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Claire Shen
Northwestern University Feinberg School of Medicine
Alex Horowitz
Northwestern University Feinberg School of Medicine
Dominic J. Vitello
Northwestern University Feinberg School of Medicine
Madison Cox
Northwestern University Feinberg School of Medicine
Amy Wells
Northwestern University Feinberg School of Medicine
Krishay Sridalla
Northwestern University Feinberg School of Medicine
Isabel Temosihue
Northwestern University Feinberg School of Medicine
Mary Kasparian
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Petra Urgacova
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Maya Panday
Northwestern University Feinberg School of Medicine
Lily Dale
Northwestern University Feinberg School of Medicine
Jasmine Machhi
Northwestern University Feinberg School of Medicine
Anastasia Chibucos
Northwestern University Feinberg School of Medicine
Vishvetha Rengaraju
Northwestern University Feinberg School of Medicine
George Molina
Brigham and Women's Hospital
David J. Bentrem

Northwestern University Feinberg School of Medicine

Qiang Zhang

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Akhil Chawla

Akhil.Chawla@nm.org

Northwestern University Feinberg School of Medicine

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Neighborhood Deprivation and Circulating Tumor DNA Provide Distinct Prognostic Signals in Localized Pancreatic Cancer

Claire Shen[1*]; Alex Horowitz, BA[1*]; Dominic J. Vitello, MD, MS[1,2]; Madison Cox, BS[1]; Amy Wells, MS[1]; Krishay Sridalla, BA[1]; Isabel Temosihue, BS, MPH[1]; Mary Kasparian, BS[3]; Petra Urgacova, BS[3]; Maya Panday[1]; Lily Dale, BS[1]; Jasmine Machhi, BS[1]; Anastasia Chibucos, BS[1]; Vishvetha Rengaraju, BS[1]; George Molina, MD, MPH[4]; David J. Bentrem, MD[1,2,3]; Qiang Zhang, MD, PhD[3]; Akhil Chawla, MD[1,2,3]

* These authors contributed to this work as co-first authors.

[1]Division of Surgical Oncology, Department of Surgery, Northwestern University Feinberg School of Medicine, 676 N Saint Clair St, Chicago, IL 60611, USA
[2]Northwestern Quality Improvement, Research & Education in Surgery, Department of Surgery, Northwestern University Feinberg School of Medicine, 676 N Saint Clair St, Chicago, IL 60611, USA
[3]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 675 N St Clair St, Chicago, IL 60611, USA
[4]Brigham and Women's Hospital, Division of Surgical Oncology, 75 Francis St, Boston, MA 02115, USA

Corresponding Author:
Akhil Chawla, MD, FACS
Arkes Family Pavilion
676 N Saint Clair St, Suite 6-096
Chicago, IL, 60611
Phone: (630) 352-5450
Fax: (630) 352-5320
Email: Akhil.Chawla@nm.org

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Structured Abstract

Purpose: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer death in the US. Socioeconomic disadvantage, measured by Area Deprivation Index (ADI), may affect outcomes beyond tumor biology. We evaluate ADI and overall survival (OS) in localized PDAC, accounting for *KRAS*-mutant circulating tumor DNA (ctDNA).

Methods: 165 patients with localized PDAC were prospectively enrolled (NCT04616131; Oct. 2020–Jan. 2026). ADI was dichotomized at the 50th national percentile. OS was compared by group and jointly with ctDNA using Kaplan-Meier analysis. Multivariable Cox assessed ADI and survival, adjusting for clinical covariates and ctDNA, and tested ADI/ctDNA interactions. C-index/likelihood ratio assessed added discriminatory value. Next-generation sequencing detected *KRAS*-mutant ctDNA.

Results: High ADI was associated with shorter OS (26.7 vs 30.5 months, p=0.035; HR 1.79, 95% CI 1.09–2.92, p=0.020). Patients with both high ADI and detectable ctDNA had the poorest survival (9.8 vs 38.3 months, p=0.005). ADI and ctDNA each independently predicted shorter survival without significant interaction; combining both improved model discrimination beyond either alone.

Conclusion: Greater area deprivation is associated with reduced survival in localized PDAC, independently of clinical and tumor biomarkers. ADI and ctDNA may have additive value for risk stratification, supporting interventions targeting social determinants alongside oncologic care.

