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Effects of age and comorbidity on survival vary according to risk grouping among patients with prostate cancer treated using radical prostatectomy

A retrospective competing-risk analysis from the K-CaP registry

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Abstract

A multicenter Korean Prostate Cancer Database (K-CaP) has been established to provide information regarding Korean patients with prostate cancer (PCa). We used the K-CaP registry to investigate the value of age and comorbidity for predicting cancer-specific mortality (CSM) and other-cause mortality (OCM) according to risk grouping.

The K-CaP registry includes 2253 patients who underwent radical prostatectomy (RP) between May 2001 and April 2013 at 5 institutions. Preoperative clinicopathologic data were collected and stratified according to the National Comprehensive Cancer Network risk criteria. Survival was evaluated using Gray's modified log-rank test according to risk category, age (<70 years vs ≥70 years), and Charlson comorbidity index (CCI) (0 vs ≥1).

The median follow-up was 55.0 months (interquartile range: 42.0–70.0 months). Competing-risk regression analysis revealed that, independent of CCI, ≥70-year-old high-risk patients had significantly greater CSM than <70-year-old high-risk patients ($P = .019$). However, <70-year-old high-risk patients with a CCI of ≥1 had similar CSM relative to ≥70-year-old patients. Survival was not affected by age or CCI among low-risk or intermediate-risk patients. Multivariate analysis revealed that a CCI of ≥1 was independently associated with a higher risk of CSM ($P = .003$), while an age of ≥70 years was independently associated with a higher risk of OCM ($P = .005$).

Age and comorbidity were associated with survival after RP among patients with high-risk PCa, although these associations were not observed among low-risk or intermediate-risk patients. Therefore, older patients with high-risk diseases and greater comorbidity may require alternative multidisciplinary treatment.

Abbreviations: ADT = androgen deprivation therapy, BMI = body mass index, CCI = Charlson comorbidity index, CSM = cancer-specific mortality, K-CaP = Korean Prostate Cancer Database, NCCN = National Comprehensive Cancer Network, OCM = other-cause mortality, PCa = prostate cancer, PSA = prostate-specific antigen, RP = radical prostatectomy, RT = radiotherapy.

Keywords: comorbidity, prognosis, prostatic neoplasm, survival

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1. Introduction

Prostate cancer (PCa) is characterized by a heterogeneous disease landscape, with low-risk localized PCa having an exceptionally protracted natural history. However, broad variations are observed in the oncologic outcomes for high-risk PCa, and the optimal treatment modality remains unclear.[1] During the last decade, radiotherapy (RT) plus androgen deprivation therapy (ADT) have been the mainstay of management for localized high-risk PCa. However, radical prostatectomy (RP) has become a potentially curative treatment for localized high-risk PCa because of improvements in surgical technique, anesthesia, and postoperative care.[2] Nevertheless, there is no consensus regarding the optimal treatment for high-risk PCa, which is presumably related to inappropriate patient grouping that is caused by inadequate analysis of risk and predictive factors. Thus, more prognostic parameters are needed to supplement the use of conventional risk prediction based on prostate-specific antigen (PSA) status, Gleason score, and clinical stage.[3–5] Moreover, prolonged life

expectancy has increased the proportion of individuals with excellent performance status relative to their biologic age. Therefore, given the importance of life expectancy after PCa treatment, patient age, and comorbidity burden are essential factors to consider when making treatment decisions.[6,7]

The overall incidence and mortality of PCa is higher among Asian men than among Western men, which is predictably related to genetic differences and acquired dissimilarities, such as diet and lifestyle.[8–11] Moreover, developing Asian countries have lower rates of PSA screening, which may explain the more aggressive PCa features and greater proportion of metastasis at diagnosis among Asian men.[12,13] Therefore, it would be difficult to adopt Western management guidelines for use among Asian men without modification.

