Determinants of Palliative Care Referral, Attendance, and Time-to-Referral After Immunotherapy Initiation in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

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Abstract

Introduction: Although an exciting advance in the treatment of head and neck squamous cell carcinoma (HNSCC), starting immunotherapy (IO) in recurrent HNSCC often marks a transition to non-curative care, underscoring the need for early palliative care (PC) referral to support advance care planning and optimize quality of life at life's end. Nonetheless, current referral practices fall short: not all who could benefit are referred, and referrals too often arrive too late to maximize impact. We evaluated factors associated with (1) receipt of a PC referral, (2) attendance at a PC visit among those referred, and (3) time from IO initiation to PC referral.

Methods: We identified patients with recurrent/metastatic HNSCC treated with IO at a single tertiary academic system (2018–2025). Demographic, clinical, and social variables were collected and summarized descriptively. For binary referral and attendance outcomes, univariable correlation analyses were conducted using Chi-square/Fisher's exact tests for categorical variables and Mann-Whitney U for continuous. Univariable linear regression was conducted for time-to-referral analysis, which was then modeled via a multivariable Cox regression. All analyses were conducted in R 4.4.1.

Results: After screening, 253 patients met eligibility criteria, and 129 (51%) were referred to PC. One-hundred eighteen (91.5%) of those referred attended a PC visit. Mean time-to-referral was 255 days after IO start (median: 83 days). On univariable analysis, age (p = 0.013, rank-biserial r [rrb] = 0.18) and local recurrence (p = 0.017, rrb = 0.15) were associated with likelihood of referral, while driving distance (p = 0.034 , rrb = 0.39) and driving time (p = 0.047, rrb = 0.36) were associated with lower probability of attending a visit if referred. On multivariable Cox regression, local recurrence (p = 0.0027, HR 2.02 [95% CI 1.39-2.92]) was associated with shorter time to referral, while older age was associated with longer time to referral (p = 0.012, HR 0.98 [95% CI 0.9618-0.9952).

Conclusions:
While over half of patients were indeed referred to PC, referral rates remain suboptimal among patients with recurrent/metastatic HNSCC receiving IO, with substantial delays from IO initiation to referral. Clinical factors such as local recurrence appear to prompt earlier referrals, while older patients may experience delays. Travel burden may reduce the likelihood of visit attendance. These findings highlight opportunities to optimize referral timing and delivery of PC in this population.

Introduction

	5-year survival (approx.)
HNSCC (overall)	50-70%[1,2]
Recurrent/metastatic HNSCC on IO	15%[3]

- Initiation of IO for recurrent/metastatic HNSCC often signals a transition to non-curative intent care
- Most patients will die within 5 years of IO initiation in this setting
- PC services are important in this population for:
  - Advance care planning
  - Symptom management and optimization of quality of life[4,5]
- Yet, research suggests that access to PC services is neither universal nor timely[6,7]
- Identifying factors that influence probability and timing of PC referral could inform targeted interventions

Objective: **Evaluate factors that influence the probability, attendance, and timing of PC referral.**

Methods

- Study cohort
  - Single tertiary academic center, 2018-2025
  - Inclusion: Recurrent/metastatic HNSCC initiating IO
  - Exclusion: <30 days follow-up after IO start, established with PC prior to recurrence/metastasis diagnosis
  - Outcomes:
    - Referral: documentation of PC referral in EHR
    - Attendance: ≥1 completed PC visit among those referred
    - Time-to-referral: days from IO start to first PC referral (pre-IO referrals coded as day 0); censored at last follow-up or death if unreferred
- Statistical analysis
  - Referral, attendance
    - Chi-square/Fisher's exact for categorical variables, Mann-Whitney U for continuous variables
  - Time-to-referral
    - Univariable linear regression
    - Multivariable Cox proportional hazards model

Demographic	Sex, age, race, ethnicity, marital status, health insurance status
Clinical	Primary cancer site, HPV status (oropharynx only), recurrence type (local/regional/distant), PD-L1 TPS, PD-L1 CPS, immunotherapy agent, concurrent chemotherapy, facility setting (community/academic), referral setting (inpatient/outpatient)*, referring specialty**, referring provider type**
Social	ADI, SVI, driving distance, driving time, metro/nonmetro status

*Attendance and time-to-referral outcomes only; **Time-to-referral outcome only

Results

Referral: 129 (51%) of 253 patients referred to PC. Select predictors:

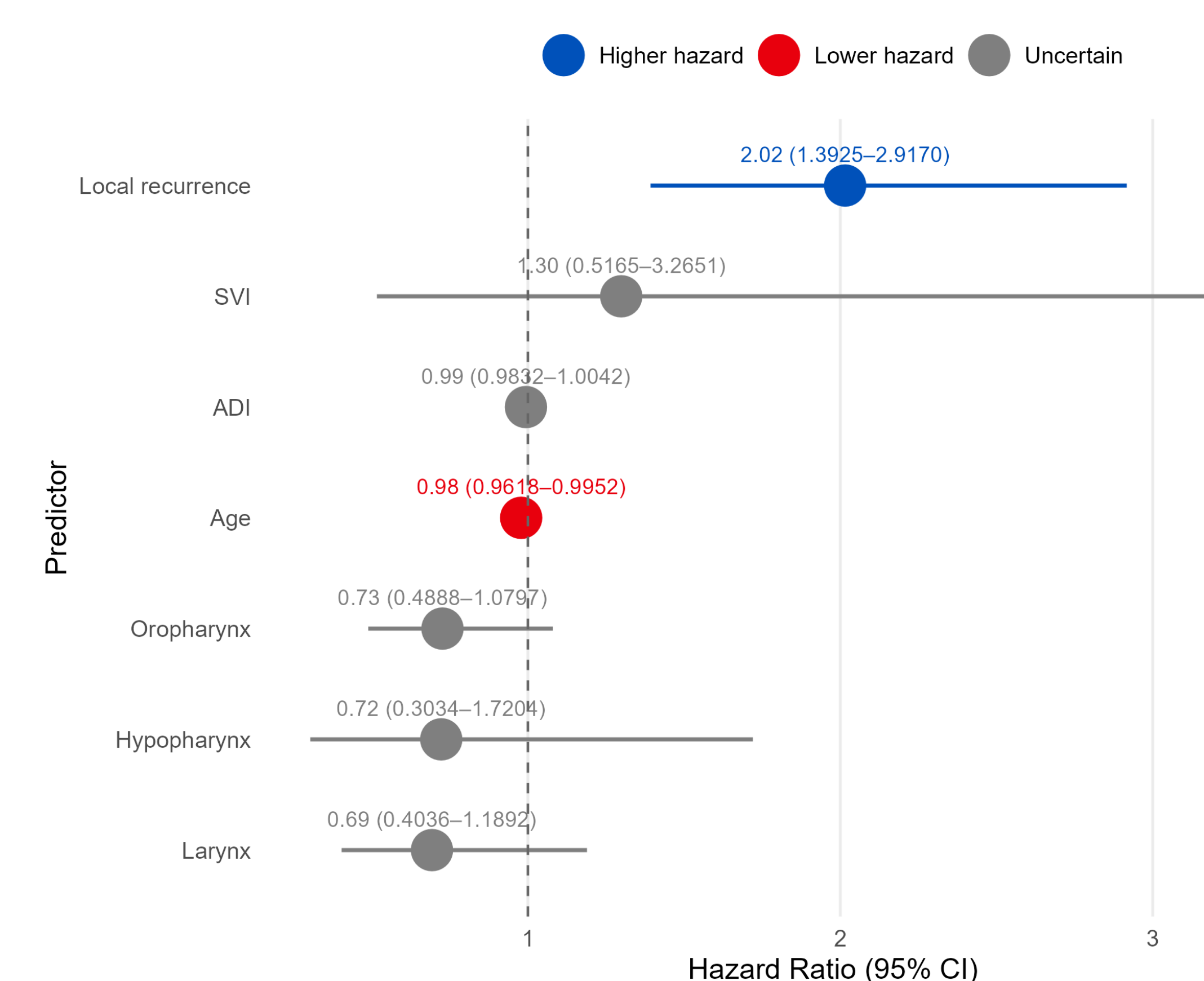|	p-value	Effect size	Effect size metric
Age	0.013	0.18	Rank-biserial r (rrb)
Local recurrence	0.017	0.15	Cramer's V
Driving distance	0.078	0.13	rrb
Driving time	0.11	0.12	rrb

Attendance: 118 (92%) of 129 patients referred attended a PC visit. Select predictors:

	p-value	Effect size	Effect size metric
Driving distance	0.034	0.39	rrb
Driving time	0.047	0.36	rrb
Concurrent chemotherapy	0.065	0.28	OR
Metro status	0.068	0.27	OR