Keywords: social determinants of health, neighborhood deprivation, biomarker, circulating tumor DNA, pancreatic ductal adenocarcinoma

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer related mortality in the United States and is projected to become the second leading cause by 2030 [1,2]. Despite advances in systemic therapy, perioperative care, and multimodality treatment, prognosis remains poor, with contemporary 5-year overall survival approximating 13% across stages [3,4]. For patients with localized disease who undergo curative intent resection, long-term outcomes are improved relative to metastatic disease; however, recurrence remains common and survival varies widely even among patients treated with similar neoadjuvant and surgical approaches [4,5].

This heterogeneity is partly explained by tumor biology and treatment response. *KRAS* driven disease is nearly ubiquitous in PDAC, and circulating tumor DNA (ctDNA), particularly mutant *KRAS* detected in plasma, has emerged as a prognostic biomarker associated with inferior survival in localized and resected disease. Alongside established clinical markers such as carbohydrate antigen 19-9 (CA19-9), ctDNA provides a tumor-derived measure of disease burden and biologic aggressiveness that is less dependent on healthcare access, offering a complementary lens through which to interpret outcome differences [6–9].

At the same time, outcomes in PDAC are shaped by structural and socioeconomic determinants of health [10–12]. Patients from socioeconomically disadvantaged neighborhoods experience later stage diagnosis, reduced likelihood of receiving surgery and multimodal therapy, and worse survival across multiple malignancies, including PDAC [13–17]. The Area Deprivation Index (ADI) is a validated, neighborhood level composite of socioeconomic disadvantage derived from U.S. Census/American Community Survey indicators spanning income, education, employment, and housing quality at the census block group level [18]. ADI

has been increasingly adopted in surgical oncology research and has demonstrated robust associations with outcomes in diverse cancer populations [11,18–20]. In PDAC, new evidence links neighborhood deprivation to differences in access to stage appropriate therapy and survival, yet the degree to which these disparities persist in contemporary neoadjuvant era cohorts, particularly after accounting for molecular biomarkers, remains incompletely understood [13–17].

A central unanswered question is whether poorer outcomes observed in socioeconomically disadvantaged neighborhoods reflect more aggressive tumor biology or structural barriers that limit the effectiveness of care delivery [21–24]. Structural disadvantages are understood to act through barriers to care continuity, supportive services, transportation, food security, and recovery resources. However, several studies have additionally found socioeconomic disadvantage to exert biologic effects via chronic stress and inflammatory signaling pathways, impacting survival outcomes across cancer types [10–12,25,26]. Pairing a neighborhood level disadvantage metric (ADI) with a tumor-derived biomarker (*KRAS* ctDNA) offers an opportunity to disentangle these pathways and clarify whether deprivation associated survival differences are attributable to biology, structure, or both.

Accordingly, we evaluate the independent and joint associations of ADI and *KRAS* ctDNA with overall survival in patients with localized PDAC enrolled in a prospective clinical trial. We hypothesized that higher ADI would be independently associated with worse survival after adjustment for clinical prognostic factors and host status, and that deprivation associated disparities would persist even after stratification by tumor biology.

Methods

Study Design and Population

We conducted a retrospective analysis of prospectively collected data from adults with localized PDAC eligible for neoadjuvant chemotherapy enrolled in an institutional biomarker feasibility trial (NCT04616131) at Northwestern Medicine between October 2020 and January 2026. Patients had histologic or cytologic confirmation of non-metastatic PDAC [27]. Clinical staging and treatment plans were determined by a multidisciplinary tumor board. All participants were managed within a standardized clinical trial framework.

The study was approved by the Northwestern University Institutional Review Board (NMHC IRB #21-012). All trial participants provided written informed consent at enrollment. This observational analysis is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [28]. Baseline clinical and demographic data were collected prospectively at enrollment, including age, sex, clinical stage, and radiographic stage (resectable vs borderline resectable). Serum CA19-9 was obtained at diagnosis.

Area Deprivation Index

Neighborhood socioeconomic disadvantage was quantified using ADI, a validated composite measure derived from U.S. Census/American Community Survey indicators across domains of income, education, employment, and housing quality. ADI was assigned at the census block group level using residential address at diagnosis linked to the University of Wisconsin Neighborhood Atlas and expressed as a national percentile (1–100), with higher values indicating greater deprivation [18]. For analysis, ADI percentile was categorized by 50th percentile: Low ADI (1–49) and High ADI (50–100) [18,20].

KRAS Circulating Tumor DNA

Blood samples for ctDNA analysis were obtained at baseline prior to initiation of therapy. *KRAS* mutations were detected using next-generation sequencing (NGS) of plasma-derived ctDNA. Peripheral blood was collected and shipped to commercial laboratories, with analyses performed using tumor-agnostic assays within 24 hours of collection. *KRAS* ctDNA status was classified as positive (detectable *KRAS* mutation) or negative (no detectable *KRAS* mutation) based on validated assay thresholds [6–8].