The internet-based multicenter Korean Prostate Cancer Database (K-CaP) was established in 2011, and is the first registry to provide comprehensive data regarding Korean PCa patients who underwent RP.[10] Thus, we used the K-CaP registry to assess the value of age and comorbidity for predicting cancer-specific mortality (CSM) and other-cause mortality (OCM) among patients with PCa who underwent RP, with stratification according to the National Comprehensive Cancer Network (NCCN) risk criteria.

2. Methods

2.1. Patient selection

Clinicopathologic data and oncologic outcomes for 3815 patients who underwent RP between May 2001 and April 2013 were retrieved from the K-CaP registry. The K-CaP registry is an internet-based, observational, and automated data-entry system that has been implemented at 5 high-volume Korean institutions: Asan Medical Center, Samsung Medical Center, Seoul National University Bundang Hospital, Seoul St Mary's Hospital, and Yonsei University Severance Hospital. Patients with incomplete data and patients who received neoadjuvant therapy were excluded from the present study. Preoperative clinicopathologic data were used to stratify 2253 patients according to the 2018 NCCN risk criteria, as follows: low risk = T-stage T1-T2a, Gleason score $\leq$6, and PSA $<$10 ng/mL; intermediate risk = T-stage T2b-T2c, or Gleason score 7 (both 3+4 and 4+3), or PSA 10 to 20 ng/mL; high risk = T-stage $\geq$T3a, or Gleason score $\geq$8, or PSA $>$20 ng/mL.[14] The present study's retrospective protocol was reviewed and approved by the Yonsei University Health System Ethics Committee, which waived the requirement for informed consent (2016-0389-001). All study procedures complied with the principles of the 1964 Declaration of Helsinki and its 2008 update.

2.2. Assessments of clinicopathologic variables

The collected clinicopathologic data included age at the operation, body mass index (BMI), medical history, Gleason score, serum PSA level at the diagnosis, clinical T and N stages, interval for progression to castration-resistant PCa, and follow-up period. Each patient's comorbidity profile was analyzed using the Charlson comorbidity index (CCI), which is the most widely used comorbidity index in surgical settings. The CCI scoring system is based on the weighted number and severity of 19 comorbidities,[15] and the present study compared absolute scores between the various patient groups. The intervals to CSM and OCM were defined based on the times from RP to death that was attributed to PCa or to other causes, respectively. Patient survival and causes of death were investigated using the National Cancer Registry Database or institutional electronic medical records.

The decisions to perform RP, as well as adjuvant or salvage therapies, were made based on each physician's discretion and the patient's preference. In general, RP was recommended for patients who desired surgical treatment or who were considered reasonable surgical candidates based on favorable clinical characteristics. The RP was performed using open retropubic, laparoscopic, or robot-assisted laparoscopic modalities, and the extent of pelvic lymph node dissection was based on the patient's risk category.

2.3. Statistical analysis

The effects of age and comorbidity were evaluated by categorizing the patients according to age ($<$70 years vs $\geq$70 years) and CCI (0 vs $\geq$1). Predictors of survival were evaluated using Fine and Gray's modified log-rank test for each risk category according to age and CCI grouping. All statistical analyses were performed using IBM SPSS software (version 21.0; IBM Corporation, Armonk, NY) and R statistical package (version 3.2.0; Institute for statistics and mathematics, Vienna, Austria). Differences with a P-value of $<.05$ were considered statistically significant.

3. Results

3.1. Clinicopathologic features

Table 1 shows the clinicopathologic features of the 2253 patients who were included in the final analysis. The proportion of patients with a CCI of $\geq$1 was higher among $\geq$70-year-old men than among $<$70-year-old men (25.2% vs 17.5%, $P < .001$). However, the younger group had more favorable preoperative Gleason score and T-stage than the older group. No significant age-related differences were observed in BMI, serum PSA levels, NCCN risk grouping, or follow-up period.

