

Four factors recorded at diagnosis identify men with low-volume de novo metastatic hormone-sensitive prostate cancer whose survival is worse than high-volume disease

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Abstract

Treatment intensification in metastatic castration-sensitive prostate cancer is guided largely by CHAARTED disease volume, yet low-volume disease is not homogeneous and some men die early. We analysed 16,530 men with de novo metastatic prostate cancer diagnosed in 2018–2023 in SEER Research Plus, restricted to biopsy-confirmed adenocarcinoma with a recorded PSA. Of every variable recorded at diagnosis, four separated clearly from the rest in a multivariable Cox model: age 80 years or over, PSA 100 ng/mL or above, liver or brain metastasis, and Gleason score 9 or above. Overall survival fell steadily with the number of factors present, by 1.67 (95% CI 1.62–1.73) per additional factor. Among 14,904 men without visceral metastasis, a group containing every low-volume man, those with two factors still did better than men with visceral metastasis, who are high volume whatever the bone count (hazard ratio 0.86, 0.79–0.94), whereas men with all three did worse (1.40, 1.24–1.59; median survival 25.7 versus 33.9 months). These 758 men were 5.1% of the non-visceral group, and 5.7% received chemotherapy against 32.0% of men with visceral metastasis. Four factors recorded at diagnosis therefore identify low-volume men whose survival is worse than high-volume disease, and who are least often treated.

Clinical trial number: not applicable.

INTRODUCTION

Treatment of metastatic castration-sensitive prostate cancer (mCSPC) has changed substantially over the past decade. Adding docetaxel to androgen deprivation therapy (ADT) prolonged survival (1), as did adding an androgen receptor signalling inhibitor (ARSI) (2–6), and triplet therapy with ADT, docetaxel and an ARSI has since shown further benefit (7, 8). As the number of options has grown, however, it remains unsettled which treatment should be given upfront to an individual patient.

The benefit of triplet therapy is not uniform across disease burden. In the volume-stratified analysis of ARASENS, the survival benefit was clear in men with high-volume disease but limited in men with low-volume disease (9). Network meta-analyses stratified by volume have reached the same conclusion (10, 11). Guidelines reflect this distinction, and the choice between doublet and triplet therapy in low-volume disease is left to individual judgement (NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer, Version 5.2026).

Low-volume disease is not, however, a homogeneous group. Some men classified as low volume die early. Recent work has refined the CHAARTED classification using biochemical and pathological factors and has shown that men classified as poor risk have a poor outcome even when their disease is low volume (12–14). Whether triplet therapy benefits these men has not been tested, but treatment is often intensified when the prognosis is judged to be poor. Identifying adverse prognostic factors within low-volume disease, and not only across volume categories, is therefore clinically important.

We analysed predictors of early death in de novo mCSPC using the SEER database, with particular attention to risk factors among men with low-volume disease.

RESULTS

Cohort

Of 35,400 men recorded with de novo metastatic prostate cancer between 2018 and 2023, 16,530 were analysed after exclusion of duplicate records, men with a preceding primary malignancy, autopsy- or death-certificate-only cases, non-adenocarcinoma histology, men without a recorded clinical Gleason score, and men without a recorded diagnostic PSA (Fig. 1). The 10,403 men excluded at the last two steps were older than those analysed (31.2% versus 17.3% aged 80 years or over), more often had visceral metastasis (17.0% versus 9.8%), and had about half the median overall survival (26.1 versus 50.4 months). The analytic cohort is therefore a relatively favourable one. Median follow-up by the reverse Kaplan–Meier method was 29.7 months. There were 5,130 deaths, of which 3,981 were attributed to prostate cancer, and median overall survival was 50.4 months. By 24 months 25.0% of men had died: 19.4% of prostate cancer and 5.6% of other causes. At that point 61.2% of all deaths had already occurred and 43.6% of the cohort remained under observation, so 24 months lies inside the median follow-up and is supported by observed rather than extrapolated data (Supplementary Figure S1).

Factors associated with early death

We first contrasted men who died within 24 months with those who survived beyond 60 months to generate candidate variables. Every variable recorded at diagnosis was then entered into a single multivariable model and ranked by the likelihood-ratio χ^2 lost when it was removed. Four variables separated clearly from the remainder: age, Gleason score, site of metastasis and PSA. Site of metastasis was examined in seven categories; liver (HR 3.79) and brain (HR 3.84) were separated by a clear step from lung (2.15) and bone (1.81), so the factor was defined as liver or brain metastasis. The four factors were age 80 years or over, diagnostic PSA of 100 ng/mL or above, liver or brain metastasis, and clinical Gleason score of 9 or above, present in 17.3%, 41.9%, 3.4% and 60.6% of men respectively. Each was independently associated with overall survival (adjusted HR 1.89, 1.48, 2.28 and 1.61; all $P < 0.001$; Fig. 2 and Table 2). The four factors were close to independent of one another, so they were summed without weighting to give a score of 0 to 4. The score was 0 in 3,349 men, 1 in 7,067, 2 in 5,067 and 3 or more in 1,047 (Table 1).

