Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Development and Validation of a Treatment-Specific Prognostic Model for Overall Survival in Patients with Metastatic Castration-Sensitive Prostate Cancer Treated with First-Line Apalutamide: A Multicenter Real-World Study

Shin Kobayashi
Asahikawa Medical University
Takuma Narita
Hirosaki University Graduate School of Medicine
Kotona Miyauchi
Asahikawa Medical University
Shun Morishita
Wakkanai City Hospital
Naoki Fujita
Hirosaki University Graduate School of Medicine
Daiki Kikuchi
Asahikawa Medical University
Noriyuki Abe
Asahikawa Medical University
Miyu Ohtani
Asahikawa Medical University
Naoki Wada
Asahikawa Medical University
Shingo Hatakeyama
Hirosaki University Graduate School of Medicine
Kazuyuki Numakura
nqf38647@nifty.com

Asahikawa Medical University

Article

Keywords: metastatic castration-sensitive prostate cancer, apalutamide, Japanese, risk model

Posted Date: August 6th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9876981/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Apalutamide plus androgen deprivation therapy (ADT) is a standard first-line treatment for metastatic castration-sensitive prostate cancer (mCSPC). However, outcomes remain heterogeneous, and prognostic factors specific to apalutamide-treated populations are not well established. We aimed to evaluate real-world outcomes and develop a treatment-specific prognostic model.

Methods

We retrospectively analyzed 208 patients with mCSPC treated with first-line apalutamide at multiple Japanese institutions. Overall survival (OS) was evaluated using Kaplan–Meier analysis and Cox proportional hazards models. Independent prognostic factors were used to construct a risk model, and performance was assessed using Harrell's concordance index (c-index) and compared with LATITUDE and CHAARTED classifications.

Results

The median baseline prostate-specific antigen level was 129 ng/mL. A deep PSA response (<0.2 ng/mL) was achieved in 68.8% of patients, and grade ≥3 adverse events occurred in 17.3%. Multivariable analysis identified primary Gleason pattern 5 (hazard ratio [HR] 4.32, P < 0.001), extent of disease ≥2 (HR 3.89, P = 0.01), and lactate dehydrogenase ≥216 U/L (HR 3.95, P = 0.002) as independent predictors of poor OS. Patients with ≥2 risk factors had significantly worse OS (HR 6.83, 95% confidence interval 2.73–17.1; P < 0.001). The proposed model showed better discrimination (c-index 0.762) than LATITUDE (0.593) and CHAARTED (0.615).

Conclusions

Clinical outcomes with apalutamide vary according to baseline disease characteristics. A simple three-factor model may improve prognostic stratification and support individualized treatment decisions in mCSPC.

Introduction

Prostate cancer is one of the most frequently diagnosed malignancies among men worldwide and remains a major cause of cancer-related mortality. According to GLOBOCAN 2020 estimates, approximately 1.4 million new cases were diagnosed globally, making it the second most commonly diagnosed cancer in men (1). In Japan, prostate cancer is the most frequently diagnosed cancer among men based on national cancer registry data (2). Despite the widespread use of prostate-specific antigen (PSA) screening, approximately 5–10% of patients present with metastatic disease at initial diagnosis (3).

The treatment landscape of metastatic castration-sensitive prostate cancer (mCSPC) has evolved substantially with the introduction of androgen receptor pathway inhibitors (ARPIs). Apalutamide, a next-generation ARPI, inhibits androgen receptor nuclear translocation and DNA binding, thereby suppressing androgen receptor–mediated tumor growth (4). The phase III TITAN trial demonstrated that the addition of apalutamide to androgen deprivation therapy (ADT) significantly improved both radiographic progression-free survival and overall survival compared with ADT alone (5, 6). These findings established apalutamide plus ADT as a standard first-line treatment option for patients with mCSPC. Large randomized trials of different ARPIs, including abiraterone and enzalutamide, have demonstrated survival benefits in mCSPC; however, differences in mechanisms of action and treatment strategies may lead to heterogeneity in treatment response and survival outcomes, potentially influencing prognostic modeling (7, 8).