3.2. Competing risk analysis

Gray's competing risk regression analysis revealed that $\geq$70-year-old patients had a significantly higher cumulative CSM rate than $<$70-year-old patients, with the exemption of low-risk patients ($P = .002$) (Fig. 1). When CCI was taken into account, high-risk $<$70-year-old patients with CCI $\geq$1 had comparable cumulative CSM rates compared to $\geq$70-year-old patients, while the cumulative CSM rate was significantly higher in $\geq$70-year-old patients with CCI $\geq$1 ($P = .019$; Fig. 2). However, CSM was not affected by age or CCI in the low-risk and intermediate-risk groups.

3.3. Predictors of survival

The Fine and Gray's analysis revealed that the risk of overall mortality was associated with older age (hazard ratio [HR]: 2.544, 95% confidence interval [CI]: 1.096–5.908; $P = .03$) and a CCI of $\geq$1 (HR: 2.409, 95% CI: 1.075–5.397; $P = .033$). Furthermore, a CCI of $\geq$1 was associated with a higher risk of CSM (HR: 4.872, 95% CI: 1.686–14.08; $P = .003$), and an age of $\geq$70 years was associated with a higher risk of OCM (HR: 10.44, 95% CI: 2.064–52.85; $P = .005$) (Table 2).

Table 1

Patient characteristics.

	Overall	Age ≥70 y	Age <70 y	P
N	2253	588 (26.1%)	1665 (73.9%)	
Age, y	65.0 (60.0–70.0)	72.0 (71.0–74.0)	63.0 (58.0–66.0)	<.001
BMI, kg/m^2	24.4 (22.7–26.1)	24.4 (22.3–26.0)	24.4 (22.8–26.1)	.567
Comorbidity				
CCI (≥1)	440 (19.5%)	148 (25.2%)	292 (17.5%)	<.001
DM	307 (13.6%)	104 (17.7%)	203 (12.2%)	.001
HTN	803 (35.6%)	257 (43.7%)	546 (32.8%)	<.001
Biopsy Gleason sum				.007
6	984 (43.7%)	233 (39.6%)	751 (45.1%)	
7	797 (35.4%)	209 (35.5%)	588 (35.3%)	
8	472 (20.9%)	146 (24.8%)	326 (19.6%)	
PSA, ng/mL	7.15 (5.04–11.6)	7.73 (5.13–12.4)	6.98 (5.0–11.4)	.403
NCCN risk criteria				.465
Low	603 (26.8%)	133 (22.6%)	470 (28.2%)	
Intermediate	986 (43.8%)	264 (44.9%)	722 (43.4%)	
High	664 (29.5%)	191 (11.5%)	473 (28.4%)	
Pathologic T stage				.010
T2	1518 (67.4%)	366 (62.4%)	1152 (69.2%)	
T3	729 (32.4%)	220 (37.5%)	509 (30.6%)	
T4	4 (0.2%)	1 (0.2%)	3 (0.2%)	
Pathologic N stage (N1)	146 (6.5%)	39 (6.9%)	107 (6.6%)	.810
Progression to CRPC	271 (12.0%)	52 (8.9%)	219 (13.2%)	.006
Follow-up period, mo	55.0 (42.0–70.0)	51.0 (37.0–66.0)	56.0 (43.0–72.0)	.154

Data are numbers (%) and medians (interquartile range, IQR).

BMI = body mass index, CCI = Charlson comorbidity index, CRPC = castration-resistant prostate cancer, DM = diabetes mellitus, GS = Gleason score, HTN = hypertension, NCCN = National Comprehensive Cancer Network, PSA = prostate-specific antigen.