Table 1
Characteristics of the cohort by number of risk factors

Characteristic	All (n = 16,530)	0 factors (n = 3,349)	1 factor (n = 7,067)	2 factors (n = 5,067)	≥ 3 factors (n = 1,047)
Age at diagnosis					
< 60	13.6	14.5	14.9	13.3	2.9
60–69	34.6	42.7	37.5	30.9	7.2
70–79	34.5	42.8	39.8	27.9	4.9
≥ 80	17.3	0.0	7.8	27.9	85.1
Race and ethnicity					
White	73.9	73.5	75.4	71.7	76.1
Black	16.9	15.9	16.0	19.6	13.2
Asian or Pacific Islander	7.3	8.7	6.7	6.9	9.3
Other or unknown	1.8	1.9	2.0	1.7	1.4
Marital status					
Married	61.8	64.5	63.2	58.4	60.1
Not married	34.1	30.9	32.9	37.6	35.7
Unknown	4.1	4.6	3.9	4.0	4.2
PSA at diagnosis (ng/mL)					
< 20	24.7	46.4	29.4	8.7	1.1
20–99	33.4	53.6	42.3	14.2	1.0
100–999	32.6	0.0	21.6	59.9	79.8
≥ 1,000	9.3	0.0	6.7	17.1	18.1
Clinical Gleason score					
6–7	14.0	40.0	12.0	2.6	0.3
8	25.3	60.0	25.3	7.5	0.8
9	50.6	0.0	52.9	74.9	80.2
10	10.0	0.0	9.8	15.0	18.7
Site of metastasis					
Values are percentages within each column.					

Characteristic	All (n = 16,530)	0 factors (n = 3,349)	1 factor (n = 7,067)	2 factors (n = 5,067)	≥ 3 factors (n = 1,047)
Age at diagnosis					
Distant lymph node only	9.2	13.8	10.3	6.1	3.3
Bone only	78.5	76.6	79.7	80.4	67.3
Lung	6.4	6.2	6.3	6.8	6.0
Liver or brain	3.4	0.0	1.2	5.1	21.6
Other or unknown	2.4	3.4	2.5	1.7	1.7
Recorded treatment					
Chemotherapy	18.7	11.2	20.5	22.7	11.7
Radiotherapy	30.2	42.3	32.5	22.0	15.9
Values are percentages within each column.					

Table 2
Multivariable Cox model for overall survival Model A – the four factors entered separately

Variable	n	Deaths	Adjusted HR (95% CI)
Age ≥ 80 years	2,858	1,253	1.89 (1.77–2.02)
PSA ≥ 100 ng/mL	6,930	2,646	1.48 (1.40–1.57)
Liver or brain metastasis	569	313	2.28 (2.04–2.56)
Gleason score ≥ 9	10,023	3,617	1.61 (1.52–1.71)
Race			
White	12,217	3,867	1.00 (reference)
Black	2,797	917	1.02 (0.94–1.10)
Asian or Pacific Islander	1,211	286	0.73 (0.64–0.82)
Other or unknown	305	60	0.79 (0.61–1.02)
Marital status			
Married	10,217	2,919	1.00 (reference)
Not married	5,640	1,983	1.30 (1.23–1.38)
Unknown	673	228	1.17 (1.02–1.34)
Year of diagnosis			
2018	2,236	1,349	1.00 (reference)
2019	2,374	1,204	0.94 (0.87–1.02)
2020	2,387	1,020	0.96 (0.88–1.05)
2021	2,923	925	0.96 (0.88–1.05)
2022	3,143	512	0.91 (0.82–1.02)
2023	3,467	120	0.75 (0.61–0.91)
Model B – number of risk factors			

Survival by number of risk factors

Survival fell steadily as the number of factors rose (Fig. 3A). Median overall survival was not reached with no factors, and was 53.9, 36.7 and 25.2 months with one, two and three factors; three-year survival was 81.6%, 65.0%, 50.9% and 34.5% (log-rank $\chi^2 = 1,049.6$, $P < 0.0001$). Adjusted hazard ratios against men with no factors were 2.11, 3.27 and 5.38, or 1.67 (95% CI 1.62–1.73) per additional factor. Cancer-

specific survival gave the same pattern (2.34, 3.77 and 5.94; Supplementary Table S1). The same gradient was present in men who are CHAARTED high volume because visceral metastasis is present (Fig. 3B, log-rank $\chi^2 = 89.3$) and in men without visceral metastasis (Fig. 3C, $\chi^2 = 869.5$, both $P < 0.0001$). The latter panel contains every low-volume man in the cohort. The score therefore adds information within, and not merely across, the volume categories.