In addition to randomized clinical trials, real-world studies have supported the effectiveness of apalutamide. The OASIS study and subsequent analyses, including those from Japanese cohorts, have demonstrated favorable biochemical responses and survival outcomes in patients treated with apalutamide-based therapy (9, 10). However, these studies have also highlighted substantial heterogeneity in clinical outcomes among patients receiving apalutamide. Importantly, most existing real-world studies have focused on treatment effectiveness or biochemical responses rather than overall survival (OS), and few have attempted to develop prognostic models specific to individual ARSI agents. Furthermore, most existing models have been derived from heterogeneous treatment populations, limiting their applicability to contemporary practice in which specific AR-targeted agents are selected. Given the increasing use of AR-targeted therapies in the first-line setting, there is a critical need for treatment-specific risk stratification based on homogeneous therapeutic cohorts (6). Furthermore, OS remains the most clinically meaningful endpoint, yet prognostic models based on OS in homogeneous ARSI-treated populations remain limited.

Treatment benefit is not uniform across all patients with mCSPC. While many patients achieve durable disease control with ARPI-based therapy, others experience less durable benefit despite initial biochemical responses (11). Established risk classifications such as LATITUDE and CHAARTED have been widely used to stratify patients according to disease burden and prognosis. However, these models were developed in the context of abiraterone- or docetaxel-based intensification strategies(7, 12). Therefore, their prognostic utility in this setting may be limited. Identifying patients who are unlikely to achieve favorable long-term outcomes with apalutamide plus ADT alone is of critical clinical importance. Such patients may benefit from treatment intensification strategies, including combination approaches incorporating chemotherapy or other systemic agents. Although several prognostic models have been proposed in mCSPC, most were developed in clinical trial populations or heterogeneous treatment settings, limiting their applicability to contemporary ARSI-treated cohorts (13, 14).

In the present study, we aimed to evaluate real-world clinical outcomes of first-line apalutamide in patients with mCSPC treated at multiple Japanese institutions and to develop a treatment-specific prognostic risk model to identify patients at increased risk of poor OS.

Materials and Methods

Study design and patient population

This retrospective multicenter cohort study was conducted by the HARPICS (Hirosaki–Asahikawa Androgen Receptor Pathway Inhibitor Comprehensive Study Group). Consecutive patients diagnosed with mCSPC who received apalutamide as first-line systemic therapy between March 2020 and July 2025 at Asahikawa Medical University, Hirosaki University, and Wakkanai City Hospital were included. This study was conducted in accordance with the STROBE guidelines for observational studies.

Eligible patients met the following criteria: (1) histologically confirmed adenocarcinoma of the prostate; (2) radiologically confirmed metastatic disease at treatment initiation; (3) initiation of apalutamide in combination with ADT as first-line systemic therapy; and (4) availability of baseline clinicopathological and laboratory data. Patients who had received prior systemic therapy for metastatic disease, except for ADT initiated within 3 months before apalutamide, were excluded.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Asahikawa Medical University (approval number: C2542) and the corresponding ethics committees of participating institutions. Owing to the retrospective nature of the study, the requirement for written informed consent was waived by the ethics committees, and an opt-out approach was applied in accordance with institutional regulations.

Data collection and variables

Clinical and pathological data were extracted from institutional medical records. Baseline variables included age at treatment initiation, serum PSA level, Gleason score at diagnosis, extent of disease (EOD) grade based on bone scintigraphy, lactate dehydrogenase (LDH) level, and presence of visceral metastases.

Primary Gleason pattern 5 was defined according to the International Society of Urological Pathology grading system. EOD grade ≥ 2 was defined as moderate to extensive skeletal involvement according to the Soloway classification. Elevated LDH was defined as ≥ 216 U/L, corresponding to the optimal cutoff derived from receiver operating characteristic curve analysis for OS status.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Missing data were handled using complete-case analysis.

Treatment

All patients received apalutamide at the standard approved dose (240 mg orally once daily) in combination with continuous ADT, including gonadotropin-releasing hormone agonists or antagonists, or prior bilateral orchiectomy. Dose modifications were performed at the discretion of the treating physicians based on toxicity and clinical judgment.

Study endpoints

The primary endpoint was OS, defined as the time from initiation of apalutamide therapy to death from any cause. Patients alive at the last follow-up were censored.

Secondary endpoints included PSA response and safety outcomes. PSA response was defined as the maximum decline from baseline during treatment; a deep response as a PSA level < 0.2 ng/mL; and a major biochemical response as a ≥ 90% decline.