4. Discussion

Advancements in the understanding of tumor microbiology and treatment modalities have generated increases in the 5-year relative survival rates for many cancers during the last decade.[16] Furthermore, rates of early diagnosis have been enhanced by changes in health perception, healthcare improvements, and advances in medical imaging. These developments will likely prolong the human lifespan, which highlights the importance of considering age and comorbidity when selecting treatment for PCa. The present study evaluated multicenter data from the K-CaP database and compared the rates of CSM and OCM among patients who were stratified based on age and comorbidity. Our competing-risk analysis revealed that in high-risk patients, older age and comorbidities were significantly associated with cumulative CSM. Notably, <70-year-old patients with CCI ≥1 had comparable cumulative CSM rates compared to ≥70-year-old patients.

The 2018 NCCN guideline recommend basing treatment decisions on the patient's life expectancy and the number and type of recurrence risk factors.[14] However, given the protracted natural history of PCa, survival is strongly associated with age and comorbidity. Thus, although the 2018 NCCN guideline recommend RP if the patient's life expectancy is expected to be >10 years, this is an imprecise and unpredictable proxy. Moreover, overall survival is strongly affected by CCI.[17] Therefore, comorbidity- and age-adjusted reference values are needed to guide counseling and the selection of surgical treatment.[18]

Briganti et al retrospectively investigated the risks of CSM and OCM in high-risk patients with PCa treated with RP, and reported that age and comorbidity were the major determinants of OCM. OCM was the leading cause of death in all patient subgroups with the exemption of young and healthy patients. This observation lends support to the notion that these patients may more likely to benefit from aggressive surgical treatment compared to older and unhealthy patients who have a higher risk of OCM.[6] Sivaraman et al also analyzed the benefits of RP for older patients with high-risk PCa according to their CCI, and reported that a higher OCM risk was observed among older patients with a CCI of ≥2, although older patients with high-risk PCa and fewer comorbidities appeared to benefit from RP.[7] Those studies provided valuable evidence that age and CCI should be considered when predicting survival among men with high-risk PCa, although those studies did not include low-risk and intermediate-risk patients. Thus, the present study evaluated Korean patients with low-, intermediate-, and high-risk disease, and revealed that age and comorbidity were only significant prognostic factors for patients with high-risk disease. Several other studies have addressed the value of comorbidity for predicting CSM and OCM outcomes among Western patients with PCa who are undergoing RP,[19–23] although their findings may not reflect the expected outcomes among Asian men. Nevertheless, because age and comorbidity were not significant prognostic factors among Korean patients with low-risk and intermediate-risk disease, the conventional risk factors (PSA status, Gleason score, and clinical stage) may provide appropriate risk stratification in this setting. However, the heterogeneous nature of high-risk PCa highlights the importance of considering all possible prognostic factors to optimize treatment selection. Therefore, our findings indicate that age and comorbidity should be considered during the management of Korean men with high-risk PCa.

Froehner et al[18] and Boehm et al[24] have reported conflicting findings regarding the prognostic value of age and comorbidity among patients with PCa. For example, Froehner et al claimed that competing mortality was associated with comorbidities