Men without visceral metastasis whose prognosis is worse than definite high volume

SEER does not record the number of bone lesions, so CHAARTED volume cannot be assigned in every man. We therefore took the 1,626 men with visceral metastasis, who are high volume whatever the bone count, as the reference and examined the remaining 14,904 men (90.2%) as the non-visceral group (Fig. 4). Within the non-visceral group, 21.1% had no factors, 43.9% had one, 30.0% had two and 5.1% had three. Adjusted hazard ratios against definite high volume were 0.27, 0.56 and 0.86 for men with none, one and two factors, all of them favourable. Men with all three factors, however, had a hazard ratio of 1.40 (95% CI 1.24–1.59, $P < 0.001$) and a median overall survival of 25.7 months against 33.9 months for definite high volume. Cancer-specific survival gave the same result (HR 1.28, 95% CI 1.11–1.47). These 758 men are 5.1% of the non-visceral group and 4.6% of the whole cohort. All of them were aged 80 years or over, because liver and brain metastasis are absent by definition and a score of three therefore requires the other three factors.

Use of chemotherapy

Among men younger than 80 years, recorded chemotherapy rose with the number of factors, from 11.2% to 21.9%, 29.4% and 41.0%. Among men aged 80 years or over it stayed between 4.0% and 6.5% whatever the score (Fig. 5A). Adjusted for age and year of diagnosis, the odds ratio for chemotherapy was 2.24, 3.37 and 4.76 for one, two and three or more factors, while the odds ratio for age 80 years or over was 0.13 (95% CI 0.11–0.16). In the 758 men without visceral metastasis and all three factors, that is the group shown to do worse than definite high volume, chemotherapy was recorded in 5.7%, against 32.0% in definite high volume (Fig. 5B).

Sensitivity analyses

The interaction between the number of factors and era of diagnosis was not significant, so the gradient was unchanged over the period in which androgen receptor pathway inhibitors came into general use ($P = 0.75$; Supplementary Figure S2). Bone metastasis, lung metastasis, distant lymph-node metastasis, the number of metastatic sites and regional node stage were each added to the final model separately. None changed the four hazard ratios by more than 8%, and adding all nine candidates together raised the C-index only from 0.628 to 0.667 (Supplementary Table S2 and Figure S3). With death from other causes treated as a competing event, the 24-month incidence of prostate cancer death rose from 6.8% with no

factors to 37.3% with three or more, a 5.5-fold increase, while other-cause death rose from 3.4% to 11.2%, a 3.3-fold increase; the gradient is therefore steeper for cancer death. Proportional hazards did not hold: the hazard ratio for three or more factors was 8.00 in the first year, 5.19 between 12 and 24 months and 4.05 thereafter, so the score separates men most sharply at the time when treatment intensification would be decided.

DISCUSSION

The number of four factors recorded at diagnosis — age 80 years or over, PSA 100 ng/mL or above, liver or brain metastasis, and Gleason score 9 or above — separated survival in de novo mCSPC in a stepwise manner, by 1.67 (95% CI 1.62–1.73) per additional factor. Among men without visceral metastasis, a group that contains every man with low-volume disease, those with two factors still did better than men who are high volume irrespective of bone count (HR 0.86, 0.79–0.94), whereas men with all three factors did worse (HR 1.40, 1.24–1.59; median 25.7 versus 33.9 months). These 758 men were 5.1% of the non-visceral group and 4.6% of the whole cohort, and chemotherapy was recorded in 5.7% of them against 32.0% of men with visceral metastasis.

What we have identified is a prognostic factor, not one that predicts benefit from triplet therapy. SEER records neither androgen deprivation nor androgen receptor signalling inhibitors, so the benefit of intensified treatment in these men cannot be examined here. A poor prognosis and a large benefit from added treatment are different things, and the present results cannot be used to choose treatment. Few factors predict which agent will work in castration-resistant disease other than BRCA and related alterations for PARP inhibition (15), and knowing at diagnosis which men are at risk of early death may be one element in planning the sequence of treatment (16).

Age contributed most among the four factors, but its interpretation requires care. For cancer-specific survival the hazard ratio for age 80 years or over was 1.70 (1.57–1.83), and with competing risks accounted for, the 24-month incidence of cancer death rose 5.5-fold from no factors to three or more against 3.3-fold for other-cause death, so the factor is unlikely to reflect competing mortality alone. At the same time chemotherapy rose with the number of factors from 11.2% to 41.0% in men younger than 80 years but stayed between 4.0% and 6.5% in older men (adjusted odds ratio 0.13, 0.11–0.16), and treatment intensification in this disease is known to be strongly determined by age (17). Docetaxel retains its efficacy in older men (18, 19), and geriatric assessment using tools such as the G8 is recommended in place of chronological age (20–22). Age here therefore carries two meanings at once: a worse prognosis and restricted access to treatment.