Outcomes

The primary endpoint was overall survival (OS), defined as time from date of diagnosis to death from any cause. Patients alive at last follow up were censored on the date of last known contact.

Statistical Analysis

All analyses and visualizations were performed in R (v4.5.1), with two-sided $P<0.05$ considered statistically significant. Baseline characteristics were summarized by ADI category by median and compared using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. OS was assessed using the Kaplan-Meier method and compared across ADI groups using log-rank tests. Univariable Cox regression further assessed risk associated with High ADI in relation to Low ADI, reported as a hazard ratio and 95% confidence interval (CI). Multivariable Cox regression adjusted for baseline clinical characteristics to evaluate the independent association between ADI, ctDNA detection, and OS. Clinical covariates were prespecified a priori and included age, sex, clinical stage, CA19-9, ADI, and *KRAS* ctDNA status.

Differences in ADI among patients with normal vs. elevated CA19-9 (>37 U/mL) were assessed by Wilcoxon rank-sum test, as well as differences in CA19-9 among patients with High

vs. Low ADI. Spearman's correlation was used to assess trends between CA19-9 and ADI continuously. Chi-square test was used to evaluate whether the proportion of patients with elevated CA19-9 differed among ADI groups. These tests were similarly performed for maximum allele frequency for *KRAS*-mutant ctDNA and ctDNA detection.

The additive discriminatory value of ADI and ctDNA for predicting OS was assessed four ways using Harrell's concordance index (c-index) for the baseline clinical model (age, sex, clinical stage, CA19-9) alone, baseline with the addition of ADI, baseline with the addition of ctDNA, and with the addition of both ADI and ctDNA jointly. Likelihood ratio tests (LRT) compared each nested model to the baseline clinical model to determine the incremental prognostic value of ADI and ctDNA. Furthermore, to evaluate the interaction between ADI and ctDNA, a Cox model containing ADI, ctDNA, and their interaction term was used. Interaction Significance was assessed using a likelihood ratio testing comparing this model to those with ADI and ctDNA main effects alone.

Results

Table 1. Baseline Patient and Clinical Characteristics Stratified by Area Deprivation Index (ADI) Group. ADI was stratified by Low (1–49) vs. High (50–100) national percentile. Comparisons were made using Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

Characteristic	**Overall** N = 165[a]	**Low ADI** N = 130	**High ADI** N = 35	***P***
Age (years)	70 (64, 76)	70 (64, 74)	73 (66, 79)	0.072
Sex				0.851
Male	83 (50.3%)	66 (50.8%)	17 (48.6%)	
Female	82 (49.7%)	64 (49.2%)	18 (51.4%)	
Clinical Stage				0.688
IA	25 (15.2%)	22 (16.9%)	3 (8.6%)	
IB	68 (41.2%)	53 (40.8%)	15 (42.9%)	
II	29 (17.6%)	22 (16.9%)	7 (20.0%)	

III	40 (24.2%)	31 (23.8%)	9 (25.7%)	
Smoking History				0.060
Yes	80 (48.5%)	58 (44.6%)	22 (62.9%)	
No	85 (51.5%)	72 (55.4%)	13 (37.1%)	
Insurance Status				>0.999
Private	45 (27.2%)	36 (27.7%)	9 (25.7%)	
Underinsured	118 (71.5%)	93 (71.5)	25 (71.4%)	
Type 2 Diabetes				0.846
Yes	66 (40.0%)	51 (39.2%)	15 (42.9%)	
No	99 (60.0%)	79 (60.8%)	20 (57.1%)	
Hypothyroidism				>0.999
Yes	30 (18.2%)	24 (18.5%)	6 (17.1%)	
No	135 (81.8%)	106 (81.5%)	29 (82.8%)	
Chronic Kidney Disease				0.605
Yes	6 (3.6%)	4 (3.1%)	2 (5.7%)	
No	159 (96.4%)	126 (96.9%)	33 (94.3%)	
Distance to Hospital (miles)	9.3 (4.9, 14.1)	9.2 (4.9, 13.3)	10.1 (4.3, 19.8)	0.415
***KRAS* ctDNA detected**				0.766
No	90 (81.8%)	71 (82.6%)	19 (79.2%)	
Yes	20 (18.2%)	15 (17.4%)	5 (20.8%)	
Received NAC				>0.999
Yes	131 (79.4%)	103 (79.2%)	28 (80.0%)	
No	34 (20.6%)	27 (20.8%)	7 (20.0%)	
Underwent Surgery				0.684
Yes	92 (55.8%)	71 (54.6%)	21 (60.0%)	
No	73 (44.2%)	59 (45.4%)	14 (40.0%)	
Radiographic Resectability				0.793
Resectable	70 (42.4%)	56 (43.1%)	14 (40.0%)	
Borderline Resectable	67 (40.6%)	51 (39.2%)	16 (45.7%)	