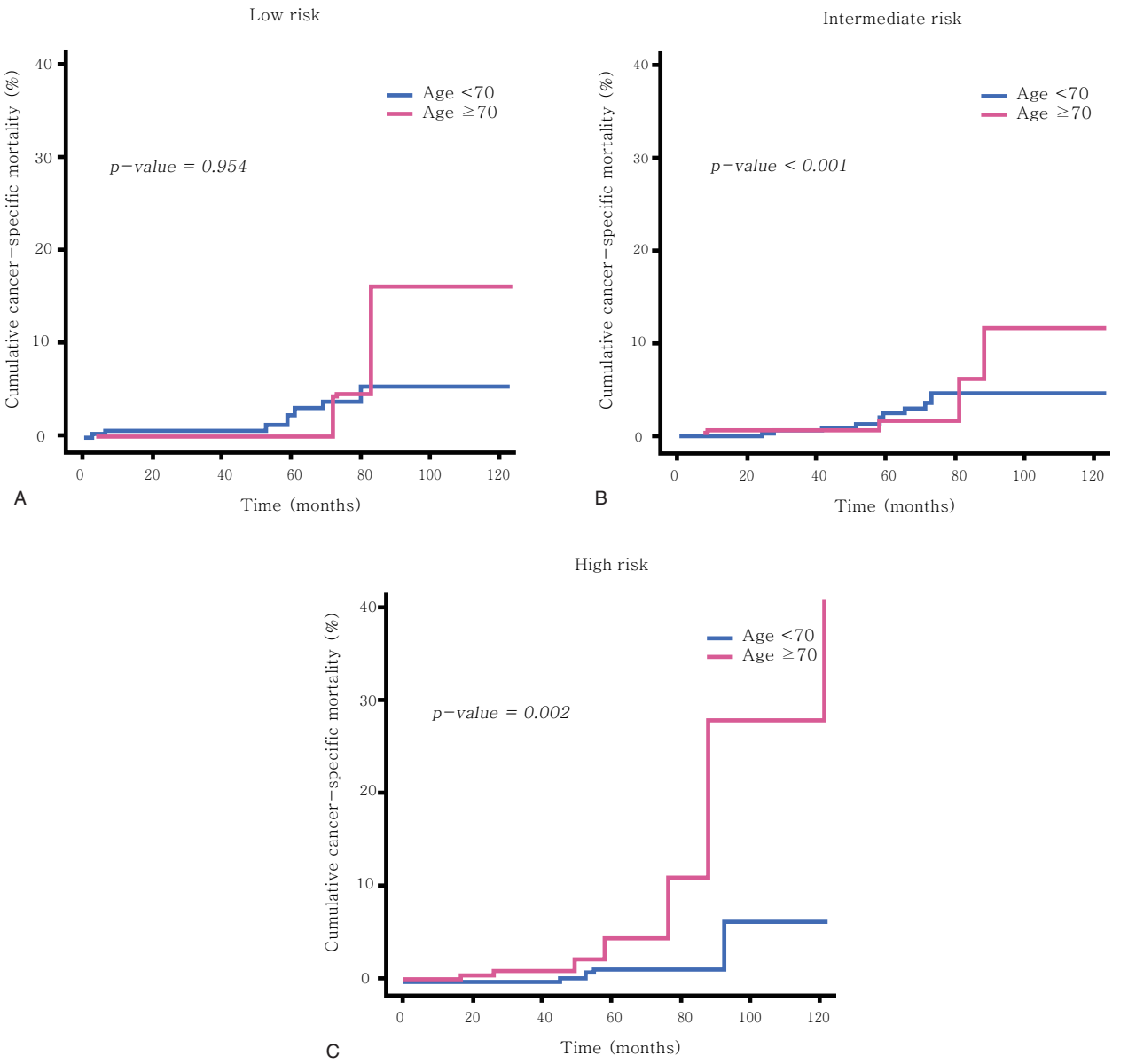

Figure 1. Cumulative survival based on Gray's competing-risk regression analysis of cancer-specific mortality according to age group (≥70 years vs <70 years) in the (A) low-risk, (B) intermediate-risk, and (C) high-risk groups.

among older patients (>70 years), such as peripheral vascular disease, cerebrovascular disease, and current smoking status. In contrast, Boehm et al suggested that age and CCI did not influence OCM or life expectancy. These discrepant findings may be related to differences in cohort selection, as Froehner et al analyzed patients with PCa who underwent surgical treatment and Boehm et al analyzed ≥66-year-old patients with nonmetastatic PCa who were stratified according to treatment type. As patients with high-risk PCa experience heterogeneous survival outcomes, the variable findings from these studies indicate that age and comorbidity should not be interpreted blindly to avoid unintended bias. The present study aimed to overcome the limitations of retrospective analyses using Fine and Gray's modified log-rank test, which provided data according to risk category, age, and CCI grouping to help identify which Korean patients are the best candidates for surgery.