Attempts to refine the CHAARTED classification with biochemical and pathological factors, and so to identify poor-prognosis men within low-volume disease, have been reported recently (12–14), and a prognostic model has been derived from pooled docetaxel trials (23). The present study differs in two ways. Prognostic markers in advanced prostate cancer have commonly relied on laboratory values such as the neutrophil-to-lymphocyte ratio (24), whereas all four factors here come from the staging record

and require neither laboratory values nor performance status, so the count can be obtained from a registry or an electronic record alone.

This study has several limitations. First, SEER does not record the number of bone lesions, so CHAARTED low volume cannot be identified exactly. The non-visceral group contains every low-volume man but also men who are high volume on bone count, and the findings should be read as applying to a group that contains low-volume disease rather than to low-volume disease itself. Second, treatment is not recorded in detail. SEER records chemotherapy, radiotherapy and surgery but not androgen deprivation, androgen receptor signalling inhibitors, radium-223 or lutetium-177 PSMA, so which agent works better in men with these factors cannot be examined. The gradient was nonetheless unchanged between men diagnosed in 2018–2020 and in 2021–2023 ($P = 0.75$; Supplementary Figure S2), the period over which these inhibitors came into general use. Third, because treatment for the hormone-sensitive phase is not recorded, the cohort includes men who did not receive what is now standard care. Chemotherapy is also known to be under-recorded in SEER; the 10,403 men excluded had a worse prognosis than those analysed, so the cohort is a relatively favourable one; proportional hazards did not hold, so the hazard ratios are averages over follow-up; and the score was not validated externally.

The number of four factors recorded at diagnosis separated the risk of early death in de novo metastatic castration-sensitive prostate cancer. Men without visceral metastasis who had all three applicable factors had a worse survival than men who are high volume irrespective of bone count, yet chemotherapy reached only a sixth as many of them. The study does not predict benefit from treatment, but it shows that a group which current volume classification calls low risk contains men who may warrant consideration for intensified treatment.

MATERIALS & METHODS

Data source and study population

We used SEER Research Plus (17 registries, November 2025 submission) and identified 35,400 men diagnosed with prostate cancer with distant metastasis between 2018 and 2023. SEER is a population-based cancer registry programme that provides de-identified case-level data for a defined proportion of the United States population. We excluded, in order, 43 duplicate records in which adenocarcinoma and neuroendocrine carcinoma had been registered as two primaries, 4,311 men with a preceding primary malignancy, 16 men known only from autopsy or a death certificate, 4,097 men with non-adenocarcinoma histology (368 neuroendocrine or small-cell and 3,729 other), 9,182 men with no recorded clinical Gleason score, and 1,221 men with no recorded diagnostic PSA. The analytic cohort comprised 16,530 men (Fig. 1). SEER has no variable indicating that a biopsy was performed, so a recorded clinical Gleason score was used in its place.

Variables and definition of the risk factors

Candidate variables were generated by contrasting men who died within 24 months with men who survived beyond 60 months. Every variable recorded at diagnosis was then entered into a single multivariable Cox model and ranked by the likelihood-ratio χ^2 lost when it was removed. Four variables separated clearly from the remainder: age, Gleason score, site of metastasis and PSA. Thresholds were placed where the dose–response relation showed a step. For age the hazard ratio was 1.45 in the eighth decade and 2.19 at 80 years or over; for Gleason score it was 1.11 at 8, which did not differ from 6–7, and 1.54 at 9 and 2.39 at 10; for PSA it was 1.08 at 20–99 ng/mL, which did not differ from below 20, and 1.45 at 100–999 ng/mL. Site of metastasis was examined in seven categories, and liver (3.79) and brain (3.84) were separated from lung (2.15) and bone (1.81) by a clear step, so the factor was defined as liver or brain metastasis. The four factors were age 80 years or over, diagnostic PSA of 100 ng/mL or above, liver or brain metastasis, and clinical Gleason score of 9 or above. They were close to independent of one another and were therefore summed without weighting to give a score of 0 to 4.

CHAARTED disease volume

SEER does not record the number of bone lesions, so CHAARTED volume cannot be assigned in every man. Men with visceral metastasis are high volume irrespective of the bone count and were used as the reference group. The remaining men contain every low-volume man in the cohort, together with men who are high volume on bone count.

Outcomes

The primary outcome was overall survival and the secondary outcome was cancer-specific survival, defined by the SEER cause-specific death classification. Follow-up was estimated by the reverse Kaplan–Meier method.

Statistical analysis

Survival was estimated by the Kaplan–Meier method and compared by the log-rank test. Hazard ratios were estimated by Cox proportional hazards models with the Efron approximation for ties, adjusted for race, marital status and year of diagnosis. Proportional hazards were examined by splitting follow-up at 12 and 24 months with delayed entry and testing the interaction between the risk count and interval by likelihood ratio. Cumulative incidence accounting for death from other causes was estimated by the Aalen–Johansen method. Discrimination was assessed by Harrell’s C statistic with bootstrap correction for optimism. Prespecified sensitivity analyses examined the interaction with era of diagnosis and the effect of adding each candidate variable to the final model separately. Tests were two-sided and P values below 0.05 were considered significant. Analyses used Python 3.11.15 with pandas 3.0.2, numpy 2.4.4, statsmodels 0.14.6, scipy 1.17.1 and matplotlib 3.10.9. In accordance with the SEER Research Data Use Agreement, cells based on counts of one to four were suppressed.

