DEVELOPMENT AND VALIDATION OF A MULTIVARIATE MODEL COMBINING CELL CYCLE PROGRESSION SCORE WITH CAPRA TO PREDICT PROSTATE CANCER MORTALITY IN A CONSERVATIVELY MANAGED COHORT

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BACKGROUND

Prostate cancer outcomes are variable and difficult to predict. Improved tools are needed to appropriately match treatment to a patient's risk of progression. We developed and validated a multivariate model to predict disease-specific mortality (DSM) by combining clinical parameters (CAPRA score) with a score based on measuring the expression level of cell cycle progression (CCP) genes.

METHODS

A multivariate Cox Proportional Hazards model was trained using 1059 patients from 4 retrospective cohorts with median clinical follow-up of 8.0 years (Table 1). Preoperative clinical information was combined in the CAPRA score (integers 0-10), which uses a point system for PSA, clinical stage, percent positive cores, Gleason score, and age at diagnosis.[1] CAPRA has been shown to be a linear predictor of both biochemical recurrence (BCR) and DSM after radical prostatectomy (RP). The numerical CCP score was derived from fixed tumor according to standard protocol.[2] Outcome was either time from diagnosis to DSM (UK cohort) or time from treatment to BCR (USA cohorts). All observations were censored at 10 years. The model was validated for predicting time from diagnosis to DSM in an independent cohort (Table 1).

TABLE 1. SOURCES OF TRAINING AND VALIDATION COHORTS

	COUNTRY	NUMBER OF PATIENTS	YEAR OF DIAGNOSIS	TISSUE SAMPLE	PRIMARY TREATMENT	OUTCOME
TRAINING:						
QMUL[2]	UK	200	1990-1996	TURP	Conservative	DSM
Scott and White Clinic[2]	USA	353	1988-1995	Surgical resection	RP	BCR
UCSF[3]	USA	388	1994-2006	Surgical resection	RP	BCR
Durham VA[4]	USA	118	1996-2006	Needle biopsy	EBRT	BCR
VALIDATION:						
QMUL[3]	UK	180	1990-1996	Needle biopsy	Conservative	DSM

Abbreviations: TURP = transurethral resection of the prostate, RP = radical prostatectomy, EBRT = external beam radiation treatment, DSM = disease-specific mortality, BCR = biochemical recurrence

COMBINED SCORE

CAPRA and CCP scores were combined in a Cox Proportional Hazards model stratified by cohort. The outcome was any adverse event, a generalization of the specific types of outcomes in different cohorts. Stratification adjusted for differences in the survival profiles that might be produced by various treatment regimes and endpoints in each cohort (Figure 1). Interactions were tested to confirm that the prognostication of CAPRA and CCP was not dependent on cohort. The coefficients obtained from this model in the training set were used to calculate the Combined Score.

VALIDATION

Combined Score = 0.39 * CAPRA + 0.57 * CCP

The Combined Score was validated on a cohort of 180 men with 33 (18%) disease-specific deaths from the UK, diagnosed by needle biopsy with clinically localized prostate cancer and conservative management.[3] The Combined Score was highly prognostic of DSM: HR = 2.27, 95% CI (1.63, 3.16) p-value = 1.2×10^{-7} (Figure 2). By likelihood ratio testing, the Combined Score was a better predictor of DSM than CAPRA alone (p-value = 0.0028). The c-index of the Combined Score was 0.76, an improvement over CAPRA (c-index 0.73).

FIGURE 1. KAPLAN-MEIER CURVES BY COHORT

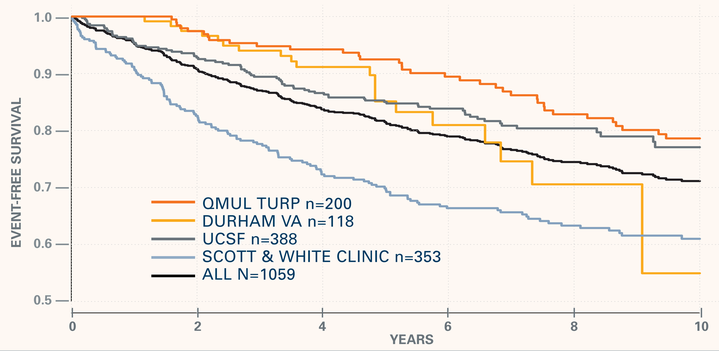


FIGURE 2. PREDICTED RISK OF 10-YEAR DEATH FROM PROSTATE CANCER IN VALIDATION COHORT FOR DIFFERENT CAPRA SCORES. DOTTED LINES ARE 95% CONFIDENCE LIMITS