Time-to-referral: Median 83 days (mean 255 days) after IO start. Select predictors:
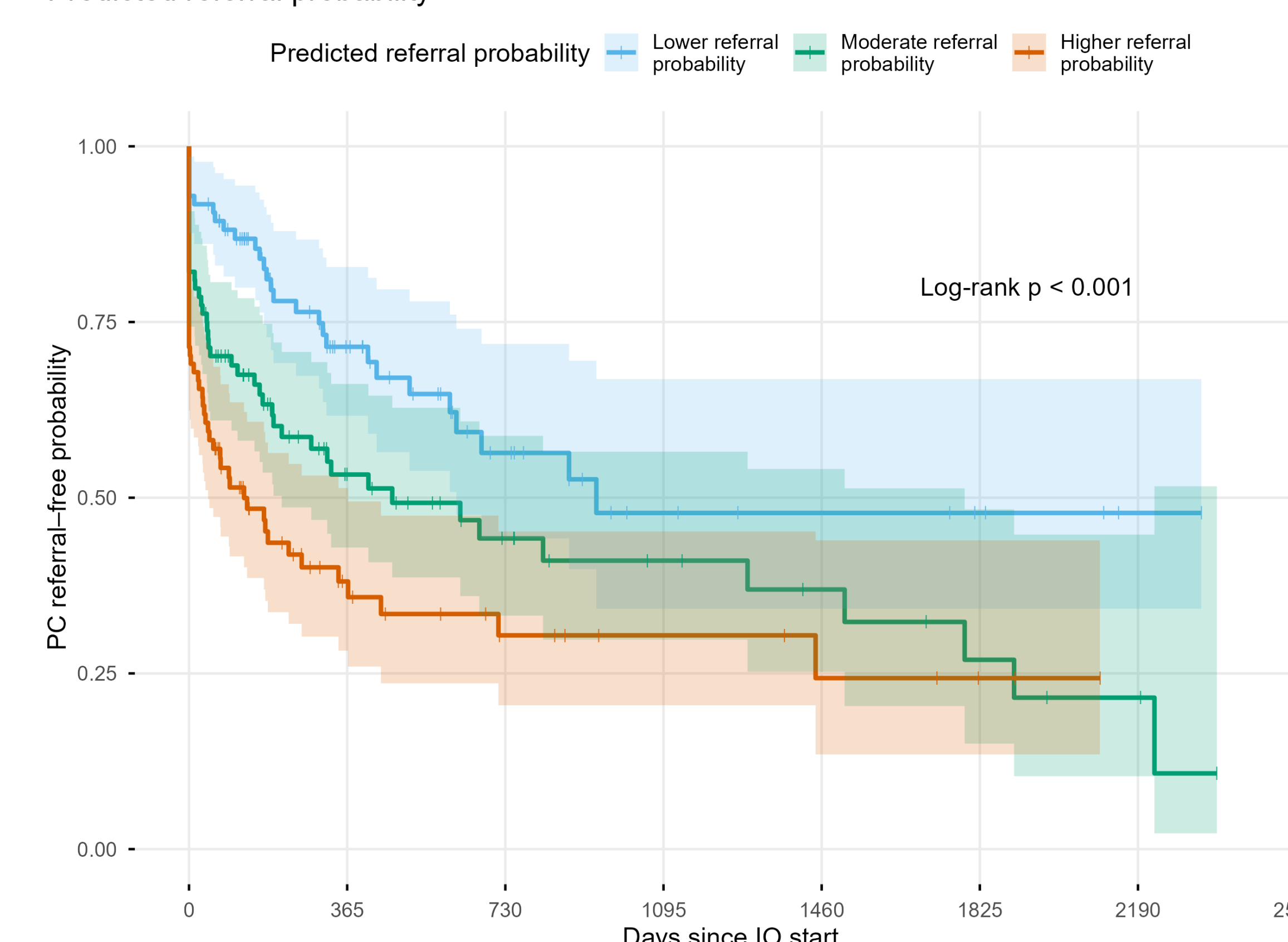
	p-value	β	Standard error
Referring specialty: Inpatient medicine/critical care	0.00009	325.9	80.4
Local recurrence	0.0077	-189.8	70.1
Area deprivation index (ADI)	0.020	3.55	1.5
Referring provider type: APP	0.023	-184.8	80.4
Referring specialty: Medical oncology	0.027	209.1	93.2
Age	0.027	-7.2	3.2
Social vulnerability index (SVI)	0.039	264.2	126.7
Site: oropharynx	0.043	163.6	80.1

Pooled Cox Model: Hazard Ratios for Time to PC Referral

Forest plot from a Cox model pooled across multiple imputations (m=5). HR>1 indicates **earlier referral** (higher hazard).

Kaplan–Meier curves for time from IO start to first PC referral, stratified by tertiles of the averaged Cox linear predictor (LP). LP tertiles: Low ≤ −0.14; Medium (−0.14–0.31); High > 0.31. Group sizes n=85/84/84. Median time to referral (days): Low 940, Medium 469, High 127. Log-rank p < 0.001.

Conclusions

- Just over half of the cohort was referred to PC, and most who were referred attended a visit
  - Opportunity for more **consistent** and **earlier referrals**
- **Access** was a barrier to attending a PC visit
- Patients with **local recurrence** tended to be referred earlier and those with **increased age** later, which may reflect concerns about symptom management, perceived prognosis, or institution-specific workflows

- **Clinical Implications:** Consider default referrals at diagnosis, EHR alerts, and expanding telehealth and rural access to PC.

Contact

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