Ethics and data use

This was a retrospective analysis of de-identified public registry data containing no information by which an individual could be identified, and institutional review board approval and informed consent were

waived. Data were obtained under a signed SEER Research Data Use Agreement. Reporting follows the RECORD statement.

Use of artificial intelligence

AI-assisted tools based on a large language model (Claude, Anthropic) were used for data processing, statistical analysis, preparation of figures and tables, and drafting parts of the manuscript in English. AI was not an author. All output was reviewed and verified by the authors, who take full responsibility for the accuracy of the analyses, their interpretation and the content of the manuscript.

Declarations

Ethics approval

Not applicable. This study is an analysis of a de-identified, publicly available dataset.

Consent to publish

Not applicable.

CONFLICTS OF INTEREST

We declare no conflicts of interests

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Author Contribution

T.K. conceived and designed the study, acquired the data, performed the statistical analysis, and prepared the figures and tables. A.H. and T.K. wrote the main manuscript text. M.Y., D.T., H.I., T.T. and K.U. contributed to the interpretation of the results. H.U., K.M. and J.T. supervised the study. All authors reviewed the manuscript.

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Data Availability

The data that support the findings of this study are publicly available from the surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (SEER Research Plus, 17 registries, November 2025 submission; <https://seer.cancer.gov/data/>). Access requires a signed SEER Research Data Use Agreement, and under the terms of that agreement the authors are not permitted to redistribute case-level data. Any investigator who completes the same agreement can obtain the identical dataset. The analysis code and the aggregate data underlying all figures and tables are available from the corresponding author on reasonable request.

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Figures

Figure 1. Cohort selection
De novo metastatic prostate cancer, SEER Research Plus, 2018–2023