Locally Advanced	28 (17.0%)	23 (17.7%)	5 (14.3%)	
Serum CA19-9 (U/mL)	161.5 (35.5, 581.5)	163.5 (38.0, 711.0)	134.5 (33.0, 422.0)	0.578

[a]Median (Q1, Q3); n (%)
Note: Percentages represent the proportion of patients within each category, calculated using the cohort size as the denominator. Minor discrepancies from 100% or full cohort size are due to missing data.

Patient Characteristics

Between October 2020 and January 2026, 165 patients with localized PDAC and recorded ADI values were enrolled (NCT04616131). The High ADI group (50–100) consisted of 35 patients, while the Low ADI group (1–49) consisted of 130 patients. Median age for the overall cohort was 70 years (IQR 64–76), and 50.3% of patients were male. Most patients presented with Stage IB disease (41.2%) and radiographically resectable tumors (42.4%). Age, sex, clinical stage, smoking history, insurance status, and comorbidity burden (diabetes mellitus, hypothyroidism, and chronic kidney disease) did not differ significantly between ADI groups. Additionally, the proportion of patients who ultimately underwent NAC and resection was balanced between groups. Testing for *KRAS*-mutant ctDNA was performed for 110 patients (66.7%); of these, 20 (18.2%) had ctDNA detected by NGS at diagnosis, with no significant difference in detection rate by ADI group (p = 0.766; **Table 1**). ADI and CA19-9 were not significantly correlated (**Figure S1**). Median follow up was 18.0 months (IQR 11.5–31.7 months).