An exploratory objective was to identify prognostic factors associated with OS and to develop a treatment-specific risk stratification model.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

OS was estimated using the Kaplan–Meier method and compared using the log-rank test. The median follow-up time was calculated using the reverse Kaplan–Meier method.

Cox proportional hazards regression models were used to evaluate associations between clinical variables and OS. Given the limited number of death events (n = 33), the number of variables included in the multivariable model was restricted to avoid model overfitting. Based on clinical relevance and prior evidence, three variables (primary Gleason pattern 5, EOD grade, and LDH) were pre-specified for inclusion in the multivariable analysis. Other variables identified in univariable analysis, including PSA, were not included in the multivariable model to maintain an appropriate events-per-variable ratio and model stability. The proportional hazards assumption was assessed using Schoenfeld residuals. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

A prognostic risk model was constructed based on independent predictors identified in the multivariable analysis. Patients were stratified according to the number of risk factors (0–1 vs. ≥2). The discriminatory ability of the model was evaluated using Harrell's concordance index (c-index). The performance of the proposed model was compared with that of LATITUDE and CHAARTED risk classifications within the same cohort.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using EZR version 1.67 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patient characteristics

A total of 208 patients with mCSPC who received first-line apalutamide were included. The median age at treatment initiation was 72 years (IQR, 66–76), and the median baseline PSA level was 129 ng/mL (IQR, 38–524).

Primary Gleason pattern 5 disease was present in 61 patients (29.3%), and EOD grade ≥ 2 was observed in 101 patients (50.2%). Visceral metastases were identified in 31 patients (14.9%). The median follow-up duration was 24 months (IQR, 14–38), with 33 death events recorded during the study period. Detailed baseline characteristics are summarized in Table 1.

Treatment outcomes

During treatment, a deep PSA response (< 0.2 ng/mL) was achieved in 143 patients (68.8%), and a ≥ 90% decline in PSA was observed in 185 patients (88.9%).

Dose reduction was required in 33 patients (15.9%), and treatment discontinuation due to adverse events occurred in 50 patients (24.0%). The median time to PSA nadir was 6 months (IQR, 3–13). Detailed treatment exposure and biochemical responses are shown in Table 2.

Safety profiles

Grade ≥ 3 adverse events occurred in 36 patients (17.3%). The most frequently observed adverse event of any grade was rash (49.0%), followed by fatigue (10.0%) and liver dysfunction (3.4%). No unexpected safety signals were observed. A detailed summary of adverse events is provided in Table 3.

Survival outcomes

At a median follow-up of 24 months, the median OS was not reached. The estimated 24-month OS rate was 88.5% (95% CI, 0.82–0.93). Kaplan–Meier curves are shown in Fig. 1.

Univariable and multivariable analyses

In univariable Cox regression analysis, primary Gleason pattern 5, EOD grade ≥ 2, elevated LDH, ALP, and PSA were associated with worse OS (Table 4).

Multivariable analysis identified primary Gleason pattern 5 (HR 4.32, 95% CI 1.85–10.13; P < 0.001), EOD grade ≥ 2 (HR 3.89, 95% CI 1.35–11.17; P = 0.01), and LDH ≥ 216 U/L (HR 3.95, 95% CI 1.68–9.28; P =

0.002) as independent predictors of poor OS. Although PSA and ALP were significant in univariable analysis, they were not included in the multivariable model as pre-specified in the Methods section. Inclusion of additional variables would have violated the recommended events-per-variable ratio. In addition, PSA and ALP may reflect tumor burden overlapping with EOD grade and LDH.

Risk stratification models

Based on these variables, a prognostic risk model was constructed. Patients were stratified into low-risk (0–1 factors) and high-risk (≥ 2 factors) groups. Patients in the high-risk group exhibited significantly worse OS compared with those in the low-risk group (HR 6.83, 95% CI 2.73–17.1; P < 0.001) (Fig. 2).

Model performance

The HARPICS model demonstrated a concordance index (c-index) of 0.762, indicating good discriminative ability. In comparison, the LATITUDE and CHAARTED risk classifications showed lower c-indices (0.593 and 0.615, respectively) within the same cohort (Table 5).