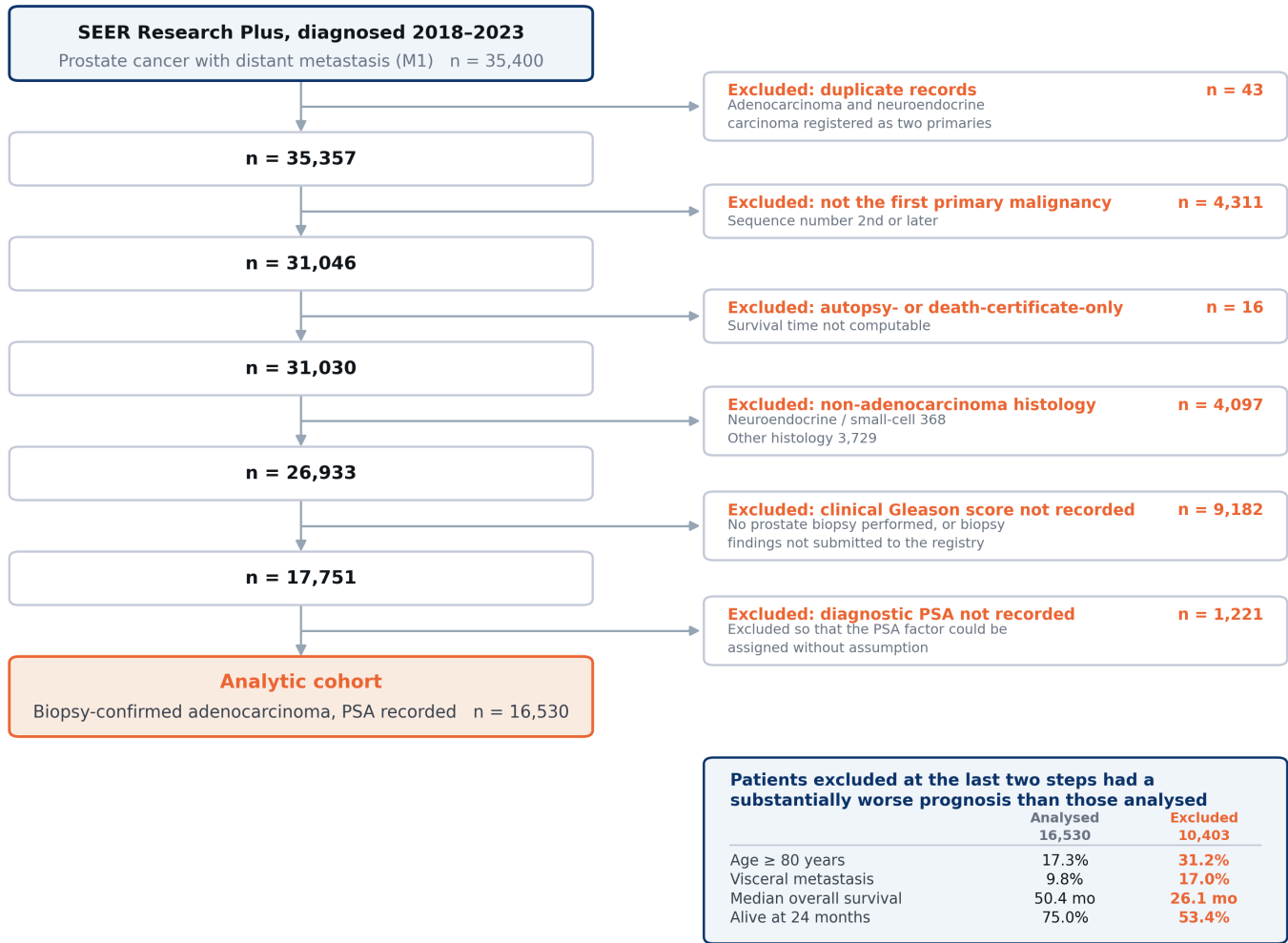


Figure 1

Selection of the analytic cohort. Men with de novo metastatic prostate cancer diagnosed in 2018–2023, SEER Research Plus. The lower right panel compares the 10,403 excluded men with the 16,530 analysed.

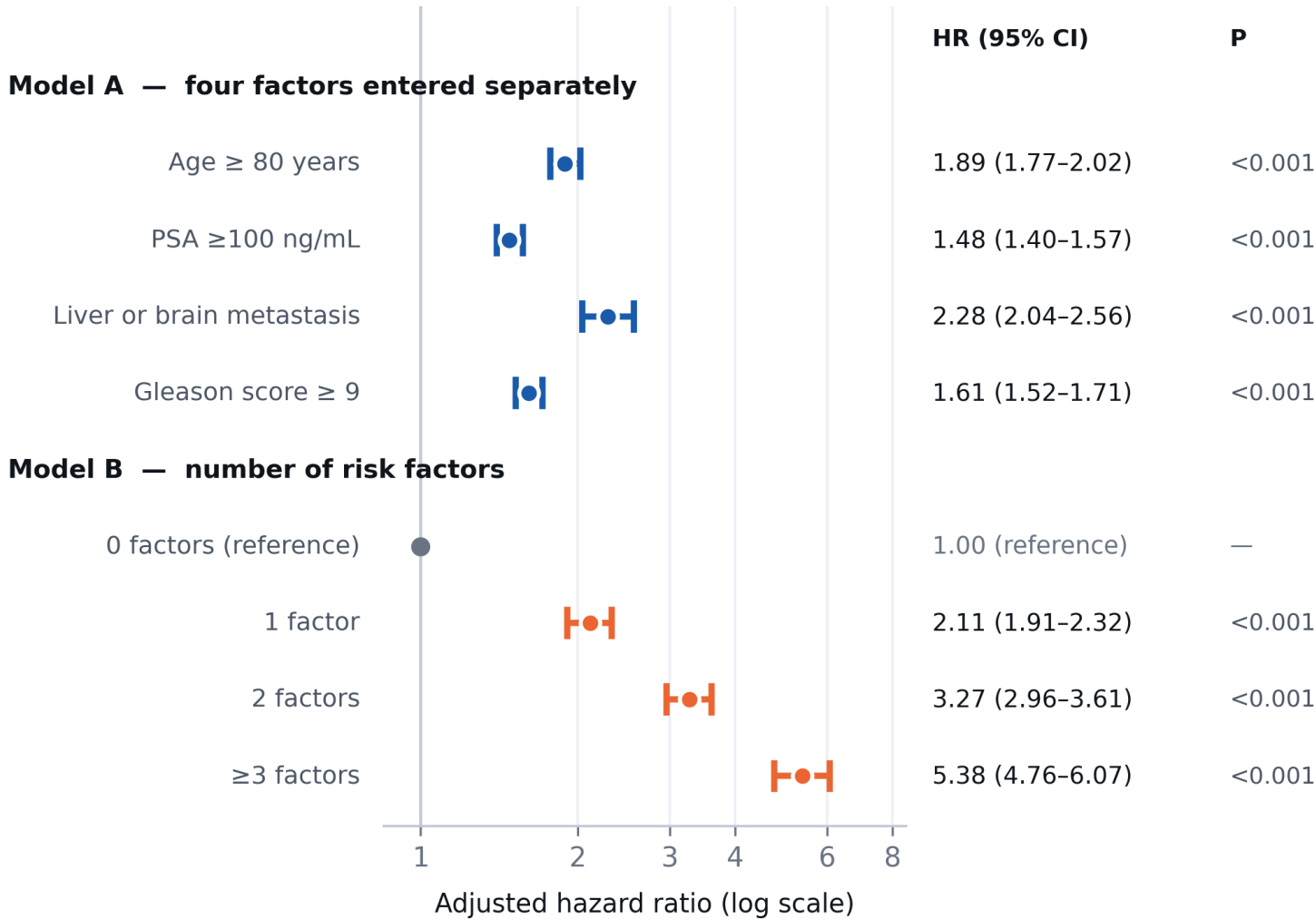


Figure 2

Adjusted hazard ratios for the four factors and for the number of factors. Adjusted for race, marital status and year of diagnosis. Overall survival.