Overall Survival by Area Deprivation Index and Circulating Tumor DNA

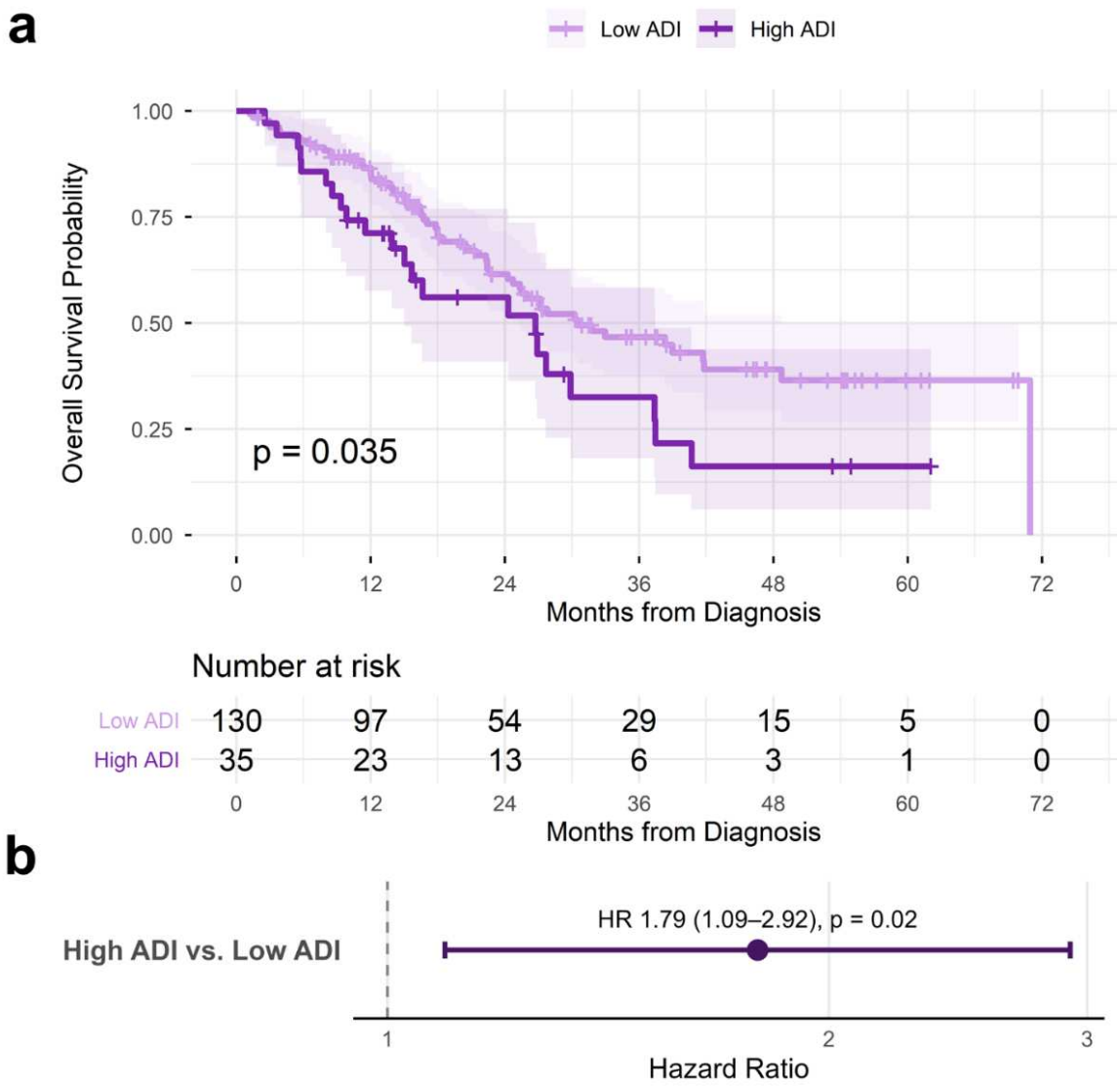


Fig. 1 Association of ADI with overall survival. a) Kaplan-Meier curves for Low ADI (0–49) patients compared with High ADI (50–100) patients. b) Forest plot of a univariable Cox model showing relative risk of the High ADI group vs. Low ADI

Patients with High ADI demonstrated significantly shorter OS (median 26.7 vs 30.4 months, p = 0.035; **Fig. 1a**). Accordingly, univariable Cox regression demonstrated that High ADI was associated with 79% increased mortality risk compared to Low ADI (HR 1.79, 95% CI 1.09–2.92, p = 0.020; **Fig. 1b**).