Discussion

Our multicenter real-world study demonstrated that first-line apalutamide plus ADT achieved favorable biochemical responses and acceptable tolerability in Japanese patients with mCSPC. These findings are broadly consistent with the efficacy observed in the TITAN trial (6) and its Japanese subgroup analysis (15), as well as with more recent real-world studies including OASIS (9), OASIS Japan (10), and the Chu-shikoku Japan Urological Consortium analysis (16), all of which support the activity of apalutamide in real-clinical practice. However, beyond confirming effectiveness, our study identified three independent predictors of poor OS, which are primary Gleason pattern 5, EOD grade ≥ 2, and elevated LDH, and integrated them into a treatment-specific prognostic model with better discrimination than the conventional LATITUDE (7) and CHAARTED classifications (12). This approach may reduce biological and therapeutic heterogeneity by focusing on a single AR-targeted agent, thereby improving the interpretability of prognostic factors.

A key strength of the present study is the therapeutic homogeneity of the cohort. Previous real-world studies have largely focused on treatment effectiveness, PSA response, or progression outcomes, rather than developing an OS-based prognostic model in a clinically homogeneous first-line apalutamide cohort (10, 16). In contrast, our cohort consisted exclusively of patients receiving first-line apalutamide without contamination from upfront abiraterone exposure. This distinction is clinically meaningful because apalutamide directly antagonizes the androgen receptor (AR), whereas abiraterone inhibits androgen biosynthesis via CYP17 blockade (17). Given these mechanistic differences, prognostic models derived from mixed-mechanism cohorts may not fully capture outcome heterogeneity in patients treated with a pure androgen receptor antagonist strategy. Moreover, emerging evidence suggests potential cross-resistance and differential treatment responses among AR-targeted agents, further supporting the need for treatment-specific prognostic modeling (18). To our knowledge, this is one of the first studies to

develop an OS–based prognostic model in a clinically homogeneous first-line apalutamide-treated mCSPC population.

The importance of a treatment-specific approach is underscored by the limitations of conventional classifications. The LATITUDE (7) and CHAARTED (12) frameworks were developed in earlier treatment eras centered on abiraterone and docetaxel intensification strategies, respectively, and were not specifically designed for apalutamide-treated populations. In our cohort, these classifications showed inferior discriminative performance compared with the HARPICS model, suggesting that treatment-specific risk stratification may provide more accurate prognostic information in the modern AR-targeted therapy era. In addition, differences in pharmacological mechanisms and treatment sequencing among AR-targeted agents may further contribute to outcome heterogeneity (19). While abiraterone suppresses androgen biosynthesis through CYP17 inhibition, apalutamide directly inhibits AR signaling at the receptor level (20). These mechanistic differences may influence tumor adaptation, resistance patterns, and clinical outcomes. Recent studies have also suggested that sequential use of AR-targeted agents may lead to cross-resistance, potentially limiting treatment efficacy (21). Therefore, prognostic models derived from mixed ARPI populations may not be directly applicable to patients treated with a single-agent ARSI strategy, further supporting the clinical relevance of a treatment-specific model.

Primary Gleason pattern 5 emerged as the strongest independent predictor of mortality. This is biologically plausible because poorly differentiated tumors exhibit increased proliferative capacity, genomic instability, and reduced dependence on AR signaling pathways (22, 23). Similarly, EOD grade ≥ 2 was independently associated with poor survival. Extensive skeletal involvement may also indicate a permissive bone microenvironment that promotes tumor progression and therapeutic resistance, as previously described in prostate cancer bone metastasis biology (24). Thus, bone metastatic burden should be interpreted not only as a quantitative measure of disease extent but also as a marker of biologically aggressive tumor–microenvironment interaction. The interaction between prostate cancer cells and the bone microenvironment has been shown to play a critical role in disease progression and therapeutic resistance (25). Elevated LDH also independently predicted poor OS. Previous meta-analytic evidence has demonstrated that elevated LDH is associated with adverse outcomes in metastatic prostate cancer (26). In addition to reflecting tumor burden, LDH may capture aggressive tumor metabolism characterized by enhanced glycolysis and lactate production. This metabolic reprogramming is a hallmark of aggressive tumor biology and has been linked to immunosuppressive tumor microenvironments and treatment resistance (27, 28). However, these biological interpretations should be considered hypothesis-generating and require validation in translational studies.