The strengths of the present study are the inclusion of a large sample of patients who underwent RP for PCa from the K-CaP database, which is the largest multicenter nationally representative Korean registry. This perspective is important, as Asian men have more aggressive PCa features at their diagnosis than Western men,[8,25–27] although there are no multicenter data regarding the prognostic value of age and comorbidity among Asian patients with PCa. Thus, the present study provides valuable regional data that can better guide the management of PCa in Korean. However, the present study also has several limitations. First, selection bias is possible, as only 2253 of 3815 patients were considered eligible for the analysis, which was mainly related to incomplete clinicopathologic data that were generated from the institution's different data collection protocols. Nevertheless, the large number of exclusions was necessary to preserve data quality and enhance the prognostic analysis. A second limitation is that the cohort only included patients who

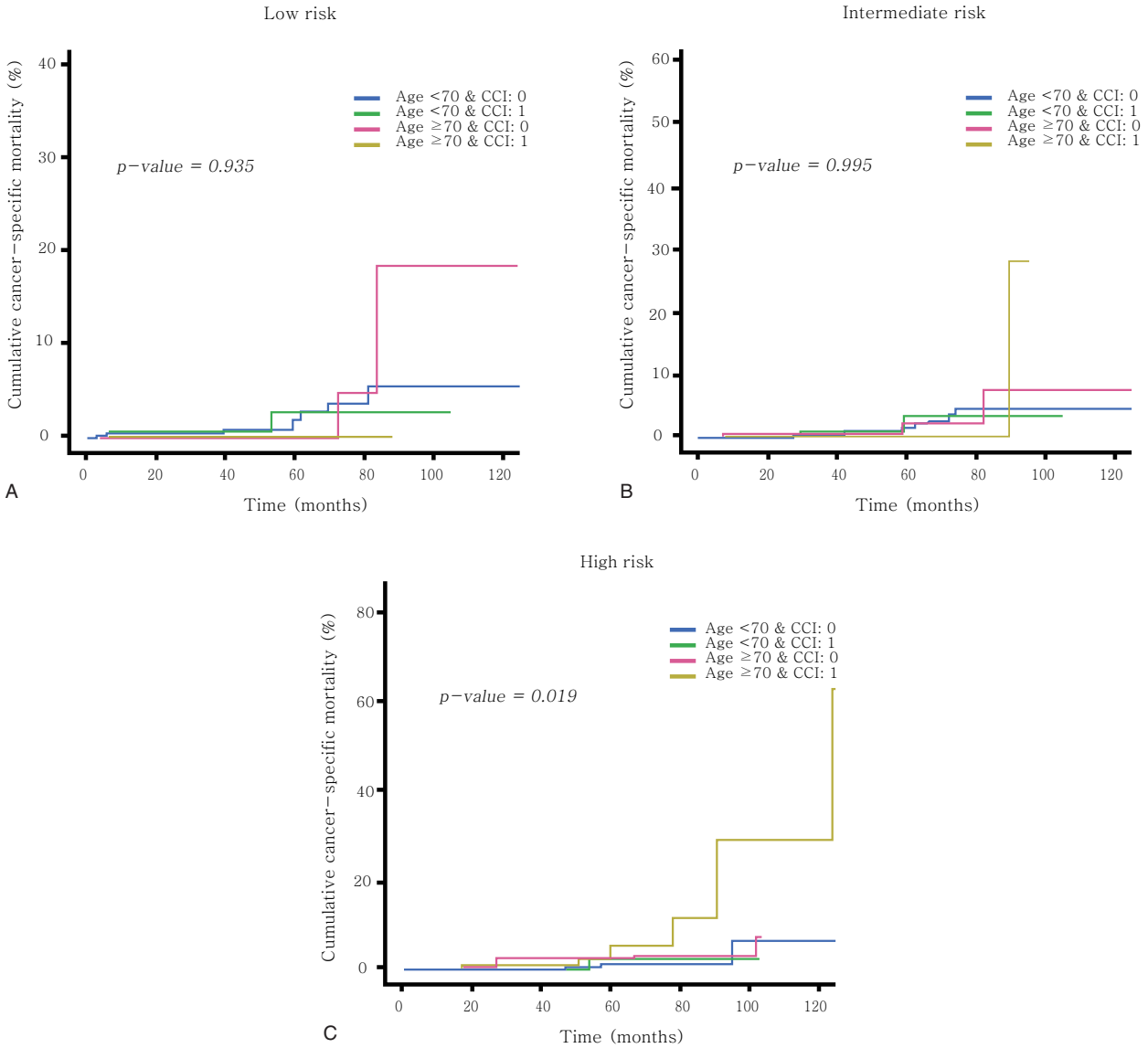

Figure 2. Cumulative survival analysis based on Gray's competing-risk regression analysis of cancer-specific mortality according to age and comorbidity grouping (≥70 years vs <70 years; CCI: 0 vs ≥1) in the (A) low-risk, (B) intermediate-risk, and (C) high-risk groups.

Table 2

Predictors of survival.

	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Overall mortality						
Age (≥70 y)	2.898	1.809–4.642	*<.001*	2.544	1.096–5.908	.030
CCI (≥1)	2.484	1.105–5.535	*.028*	2.409	1.075–5.397	.033
PSA	0.997	0.979–1.016	*.759*	0.999	0.961–1.038	.963
Pathologic GS (≥8)	1.106	0.603–2.027	*.746*	0.481	0.107–2.175	.342
Pathologic T stage (≥pT3)	1.134	0.699–1.840	*.611*	0.747	0.349–2.128	.862
Cancer-specific mortality						
Age (≥70 y)	1.872	0.957–3.663	*.057*	0.892	0.254–3.141	.859
CCI (≥1)	4.848	1.680–13.99	*.004*	4.872	1.686–14.08	.003