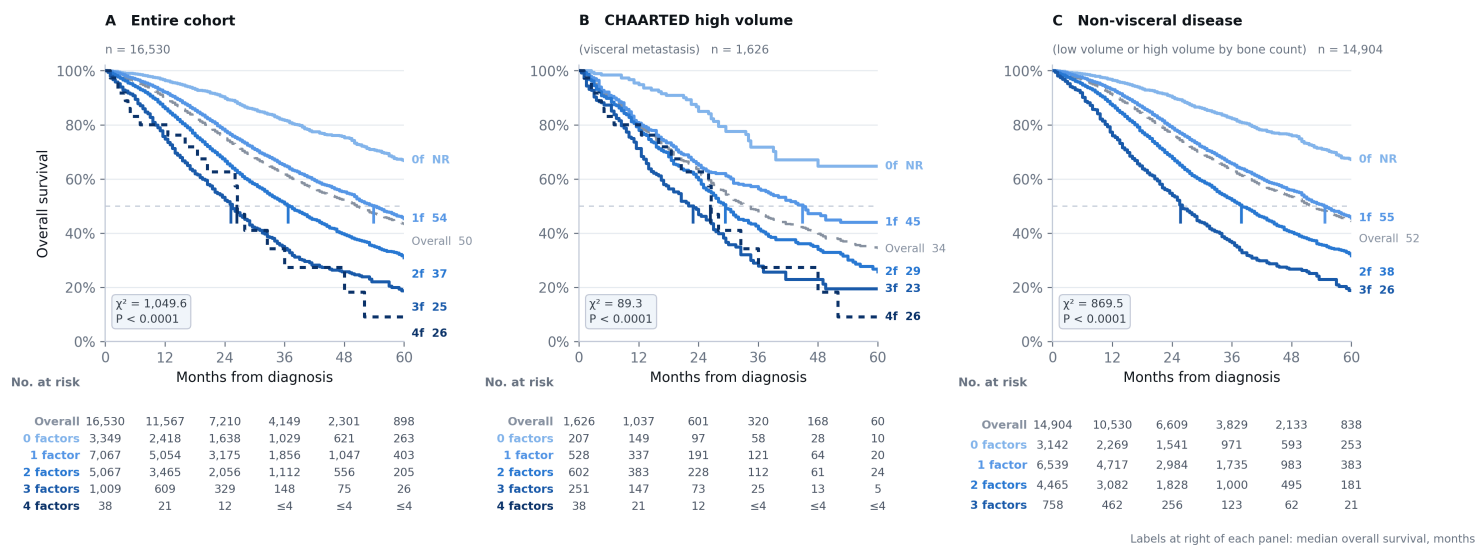


Figure 3

Overall survival by number of risk factors, in the whole cohort (A), in men who are CHARTED high volume because visceral metastasis is present (B), and in men without visceral metastasis (C). Panel C contains every low-volume man in the cohort, together with men who are high volume on bone lesion count, which SEER does not record. The four factors are age ≥ 80 years, PSA ≥ 100 ng/mL, liver or brain metastasis, and Gleason score ≥ 9 . Grey dashed line, whole cohort of each panel; dotted line, four-factor group. In panel C the maximum score is three, because liver or brain metastasis is absent by definition.