An additional clinically relevant observation is the dissociation between deep PSA response and long-term outcomes. Although PSA responses were frequent, patients with adverse baseline characteristics still experienced poor survival, suggesting that early biochemical response alone does not fully capture underlying disease aggressiveness (29). While PSA decline has been associated with survival outcomes in mCSPC, its role as a surrogate endpoint remains limited, particularly in ARSI-treated populations (11). These findings underscore the importance of baseline risk stratification even among patients achieving

deep PSA responses. In this study, PSA was not included in the multivariable model due to the limited number of events and the need to preserve model stability; therefore, its independent prognostic value should be interpreted with caution.

The clinical implication of our model is straightforward. Patients with 0–1 adverse factors showed favorable survival and appear to be appropriate candidates for standard first-line apalutamide plus ADT. In contrast, those with 2–3 adverse factors had substantially worse outcomes despite treatment, indicating that this subgroup may warrant closer monitoring, earlier treatment intensification, or prioritization for clinical trials. Rather than replacing established disease-volume classifications, the HARPICS model may complement them by providing a treatment-specific estimate of prognosis in patients selected for apalutamide.

Several limitations should be acknowledged. First, the retrospective design of this study introduces potential risks of selection bias and unmeasured confounding. Although the number of variables was restricted, the relatively small number of events may still limit the robustness of the model. Second, although this was a multicenter cohort, the number of death events was relatively limited in relation to the number of candidate predictors. This may affect the stability of the multivariable model and increase the risk of overfitting. Third, internal validation procedures, such as bootstrapping, were not performed, and model calibration was not formally assessed. Therefore, the possibility of optimism in model performance and limited accuracy in absolute risk estimation cannot be excluded. Fourth, the LDH cutoff was derived from the same dataset using a data-driven approach, which may have further contributed to model optimism. Fifth, post-progression treatment strategies were not standardized and may have influenced OS outcomes. Sixth, molecular and genomic data were not available, preventing integration of biological markers that may improve prognostic accuracy. Finally, all patients were Japanese, and therefore the generalizability of the findings to other populations remains uncertain. Despite these limitations, the strength of this study lies in the therapeutic homogeneity of the cohort, which enabled evaluation of prognosis in a clinically consistent first-line apalutamide-treated population. Future studies with external validation and integration of molecular data are warranted.

Conclusions

First-line apalutamide demonstrated favorable real-world activity in Japanese patients with mCSPC, although outcomes remained heterogeneous. We developed a simple treatment-specific prognostic model based on primary Gleason pattern 5, EOD grade ≥ 2, and elevated LDH that outperformed LATITUDE and CHAARTED within this cohort. To our knowledge, this is one of the first studies to develop an OS–based prognostic model derived from a clinically homogeneous cohort treated exclusively with first-line apalutamide, without contamination from abiraterone-based therapy. External validation is warranted.

Declarations

Funding This study was partially supported by the Grants-in-Aid for Scientific Research, Japan (Grant No. 24K12502).

Conflict of Interest

The other authors have no conflicts of interest.

Ethics Approval

This study was approved by the Institutional Review Board of Asahikawa Medical University (Approval No. C2542) and was conducted in accordance with the Declaration of Helsinki.

Consent to Participate

The requirement for written informed consent was waived because of the retrospective design, and an opt-out approach was applied.

Consent for Publication

All authors approved for the manuscript to be published.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

Author Contributions

Shin Kobayashi: Data acquisition and analysis and manuscript drafting. Takuma Narita: Data acquisition and analysis. Kotona Miyauchi: Data acquisition and analysis and manuscript drafting. Shun Morishita: Data acquisition. Naoki Fujita: Data acquisition. Daiki Kikuchi: Data acquisition. Noriyuki Abe: Data acquisition. Miyu Ohtani: Data acquisition. Naoki Wada: Data acquisition. Shingo Hatakeyama: Data acquisition, analysis, and main author for manuscript revision. Kazuyuki Numakura: Study planning, manuscript drafting, data acquisition, analysis, and main author for manuscript revision.

Acknowledgments

We are thankful to Fuyumi Onodera and Yuki Imaie for their efforts in obtaining patient data.

References

1. Sung, H. et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **71** (3), 209–249 (2021).
2. Foundation for Promotion of Cancer Research. Cancer Statistics in Japan 2022. (2022).