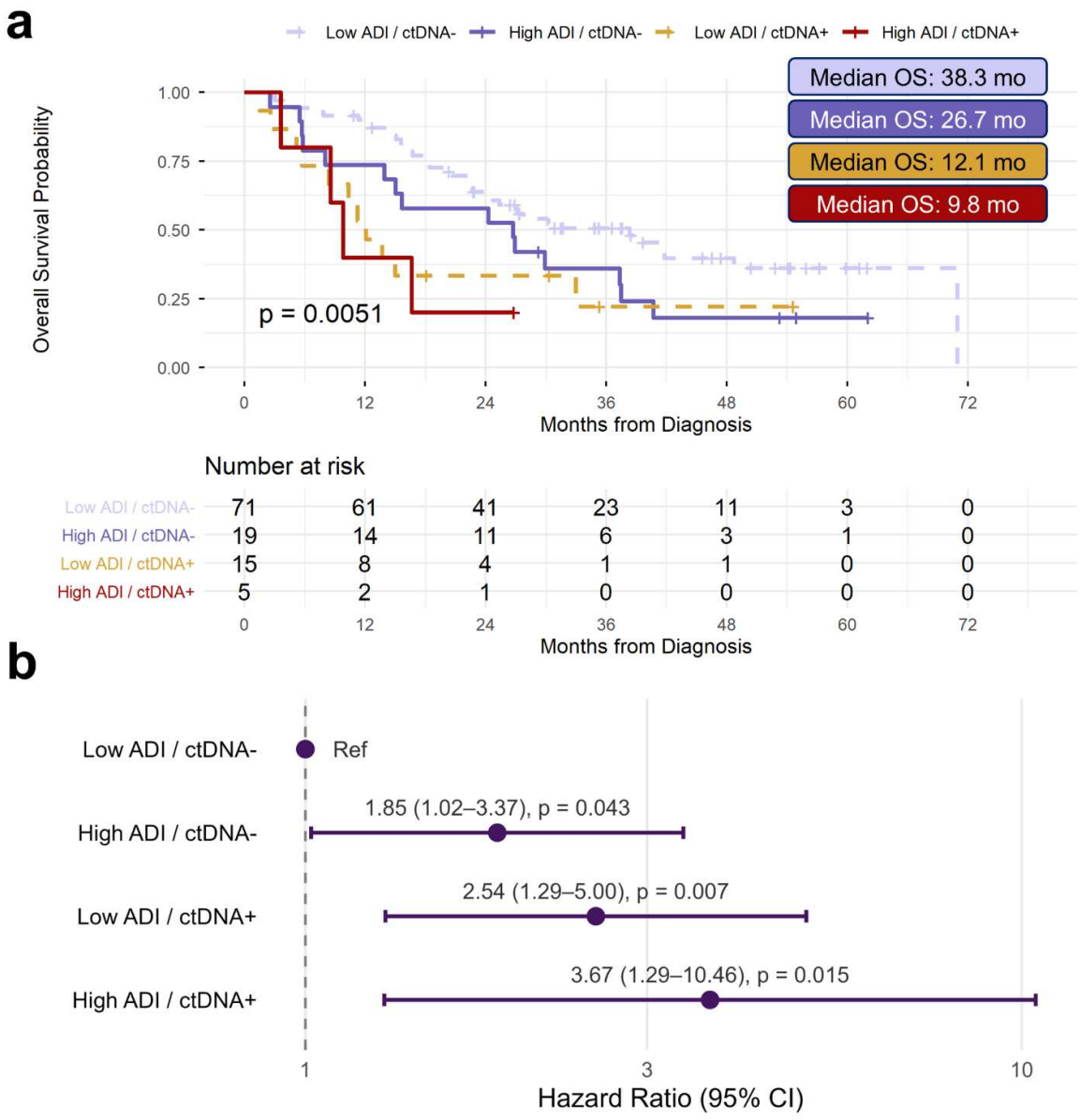


Figure 2. Joint effects of ADI and ctDNA detection. a) Kaplan-Meier curve showing a four-way split by ADI and ctDNA detection, including Low ADI/ctDNA-negative, High ADI/ctDNA-negative, Low ADI/ctDNA-positive, and High ADI/ctDNA-positive. b) Forest plot showing hazard ratio of each group vs. the Low ADI/ctDNA-negative group

Additionally, stratifying patients into four groups based on ADI group and ctDNA status demonstrated a gradient in survival, with the best outcomes in the Low ADI/ctDNA-negative group and the worst outcomes in the High ADI/ctDNA-positive group, suggesting an additive effect. Median OS was 38.3 months for Low ADI/ctDNA-negative, 26.7 months for High

ADI/ctDNA-negative, 12.1 months for Low ADI/ctDNA-positive, and 9.8 months in patients who were High ADI/ctDNA-positive (p=0.005; **Fig. 2a**). In a univariable Cox model, hazard ratio also increases progressively across these groups; patients with High ADI and detectable ctDNA had greater than threefold higher risk compared to patients with Low ADI and undetectable ctDNA (HR 3.67, 95% CI 1.29–10.46, p=0.015; **Fig. 2b**).

Independent and Additive Prognostic Value of Neighborhood Deprivation and Tumor Biology

We next evaluated whether ADI and ctDNA were each independently associated with OS. Using a multivariable Cox model, we found that High ADI (adjusted HR 1.79, 95% CI 1.01–3.17, p = 0.047) and *KRAS* ctDNA positivity (adjusted HR 2.14, 95% CI 1.15–3.98, p = 0.017; **Fig. 3**) were associated with shorter OS, even after adjustment for other clinical factors, including clinical stage, CA19-9, sex, and age.

Furthermore, adding both ADI and ctDNA improved model discrimination compared to the baseline clinical model of stage, CA19-9, sex, and age. While the baseline Harrell's c-index was 0.643, adding ADI alone as a covariate increased the c-index to 0.664 (LRT p = 0.022). Adding ctDNA status alone as a covariate to the baseline model further increased c-index to 0.676 (LRT p = 0.014). Subsequently, adding both ADI and ctDNA together to the baseline resulted in the highest c-index (0.690, LRT p = 0.0046 vs. baseline; **Table 2a**). This demonstrates the distinct signals that ADI and ctDNA each provide for risk stratification.

Table 2. Model discrimination and interaction analysis for ADI and ctDNA

a) Harrel's c-index for model discrimination with baseline clinical model alone (stage, CA19-9, age, sex), baseline plus ADI alone, baseline plus ctDNA detection alone, and baseline plus both ADI and ctDNA detection. Likelihood ratio test p-values describe differences vs. baseline c-index.

	c-index (SE)	**LRT p-value vs. baseline**
Baseline clinical model	0.643 (0.036)	**-**
Baseline + ADI	0.664 (0.034)	**0.022**
Baseline + ctDNA	0.676 (0.036)	**0.014**

Baseline + ADI + ctDNA	0.690 (0.033)	**0.005**

b) Cox model describing the risk contributions of each ADI and ctDNA alone, as well as effect modification through their interaction.