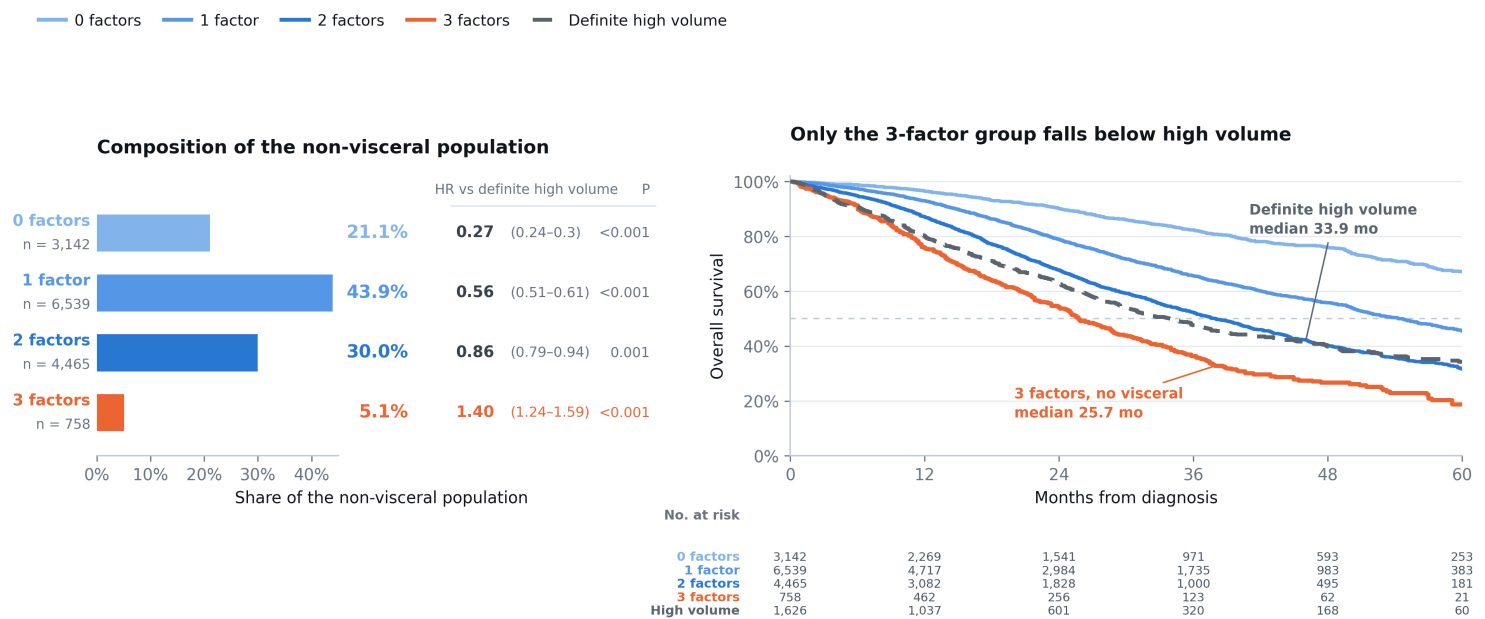


Figure 4

Men without visceral metastasis compared with men with visceral metastasis, who are high volume irrespective of bone lesion count. Left, composition of the non-visceral group and hazard ratios against definite high volume. Right, overall survival. Adjusted for race, marital status and year of diagnosis. In the non-visceral group the maximum score is three, because liver or brain metastasis is absent by definition.

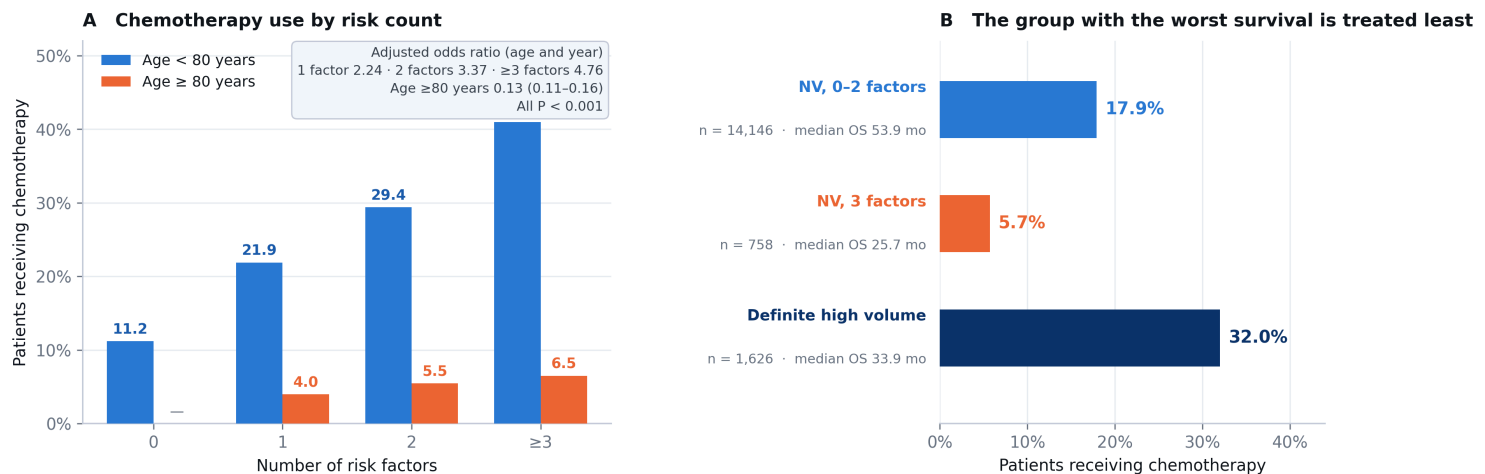


Figure 5

Recorded use of chemotherapy. (A) By number of risk factors and age group; odds ratios are adjusted for age and year of diagnosis. (B) The three groups of Figure 4. SEER records chemotherapy but not androgen deprivation or androgen receptor pathway inhibitors.

Supplementary Files

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