3. Siegel, R. L., Miller, K. D., Wagle, N. S. & Jemal, A. Cancer statistics, 2023. *CA Cancer J. Clin.* **73** (1), 17–48 (2023).
4. Smith, M. R. et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl. J. Med.* **378** (15), 1408–1418 (2018).
5. Chi, K. N. et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. *N Engl. J. Med.* **381** (1), 13–24 (2019).
6. Chi, K. N. et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. *J. Clin. Oncol.* **39** (20), 2294–2303 (2021).
7. Fizazi, K. et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol.* **20** (5), 686–700 (2019).
8. Davis, I. D. et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl. J. Med.* **381** (2), 121–131 (2019).
9. Maughan, B. L. et al. Survival outcomes of apalutamide as a starting treatment: impact in real-world patients with metastatic hormone sensitive prostate cancer (OASIS). *Prostate Cancer Prostatic Dis.* **28** (4), 865–873 (2025).
10. Shiota, M. et al. The impact of androgen receptor pathway inhibitors as starting treatment in metastatic castration-sensitive prostate cancer on patient outcomes (OASIS Japan). *Sci. Rep.* **15** (1), 13598 (2025).
11. Yamada, Y. et al. Characterization of PSA dynamics and oncological outcomes in patients with metastatic hormone-sensitive prostate cancer treated with androgen receptor signaling inhibitors. *Int. J. Clin. Oncol.* **30** (3), 539–550 (2025).
12. Kyriakopoulos, C. E. et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. *J. Clin. Oncol.* **36** (11), 1080–1087 (2018).
13. Glass, T. R., Tangen, C. M., Crawford, E. D. & Thompson, I. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. *J. Urol.* **169** (1), 164–169 (2003).
14. Gravis, G. et al. Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies. *Eur. Urol.* **73** (6), 847–855 (2018).
15. Uemura, H. et al. Apalutamide for metastatic, castration-sensitive prostate cancer in the Japanese population: A subgroup analysis of the randomized, double-blind, placebo-controlled phase 3 TITAN study. *Int. J. Urol.* **28** (3), 280–287 (2021).
16. Tohi, Y. et al. Real-world prostate-specific antigen response and progression to castration-resistant prostate cancer among men with metastatic castration-sensitive prostate cancer treated with apalutamide: a multi-institutional study in the Chu-shikoku Japan Urological Consortium. *Jpn J. Clin. Oncol.* **54** (2), 167–174 (2024).

17. de Bono, J. S. et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl. J. Med.* **364** (21), 1995–2005 (2011).
18. Miyake, H. et al. Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer. *Clin. Genitourin. Cancer*. **15** (4), e591–e7 (2017).
19. Watson, P. A., Arora, V. K. & Sawyers, C. L. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat. Rev. Cancer*. **15** (12), 701–711 (2015).
20. Crawford, E. D. et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. *Prostate Cancer Prostatic Dis.* **22** (1), 24–38 (2019).
21. Buck, S. A. J., Koolen, S. L. W., Mathijssen, R. H. J., de Wit, R. & van Soest, R. J. Cross-resistance and drug sequence in prostate cancer. *Drug Resist. Updat*. **56**, 100761 (2021).
22. Bluemn, E. G. et al. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. *Cancer Cell.* **32** (4), 474–489 (2017). e6.
23. Jamroze, A., Chatta, G. & Tang, D. G. Androgen receptor (AR) heterogeneity in prostate cancer and therapy resistance. *Cancer Lett.* **518**, 1–9 (2021).
24. Roodman, G. D. Mechanisms of bone metastasis. *N Engl. J. Med.* **350** (16), 1655–1664 (2004).
25. Logothetis, C. J. & Lin, S. H. Osteoblasts in prostate cancer metastasis to bone. *Nat. Rev. Cancer*. **5** (1), 21–28 (2005).
26. Mori, K. et al. Prognostic Value of Lactate Dehydrogenase in Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. *Clin. Genitourin. Cancer*. **17** (6), 409–418 (2019).
27. Wang, Z. H., Peng, W. B., Zhang, P., Yang, X. P. & Zhou, Q. Lactate in the tumour microenvironment: From immune modulation to therapy. *EBioMedicine* **73**, 103627 (2021).
28. Liberti, M. V. & Locasale, J. W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem. Sci.* **41** (3), 211–218 (2016).
29. Armstrong, A. J. et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *J. Clin. Oncol.* **37** (32), 2974–2986 (2019).