PSA	0.999	0.977–1.022	*.939*	1.001	0.956–1.047	.976
Pathologic GS (≥8)	1.252	0.571–2.745	*.574*	0.978	0.846–1.134	.762
Pathologic T stage (≥pT3)	1.221	0.638–2.337	*.546*	1.003	0.344–2.929	.995
Other cause mortality						
Age (≥70 y)	4.768	2.352–9.665	*<.001*	10.44	2.064–52.85	.005
CCI (≥1)	0.632	0.127–3.136	*.574*	1.654	0.333–8.214	.538
PSA	0.994	0.964–1.025	*.705*	1.003	0.948–1.061	.925
Pathologic GS (≥8)	0.932	0.357–2.436	*.886*	1.313	0.238–7.242	.754
Pathologic T stage (≥pT3)	1.034	0.498–2.148	*.928*	0.625	0.117–3.328	.580

Data are expressed as means ± standard deviations or number of patients (%), as appropriate.

CCI = Charlson comorbidity index, CI = confidence interval, GS = Gleason score, HR = hazard ratio, PSA = prostate-specific antigen.

underwent RP, and men who received other treatments were excluded. Although many researchers have indicated that RP provides acceptable results for patients with low-risk, intermediate-risk, and high-risk PCa, there is no consensus regarding whether RP is superior to other treatments.[28–30] Thus, further studies are needed to compare RP and other treatments. A third limitation is that the patients were treated at multiple institutions, and the survival outcomes may have been influenced by variations in surgeon experience and skill.[31]

5. Conclusion

The present study revealed that age and comorbidity could predict survival among patients with high-risk PCa who underwent RP, although this relationship was not observed among patients with low-risk or intermediate-risk disease. However, given the protracted natural history of PCa, studies are needed to evaluate the risk of OCM among elderly patients with comorbidities and high-risk disease. Alternative multidisciplinary treatment may be needed for patients who are not expected to benefit from RP in this setting.

Author contributions

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