Variable	**HR**	**95% CI**	***P***
ADI			
Low	Ref		
High	1.853	1.019–3.371	**0.043**
ctDNA			
Undetectable	Ref		
Detectable	2.561	1.302–5.036	**0.006**
High ADI × ctDNA interaction	0.826	0.243–2.803	0.760

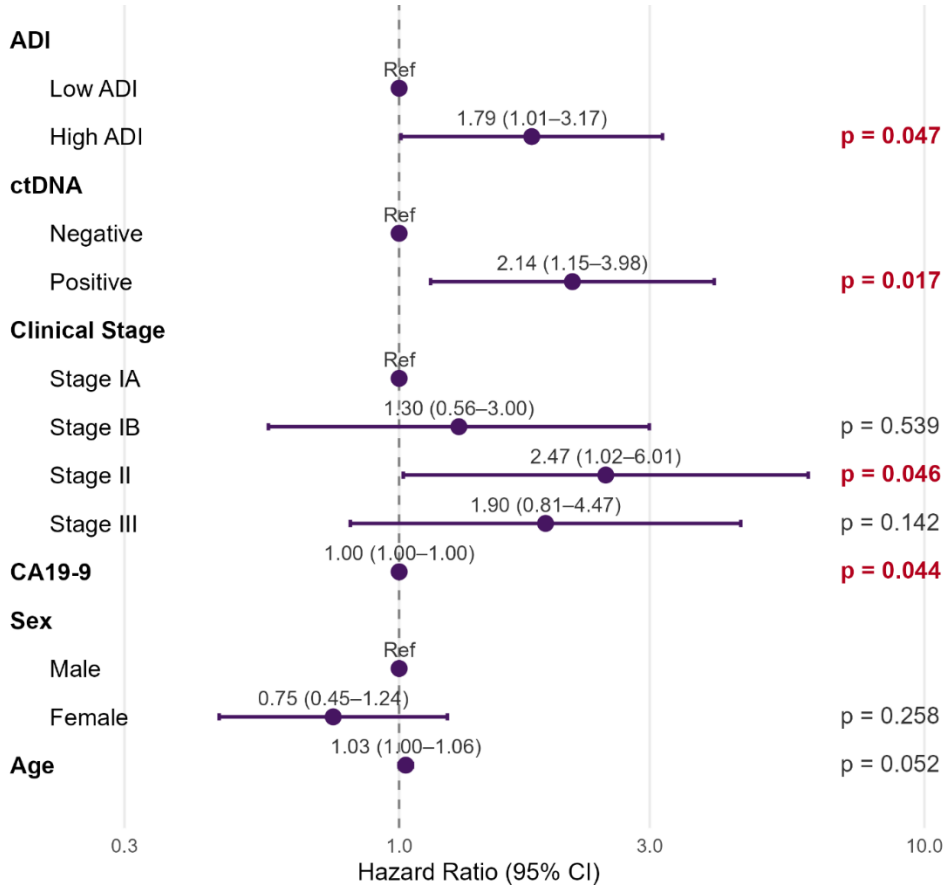


Figure 3. Independent contributions of ADI and ctDNA detection. Multivariable Cox regression including ADI, ctDNA, clinical stage, CA19-9, sex, and age as covariates

Additionally, consistent with their independent prognostic value, there was no evidence of interaction between ADI and *KRAS* ctDNA status. While ADI and ctDNA were each significantly associated with survival, an interaction model demonstrated that the individual effect of each marker did not significantly alter the other (HR 0.826, 95% CI 0.243–2.803, p = 0.760; **Table 2b**), meaning that having detectable ctDNA neither increased nor decreased the risk of High ADI, and vice versa. Similarly, ctDNA detection nor quantity in maximum allele frequency (MAF) did not correlate with ADI group or continuous percentile (**Figure S2**). Alongside the poorest prognosis for patients with both High ADI/ctDNA-positivity and the improved model discrimination when incorporating both markers, these data suggest an additive rather than synergistic effects of ADI and ctDNA on survival.

Discussion

In this prospective cohort of patients with localized PDAC treated with contemporary neoadjuvant chemotherapy, we demonstrate that ADI is a strong and independent predictor of survival. Importantly, the association between higher ADI and worse survival persisted after adjustment for clinical stage, age, sex, serum CA19-9, and *KRAS*-mutant ctDNA. Our previous work has identified *KRAS*-mutant ctDNA as a strong potential predictive biomarker in PDAC for overall survival, consistent with other ctDNA studies in PDAC and other cancers.[6,8,29–34] However, the role of neighborhood socioeconomic disadvantage in the context of other biomarkers, including CA19-9 and ctDNA, has yet to be fully described. The findings in this study indicate that structural disadvantage confers prognostic risk beyond tumor aggressiveness alone.

