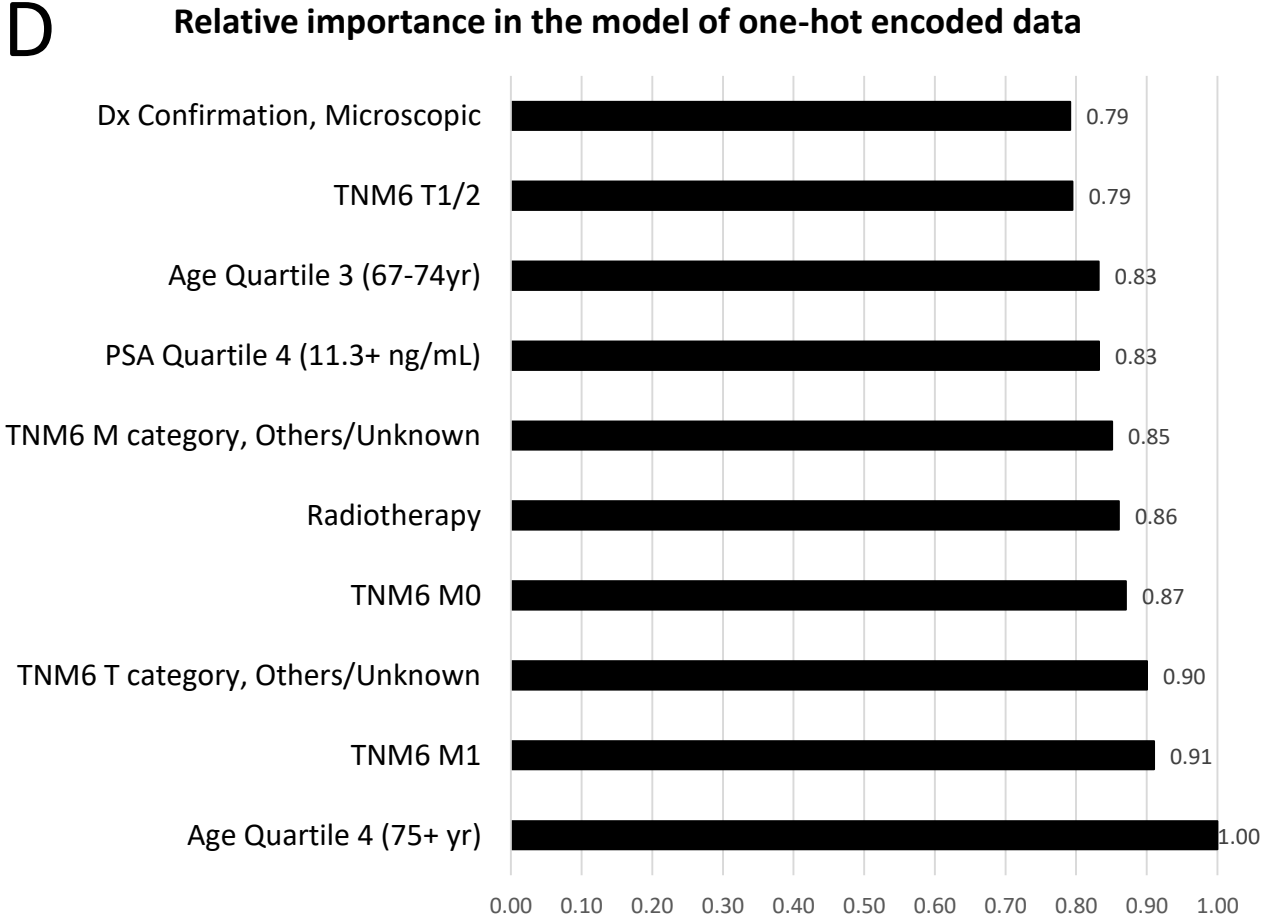

A
Number of iterations
0
200
400
600
800
0
5
10
15
Number of variables
.595
.59
.585
.58
.575
Accuracy in validation sets