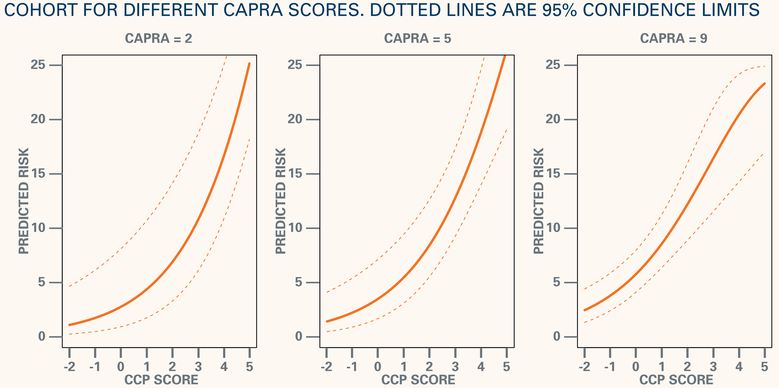
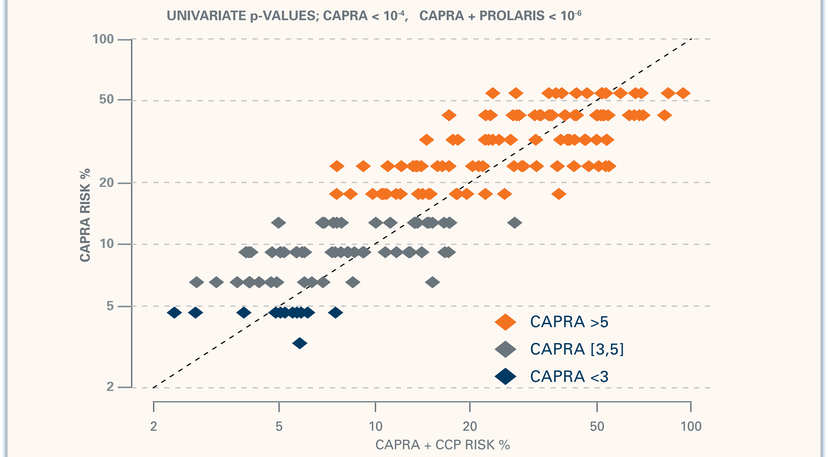


FIGURE 3. ADDED DISCRIMINATION BY CCP SCORE. SCATTER PLOT OF THE 10-YEAR PREDICTED RISK OF DSM FOR THE COMBINED SCORE (CAPRA + CCP ON THE X-AXIS) VERSUS CLINICAL PARAMETERS ONLY (CAPRA ON THE Y-AXIS). THE LEVEL OF THE PATIENT'S CAPRA RISK IS INDICATED BY DOT COLOR (LOW, INTERMEDIATE, OR HIGH).



CONCLUSIONS

1. A multivariate risk predictor consisting of clinical information (CAPRA) and molecular data (CCP) was trained in a set of 4 diverse prostate cancer cohorts. Both CAPRA and CCP conferred similar prognostic information regardless of cohort composition, treatment, or specific outcome.
2. Combined Score was validated on needle biopsies in a conservatively managed cohort with death-specific mortality as the outcome.
3. Combined Score provides prognostic information beyond clinical variables alone, and can be used to differentiate aggressive from indolent cancer at diagnosis.
4. The Combined Score was a better predictor of outcome than CAPRA alone.

REFERENCES

1. Cooperberg et al. *Jour Urology* 2005; 173: 1938-42.
2. Cuzick et al. *Lancet Oncol* 2011; 12(3): 245-55.
3. Cuzick et al. *Br J Cancer* 2012; 106(6): 1095-9.
4. Cooperberg et al. Presented AUA 2012. *Publication Pending.*
5. Freedland et al. Presented SUO 2012. *Publication Pending.*

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