Our results extend prior studies linking socioeconomic disadvantage to pancreatic cancer outcomes by demonstrating that deprivation-associated disparities remain evident even within a

prospective clinical trial setting with protocol directed care [14–17,20]. The lack of statistical interaction between ADI and *KRAS* ctDNA suggests that neighborhood deprivation and adverse tumor biology operate through largely independent pathways to influence survival. This distinction is clinically meaningful, as it challenges the assumption that poorer outcomes among socioeconomically disadvantaged patients are solely attributable to delayed diagnosis or more aggressive disease biology.

Multiple mechanisms likely underlie the observed association between neighborhood deprivation and survival. Patients residing in highly deprived neighborhoods face structural barriers that may compromise the effectiveness of multimodal cancer care, including limited access to high-quality healthcare facilities, reduced availability of supportive services, transportation challenges, food insecurity, and housing instability. These factors may impede treatment adherence, delay recognition and management of therapy related toxicities, and limit access to post-protocol or salvage therapies, even when initial treatment is standardized [35,36]. Beyond healthcare access, emerging evidence suggests that neighborhood disadvantage may influence cancer outcomes through biologic pathways. Chronic psychosocial stress associated with socioeconomic deprivation has been linked to dysregulated neuroendocrine signaling and pro-inflammatory gene expression patterns, collectively termed the conserved transcriptional response to adversity (CTRA) [25,26]. These pathways have been associated with impaired immune surveillance, resistance to therapy, and worse oncologic outcomes, raising the possibility that neighborhood context may shape host tumor interactions in ways not fully captured by conventional clinical biomarkers [37,38].

The finding that *KRAS* ctDNA-negative patients from High ADI neighborhoods experienced worse survival than their counterparts from Low ADI neighborhoods is particularly

notable. Our prior studies have shown that *KRAS* ctDNA is a robust prognostic biomarker in PDAC, with detection consistently associated with inferior survival across disease stages [6–9]. However, these data suggest that favorable tumor biology does not fully mitigate the adverse impact of structural disadvantage. Conversely, patients with both high ADI and detectable *KRAS* ctDNA experienced the poorest OS, potentially representing an additive effect of adverse biology compounded by structural barriers.

This work complements and extends prior studies suggesting that treatment at high-volume centers or within multidisciplinary care models can reduce, but not fully eliminate, socioeconomic disparities [4,27,39]. Persistent disparities observed even in clinical trial populations mirror findings from large cooperative group studies, where patients from more deprived areas experienced worse survival despite access to protocol directed therapy [40]. This pattern underscores that drives of disparity often lie beyond the immediate clinical encounter, reflecting cumulative social, environmental, and physiologic disadvantage.

We find that combining ADI and ctDNA individually improves risk stratification. Moreover, we demonstrate that incorporating both further increases model discrimination. Given the independent and potentially additive effects of ctDNA and ADI, this improved predictive value supports the integration of ADI along with current markers through treatment. The clinical and policy implications of these findings may include incorporating neighborhood level metrics such as ADI into risk stratification, potentially identifying patients at elevated risk who could benefit from enhanced supportive interventions. Evidence-based strategies such as patient navigation programs, integration of social work and nutrition services into oncology care, financial and transportation assistance, and expansion of multidisciplinary clinics designed to address both medical and social needs could improve outcomes for socioeconomically

disadvantaged patients [27,41]. Broader community level interventions addressing food insecurity, housing instability, and access to preventive and primary care services may further mitigate deprivation associated disparities at a population level [42–44].

This study has several strengths, including prospective enrollment, detailed clinical and biomarker data, and use of a validated, granular measure of neighborhood disadvantage. Limitations include the single institution design, which may limit generalizability, and the inability to directly measure individual level socioeconomic factors or intermediate mechanisms such as treatment adherence, toxicity management, and access to post-protocol therapies. Future studies should evaluate these pathways and test targeted interventions aimed at reducing structural barriers in highly deprived communities.

In conclusion, neighborhood socioeconomic deprivation is an independent predictor of survival in localized PDAC, operating through mechanisms distinct from tumor biology. The magnitude of the observed disparities highlights the urgent need to address structural determinants of health as a core component of high-quality pancreatic cancer care. Integrating ADI into clinical risk assessment may facilitate more equitable outcomes by enabling targeted, multidisciplinary support for patients at greatest risk.

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