Tables

Tables are available in the Supplementary Files section.

Figures

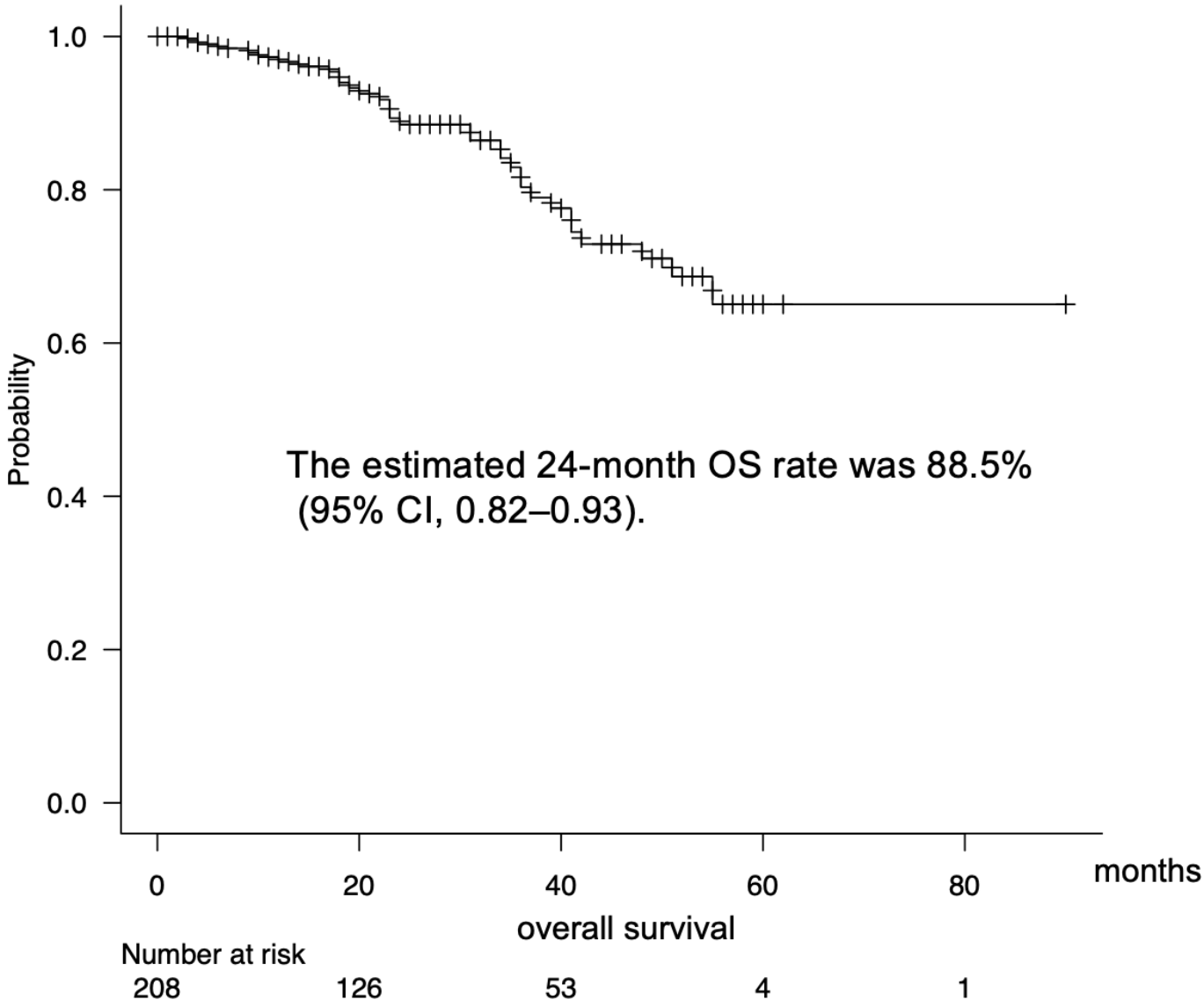


Figure 1

Kaplan–Meier curve of overall survival in patients with metastatic castration-sensitive prostate cancer treated with first-line apalutamide. The estimated 24-month overall survival rate was 88.5% (95% CI 0.82–0.93).