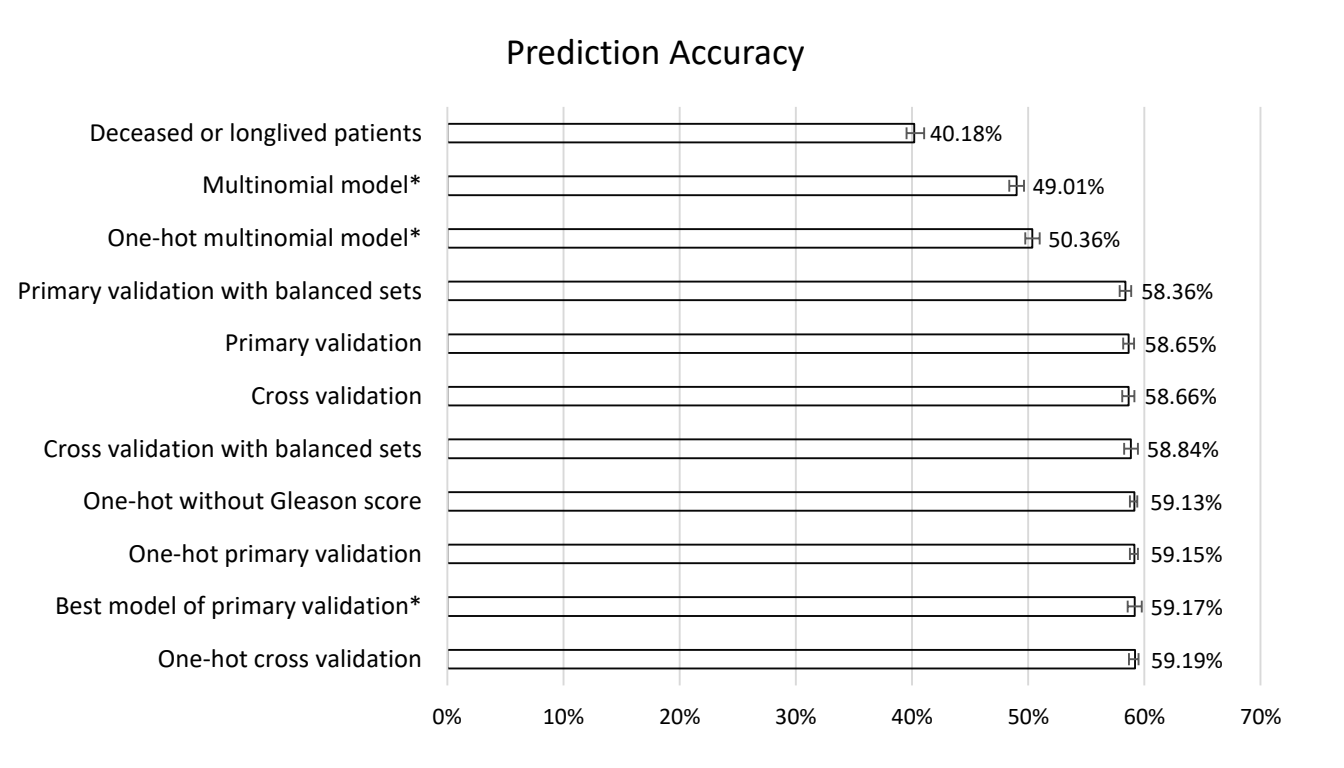

B
Number of iterations
0
200
400
600
800
0
5
10
15
Number of variables
.596
.594
.592
.59
.588
.586
Accuracy in validation sets

C


Relative importance in the model of conventionally encoded data
Race
0.84
% of Person in poverty*
0.85
Radiotherapy
0.86
% of Education attaintment*
0.89
Dx confirmation
0.91
PSA level*
0.94
TNM6 T category
0.94
Age*
0.95
TNM6 M category
1.00
TNM6 N category
1.00
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00

D


Relative importance in the model of one-hot encoded data
Dx Confirmation, Microscopic
0.79
TNM6 T1/2
0.79
Age Quartile 3 (67-74yr)
0.83
PSA Quartile 4 (11.3+ ng/mL)
0.83
TNM6 M category, Others/Unknown
0.85
Radiotherapy
0.86
TNM6 M0
0.87
TNM6 T category, Others/Unknown
0.90
TNM6 M1
0.91
Age Quartile 4 (75+ yr)
1.00
0.00 0.10 0.20 0.30 0.40 0.50 0.60 0.70 0.80 0.90 1.00


Prediction Accuracy
Deceased or longlived patients
40.18%
Multinomial model*
49.01%
One-hot multinomial model*
50.36%
Primary validation with balanced sets
58.36%
Primary validation
58.65%
Cross validation
58.66%
Cross validation with balanced sets
58.84%
One-hot without Gleason score
59.13%
One-hot primary validation
59.15%
Best model of primary validation*
59.17%
One-hot cross validation
59.19%
0%
10%
20%
30%
40%
50%
60%
70%