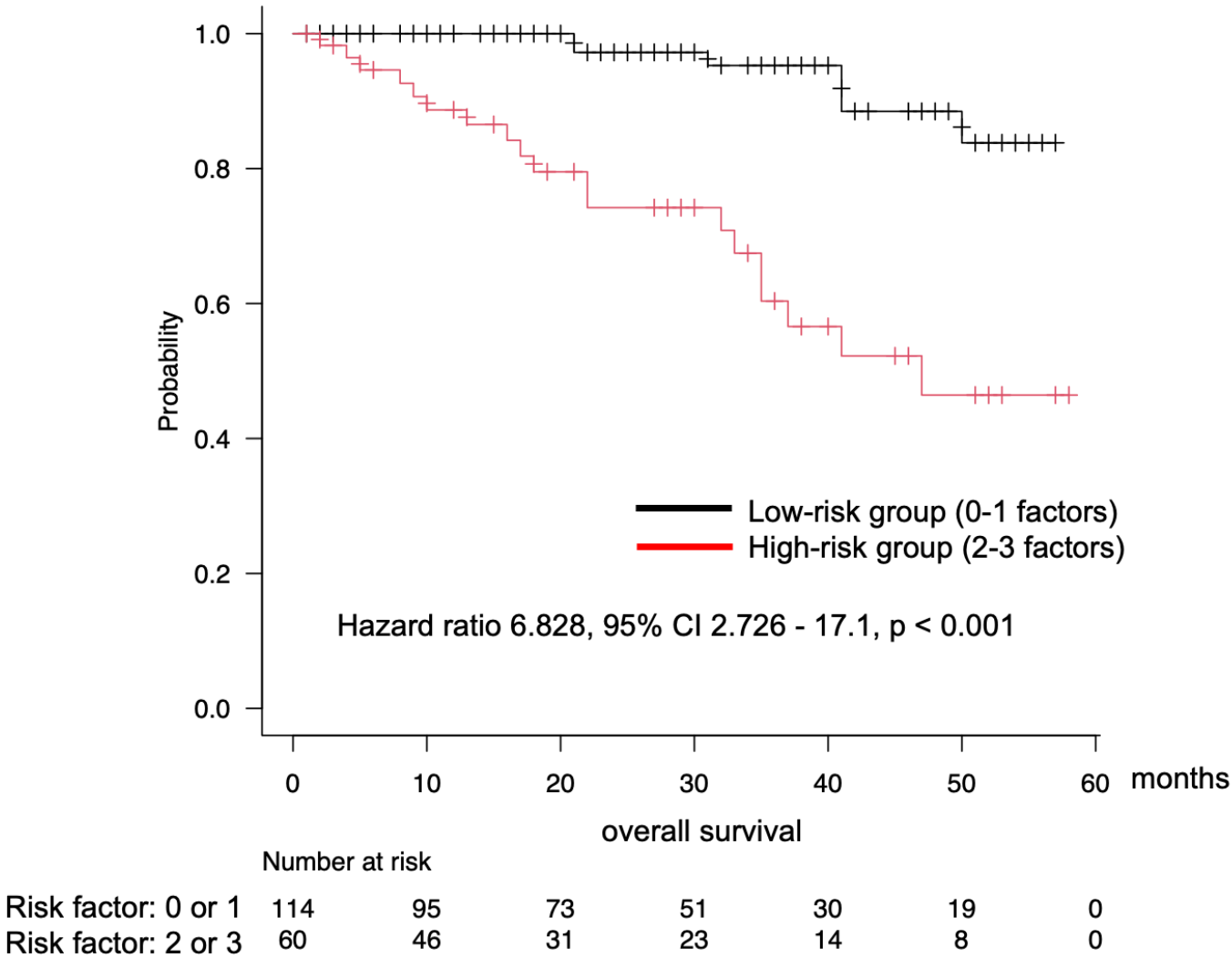


Figure 2

Kaplan–Meier curves of overall survival stratified by risk group in patients with metastatic castration-sensitive prostate cancer treated with apalutamide.

Patients were stratified according to the number of risk factors (0–1 vs. ≥2 factors). Overall survival was significantly worse in patients with 2–3 risk factors compared with those with 0–1 risk factor (hazard ratio 6.828, 95% confidence interval 2.726–17.1; P < 0.001).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx