Original Article

Hepatopancreatobiliary malignancies: time to treatment matters

Daniel M. Kerekes[1]^, Alexander E. Frey[1], Baylee F. Bakkila[2], Caroline H. Johnson[3], Robert D. Becher[1], Kevin G. Billingsley[1], Sajid A. Khan[1]

[1]Department of Surgery, Yale School of Medicine, New Haven, CT, USA; [2]Yale School of Medicine, New Haven, CT, USA; [3]Department of Environmental Health Sciences, Yale School of Public Health, Yale University, New Haven, CT, USA

Contributions: (I) Conception and design: DM Kerekes, AE Frey, SA Khan; (II) Administrative support: DM Kerekes; (III) Provision of study materials or patients: SA Khan; (IV) Collection and assembly of data: DM Kerekes, AE Frey; (V) Data analysis and interpretation: DM Kerekes, AE Frey, SA Khan, KG Billingsley; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sajid A. Khan, MD. Associate Professor of Surgery (Oncology), Yale School of Medicine, PO Box 208062, New Haven, CT 06520-8062, USA. Email: Sajid.Khan@yale.edu.

Background: Initiation of oncologic care is often delayed, yet little is known about delays in hepatopancreatobiliary (HPB) cancers or their impact. This retrospective cohort study describes trends in time to treatment initiation (TTI), assesses the association between TTI and survival, and identifies predictors of TTI in HPB cancers.

Methods: The National Cancer Database was queried for patients with cancers of the pancreas, liver, and bile ducts between 2004 and 2017. Kaplan-Meier survival analysis and Cox regression were used to investigate the association between TTI and overall survival for each cancer type and stage. Multivariable regression identified factors associated with longer TTI.

Results: Of 318,931 patients with HPB cancers, median TTI was 31 days. Longer TTI was associated with increased mortality in patients with stages I–III extrahepatic bile duct (EHBD) cancer and stages I–II pancreatic adenocarcinoma. Patients treated within 3–30, 31–60, and 61–90 days had median survivals of 51.5, 34.9, and 25.4 months (log-rank P<0.001), respectively, for stage I EHBD cancer, and 18.8, 16.6, and 15.2 months for stage I pancreatic cancer, respectively (P<0.001). Factors associated with increased TTI included stage I disease (+13.7 days *vs.* stage IV, P<0.001), treatment with radiation only (β=+13.9 days, P<0.001), Black race (+4.6 days, P<0.001) and Hispanic ethnicity (+4.3 days, P<0.001).

Conclusions: Some HPB cancer patients with longer time to definitive care experienced higher mortality than patients treated expeditiously, particularly in non-metastatic EHBD cancer. Black and Hispanic patients are at risk for delayed treatment. Further research into these associations is needed.

Keywords: Bile ducts, extrahepatic; time-to-treatment; survival analysis; health inequities

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Introduction

The increasing complexity of cancer care is driving a national trend towards increasing time from diagnosis to treatment initiation for many cancers (1-3). Moreover, resource constraints due to the COVID-19 pandemic have exacerbated existing delays by forcing many institutions to systematically postpone cancer treatment further (4-7). On a case-by-case basis, due to the complexity, cost, and duration of care, treatment for an individual may be further delayed for a multitude of patient-, provider-, or facility-driven

^ ORCID: 0000-0001-9467-1486.

reasons. However, the impact of delays in oncologic care on patient outcomes, particularly for hepatopancreatobiliary (HPB) cancers, is unclear; in the case of biliary cancer specifically, evidence is absent.

The association between time to treatment initiation (TTI) and survival has been investigated in multiple cancer types previously. Studies in head and neck cancer and some gastrointestinal (GI) cancers have concluded that there is no association between treatment delay and survival (8-14), while investigations in renal, endometrial, bladder, and other GI cancers have suggested that survival decreases with longer TTI (1,11,15-18). For some cancers, including breast, prostate, testicular, and non-small cell lung cancer, the existing literature is conflicting (11,15,19-22).

These diverse results may reflect not only differences in study design and power, but also tumor biology and response to therapy. Cancers with favorable tumor biology (such as prostate cancer) or for which highly efficacious treatments exist (such as testicular cancer) may have outcomes that sometimes but do not reproducibly worsen with lengthening TTI, as these diseases are either unlikely to progress over a few months or are likely to be adequately treated despite any progression (23,24). On the other hand, disease with an attenuated response to current therapy (such as late stage pancreatic cancer) might fail to demonstrate an association with TTI, since therapy is often ineffective regardless of relative tumor burden (25). In a third category, cancers with aggressive tumor biology but relatively effective treatment for some stages of disease (such as early stage gastric cancer) might be found to have increased mortality with delays in care.

HPB cancers have 5-year survival rates on the order of 30–40% for localized disease, but only 2–3% for metastatic disease—among the lowest of all malignancies (26,27). It follows that outcomes of these aggressive cancers may be meaningfully compromised by even short periods of unchecked progression; however, data on the association between TTI and survival in HPB cancers is extremely limited and derived from relatively small cohorts (9,10,18).

In the current study, we evaluate the association between TTI and overall survival in a national cohort of patients with liver, pancreas, and intrahepatic or extrahepatic bile duct (EHBD) cancers of all stages, and determine clinical and demographic factors associated with increased risk of delayed treatment. A secondary aim was to describe national trends in TTI related to HPB cancers. We present the following study in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-1067/rc).

Highlight box

Key findings

- Longer time to treatment initiation is associated with worse overall survival in patients with stage I–III extrahepatic bile duct cancer and stage I–II pancreatic cancer.
- Black and Hispanic patients with hepatopancreatobiliary cancer experience greater delays in care than white patients.

What is known and what is new?

- Time to treatment initiation is known to be a contributing factor to patient outcome for some aggressive malignancies.
- Our data identify early-stage extrahepatic bile duct and pancreatic cancer as malignancies for which time to treatment is associated with survival and suggest racial disparities in time to treatment exist.

What is the implication, and what should change now?

- The results suggest that initiating treatment less than 30 days from diagnosis is associated with longer patient survival for patients with early-stage extrahepatic bile duct or pancreatic cancer.
- Care for all patients with these malignancies should be expedited.

Methods

Database

This study was a retrospective analysis of the patients and variables reported in the National Cancer Database (NCDB). The NCDB is a clinical oncology database that collects demographic variables and treatment details for all patients with a cancer diagnosis treated at a Commission on Cancer-accredited facility (28). Data are extracted from medical records by trained tumor registrars.

The NCDB reports TTI for each case, defined as "the number of days between Date of Initial Diagnosis (NAACCR Item #390) and the Date of First Course of Treatment [surgery, radiation, systemic, or other therapy] (NAACCR Item #1270) of the patient began at any facility" (29). The date of initial diagnosis is recorded as the date of earliest confirmation of the tumor, whether clinically or histologically, as documented in the medical record by a treating physician.

As the NCDB is a deidentified database, this research study did not qualify as human subjects research and did not meet criteria for review following processes outlined by our Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki (as revised

in 2013).

Study population

The NCDB Participant User Files for cancers of the pancreas, liver, and intrahepatic and EHBDs were acquired for patients diagnosed between 2004 and 2017. Inclusion criteria were histology demonstrating the most common malignancies for each organ, as detailed in Table S1. Neuroendocrine tumors were excluded. Only patients 18 years or older were included. Sample size was determined by number of cases reported in the NCDB.

Patients with no TTI data were excluded. Patients with TTI less than 3 days were also excluded, as these patients evidently did not follow a conventional treatment pathway, diagnostic surgeries may have been misinterpreted as curative resections, and a patient's treatment on the day of or days following cancer diagnosis may have been initiated in a non-elective setting. Patients with TTI greater than 1 year (365 days) were also excluded, as were patients with unknown staging.

Statistical analysis

The primary outcome was overall survival. The primary predictor variable was TTI. TTI was divided into four categories: 3–30, 31–60, 61–90, and 91–365 days. These categories were chosen as clinically relevant and easily interpretable end points.

Demographic and clinical characteristics were reported for each TTI group, with differences in prevalence of variables across the groups assessed using chi-squared (χ^2) tests or one-way analysis of variance (ANOVA). Post-hoc z-tests for categorical variables and Tukey's Honestly Significant Difference (HSD) for the continuous variables were used to make pairwise comparisons between TTI groups with a significant omnibus test; α (alpha) of 0.05 corrected with Bonferroni adjustment was utilized as an adjusted significance threshold.

Temporal TTI trends were examined across years stratified by a variety of demographic and treatment variables, with medians compared using a one-way ANOVA test followed by Tukey's HSD for pairwise comparisons, with Bonferroni adjustment applied.

Kaplan-Meier survival analysis and log-rank testing were performed to compare survival between patients in the prespecified TTI time frames for every stage of each cancer type. Patients diagnosed in 2017 were excluded from survival analyses, as survival information was not available for these patients at the time of the primary analysis. Patients lost to follow up were censored at time lost. $P<0.05$ was considered significant. Multivariable Cox hazards regressions adjusting for age (<65 *vs.* ≥65), sex, year of diagnosis (before or after 2013), race, Hispanic ethnicity, geographic region, facility urbanicity, patient insurance, facility type, and Charlson-Deyo score were performed to estimate hazard ratios associated with each TTI time frame for every stage of all cancer types.

These factors were chosen as covariates because each is either a known prognostic factor for HPB cancer or has been shown to be related to health or healthcare disparities for these tumors (30-34). Age and year of diagnosis were categorized as binary variables. An age cutoff of 65 was chosen as previous studies have demonstrated risk for adverse outcome after treatment of HPB cancers increases beginning at age ≥65 (35-37). Year of diagnosis was included to adjust for evolutions in management and healthcare delivery over time, with the median year of diagnosis [2013] used as a split point.

Sensitivity analyses were conducted to assess the influence of covariate adjustment and TTI categorization on the results of the survival analyses. Results of Cox regressions with progressive covariate adjustment are reported, and the fully-adjusted Cox regression was additionally performed with TTI as a binary variable with split point at TTI of 30 days and again with split point at 60 days.

Linear regression adjusting for the same covariates and additionally for treatment at more than one facility, treatment modality, and cancer type was performed with TTI in days as the continuous dependent variable to identify factors associated with TTI.

For all analyses, cases with missing data were excluded by listwise deletion on an analysis-by-analysis basis, as most variables had fewer than 5% of values missing. Data were analyzed using IBM SPSS Statistics, version 26 (IBM Corporation, Armonk, New York) and RStudio, version 1.4.1717 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population characteristics

During the study period, there were 737,400 HPB cancer cases. After exclusion criteria were applied (Figure S1), 318,931 patients were left for analysis: 23,934 with EHBD

cholangiocarcinoma or adenocarcinoma, 180,714 with pancreatic adenocarcinoma or ductal carcinoma, 98,515 with hepatocellular cancer (HCC), and 15,768 with intrahepatic bile duct (IHBD) cholangiocarcinoma or adenocarcinoma.

Patient and treatment facility characteristics of each TTI cohort are reported in *Table 1*. In the study population, 48.6% of patients were treated within 3 to 30 days, 31.6% in 31 to 60 days, 10.9% in 61 to 90 days, and 8.8% in >90 days. The proportions treated in each time frame varied by cancer type (Table S2). Median TTI was 31 days (IQR, 18–49 days) for EHBD cancer, 26 days (IQR, 16–40 days) for pancreatic cancer, 48 days (IQR, 28–79 days) for HCC, and 37 days (IQR, 22–58 days) for IHBD cancer. Mean follow up for the cohort was 21.6 months, and was longer for patients with longer TTI.

Some characteristics were observed to have stepwise lower representation with each increase in TTI (i.e., were overrepresented in the early treatment groups), such as White race (84%, 82%, 79%, 75%, respectively), treatment in a comprehensive (33%, 27%, 25%, 20%) or a network (14%, 13%, 12%, 11%) facility, Charlson-Deyo score 0 (66%, 63%, 58%, 55%), and treatment with chemotherapy only (50%, 48%, 45%, 43%) or with combination therapy (33%, 31%, 25%, 21%) (*Table 1*). In contrast, other characteristics had a stepwise higher representation with each increase in TTI (i.e., were overrepresented in the delayed treatment groups), including Hispanic ethnicity (6%, 7%, 10%, 13%), median income <$38,000 (17%, 18%, 20%, 22%), treatment at an academic facility (48%, 55%, 59%, 66%), Charlson-Deyo score of 3 or greater (5%, 7%, 10%, 13%), and treatment with surgery only (11%, 14%, 17%, 21%) or radiation only (3%, 6%, 11%, 13%). All pairwise differences in proportions between each TTI group for the above variables were statistically significant.

Trends over time

Temporal trends for TTI by cancer type, cancer stage, facility type, and treatment modality were examined in *Figure 1*. Median TTI was persistently longest over the years studied for liver cancer, stage I disease, treatment at an academic facility, and treatment with radiation only. A general trend of increasing median TTI from 2004 to 2017 for all patients was observed, and was most pronounced for liver cancer (median of 42 days in 2004 *vs.* 52 days in 2017, P<0.001), stage I cancer (35 *vs.* 47 days, P<0.001) and treatment with radiation only (33 *vs.* 61 days, P<0.001).

Survival

Kaplan-Meier survival analysis was performed for every stage of each cancer, stratified by the predefined TTI groups. For stage I EHBD cancer, there was a stepwise significant (pairwise log-rank P<0.005 for each step) decrease in survival associated with each increase in TTI for the first three TTI periods: median overall survivals for TTI 3–30, 31–60, 61–90, and >90 days were 51.5, 34.9, 25.4, and 22.0 months, respectively (*Figure 2A*). The decrease in survival between the third and fourth TTI periods did not reach statistical significance (P=0.191). A stepwise significant (P<0.05 for each step) decrease in survival was also observed for the first three TTI periods for stage II and III EHBD cancer (median survivals 27.4, 25.2, 23.6 months and 20.3, 18.1, 16.8 months, respectively) (*Figure 2B,2C*). There was a reversal of trend for stage IV EHBD cancer, with longer TTI associated with increased survival (*Figure 2D*).

For stage I pancreatic cancer, median overall survival was significantly (P<0.01) longer for patients who were treated within 3–30 *vs.* 31–60 and 61–90 days (18.8, 16.6, and 15.2 months, respectively) (*Figure 3A*). This trend also held true for stage II pancreatic cancer, with median survival of the first three TTI groups of 16.9, 16.2, and 15.6 months, respectively. Survival differences between TTI groups for other stages of pancreatic cancer and for all stages of hepatocellular and IHBD cancer were not clinically significant, or there was an increase in survival with longer TTI (*Figure 3*, Figures S2,S3).

Multivariable Cox proportional hazards regressions were performed to determine the magnitude of association between TTI group and survival, adjusting for ten clinical and demographic factors (see *Methods*). TTI of 3–30 days was used as the reference group; results are reported in *Table 2*. Hazard ratios were significant and greater than one for all TTI groups of stages I–III EHBD cancer except for TTI >90 days for stage II, which was greater than one but did not reach significance (P=0.055). Hazard ratios were also significant and greater than one for stage I and II pancreatic cancer for TTI 31–60 and 61–90 days.

The robustness of these survival associations was confirmed by sensitivity analyses (Tables S3-S7), which had similar results. In some models, the hazard ratio associated with TTI >90 days for stage II EHBD cancer was statistically significant. Results were also similar when TTI was considered as a binary variable, whether delayed treatment was defined as >30 or >60 days (Table S7).

Table 1 Patient and treatment facility characteristics for all subjects stratified by time to treatment

Characteristics	Time to treatment initiation (days)				Total (n=318,931)
	3–30 (n=155,126)	31–60 (n=100,849)	61–90 (n=34,788)	91+ (n=28,168)	
Age (years), mean ± SD	65.2±11.0[a]	65.9±10.8[b]	65.6±10.7[c]	63.8±10.3[d]	65.3±10.9
Sex (male), n [%]	88,657 [57][a]	60,015 [60][b]	22,565 [65][c]	19,415 [69][d]	190,652 [60]
Race, n [%]					
White	128,875 [84][a]	81,348 [82][b]	27,081 [79][c]	20,992 [75][d]	258,296 [82]
Black	16,838 [11][a]	12,671 [13][b]	4,946 [14][c]	4,578 [16][d]	39,033 [12]
Other	7,913 [5][a]	5,849 [6][b]	2,423 [7][c]	2,287 [8][d]	18,472 [6]
Unknown	1,500 [1]	981 [1]	338 [1]	311 [1]	3,130 [1]
Ethnicity, n [%]					
Hispanic	9,039 [6][a]	7,036 [7][b]	3,206 [10][c]	3,534 [13][d]	22,815 [7]
Non-Hispanic	139,194 [94][a]	89,987 [93][b]	30,338 [90][c]	23,694 [87][d]	283,213 [93]
Unknown	6,893 [4]	3,826 [4]	1,244 [4]	940 [3]	12,903 [4]
Facility location, n [%]					
Northeast	33,199 [22][a]	23,713 [24][b]	7,783 [23][c]	6,337 [23][c]	71,032 [23]
South	56,429 [37][a]	35,757 [36][b]	12,614 [37][a,b]	10,049 [36][b]	114,849 [37]
Midwest	41,928 [27][a]	24,222 [24][b]	7,620 [22][c]	5,221 [19][d]	78,991 [25]
West	21,323 [14][a]	15,939 [16][b]	6,431 [19][c]	6,286 [23][d]	49,979 [16]
Unknown	2,247 [1]	1,218 [1]	340 [1]	275 [1]	4,080 [1]
Facility county, n [%]					
Metropolitan	126,856 [85][a]	82,894 [85][b]	28,880 [86][c]	23,681 [87][d]	262,311 [85]
Urban	20,254 [14][a]	12,827 [13][a]	4,215 [13][b]	3,146 [12][c]	40,442 [13]
Rural	2,689 [2][a]	1,553 [2][b]	485 [1][b,c]	336 [1][c]	5,063 [2]
Unknown	5,327 [3]	3,575 [4]	1,208 [4]	1,005 [4]	11,115 [4]
Median income, n [%]					
<$38,000	24,676 [17][a]	17,073 [18][b]	6,518 [20][c]	5,761 [22][d]	54,028 [18]
$38,000–$47,999	32,950 [23][a]	21,931 [23][b]	7,796 [24][c]	6,148 [24][b,c]	68,825 [23]
$48,000–$62,999	39,060 [27][a]	25,190 [27][a]	8,529 [27][a]	6,831 [26][a]	79,610 [27]
≥$63,000	49,832 [34][a]	29,732 [32][b]	9,330 [29][c]	7,143 [28][d]	96,037 [32]
Unknown	8,608 [6]	6,923 [7]	2,615 [8]	2,285 [8]	20,431 [6]
No high school degree, n [%]					
>21.0%	23,980 [16][a]	16,836 [18][b]	6,822 [21][c]	6,363 [25][d]	54,001 [18]
13.0–20.9%	36,420 [25][a]	24,704 [26][b]	8,763 [27][c]	7,277 [28][c]	77,164 [26]
7.0–12.9%	47,744 [33][a]	30,801 [33][a]	10,123 [32][b]	7,598 [29][c]	96,266 [32]
<7.0%	38,455 [26][a]	21,626 [23][b]	6,479 [20][c]	4,661 [18][d]	71,221 [24]
Unknown	8,527 [6]	6,882 [7]	2,601 [8]	2,269 [8]	20,279 [6]

Table 1 (*continued*)

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Characteristics	Time to treatment initiation (days)				Total (n=318,931)
	3–30 (n=155,126)	31–60 (n=100,849)	61–90 (n=34,788)	91+ (n=28,168)	
Insurance, n [%]					
None	4,558 [3][a]	2,653 [3][b]	1,095 [3][a]	1,065 [4][c]	9,371 [3]
Private	58,399 [38][a]	34,108 [35][b]	10,862 [32][c]	8,894 [32][c]	112,263 [36]
Government	89,014 [59][a]	61,804 [63][b]	22,105 [65][c]	17,659 [64][c]	190,582 [61]
Unknown	3,155 [2]	2,284 [2]	726 [2]	550 [2]	6,715 [2]
Facility type, n [%]					
Community	8,745 [6][a]	5,038 [5][b]	1,486 [4][c]	981 [4][d]	16,250 [5]
Comprehensive	50,035 [33][a]	27,334 [27][b]	8,432 [25][c]	5,508 [20][d]	91,309 [29]
Academic	73,146 [48][a]	54,531 [55][b]	20,415 [59][c]	18,320 [66][d]	166,412 [53]
Network	20,953 [14][a]	12,728 [13][b]	4,115 [12][c]	3,084 [11][d]	40,880 [13]
Unknown	2,247 [1]	1,218 [1]	340 [1]	275 [1]	4,080 [1]
Year of diagnosis, n [%]					
2004–2012	81,361 [52][a]	48,403 [48][b]	16,551 [48][b]	13,372 [48][b]	159,687 [50]
2013–2017	73,765 [48][a]	52,446 [52][b]	18,237 [52][b]	14,796 [53][b]	159,244 [50]
Charlson-Deyo score, n [%]					
0	101,645 [66][a]	63,187 [63][b]	20,213 [58][c]	15,473 [55][d]	200,518 [63]
1	36,650 [24][a]	23,813 [24][a]	8,280 [24][a]	6,592 [23][a]	75,335 [24]
2	9,336 [6][a]	6,989 [7][b]	2,900 [8][c]	2,472 [9][c]	21,697 [7]
3+	7,495 [5][a]	6,860 [7][b]	3,395 [10][c]	3,631 [13][d]	21,281 [7]
Treatment at >1 CoC facility, n [%]					
Yes	30,725 [20][a]	22,740 [23][b]	7,739 [22][b]	5,664 [20][a]	66,868 [21]
No	124,401 [80][a]	78,109 [77][b]	27,049 [78][b]	22,504 [80][a]	252,063 [79]
Primary surgery only, n [%]					
Yes	16,706 [11][a]	14,022 [14][b]	5,832 [17][c]	5,829 [21][d]	42,389 [13]
No	135,820 [89][a]	85,489 [86][b]	28,579 [83][c]	22,020 [79][d]	271,908 [87]
Unknown	2,600 [2]	1,338 [1]	377 [1]	319 [1]	4,634 [2]
Radiation only, n [%]					
Yes	4,335 [3][a]	5,424 [6][b]	3,648 [11][c]	3,478 [13][d]	16,885 [5]
No	147,731 [97][a]	93,678 [94][b]	30,552 [89][c]	24,247 [87][d]	296,208 [95]
Unknown	3,060 [2]	1,747 [2]	588 [2]	443 [2]	5,838 [2]
Chemotherapy only, n [%]					
Yes	75,900 [50][a]	46,871 [48][b]	15,205 [45][c]	11,779 [43][d]	149,755 [48]
No	75,574 [50][b]	51,825 [52][b]	18,869 [55][c]	15,784 [57][d]	162,052 [52]
Unknown	3,652 [2]	2,153 [2]	714 [2]	605 [2]	7,124 [2]

Table 1 (*continued*)

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Characteristics	Time to treatment initiation (days)				Total (n=318,931)
	3–30 (n=155,126)	31–60 (n=100,849)	61–90 (n=34,788)	91+ (n=28,168)	
Combination therapy[e], n [%]					
Yes	51,585 [33][a]	30,964 [31][b]	8,776 [25][c]	5,967 [21][d]	97,292 [31]
No	102,803 [67][a]	69,544 [69][b]	25,920 [75][c]	22,135 [79][d]	220,402 [69]
Unknown	738 (0.5)	341 (0.3)	92 (0.3)	66 (0.2)	1,237 (0.4)
Follow-up (months), mean ± SD	18.8±24.0[a]	21.9±25.0[b]	25.4±26.4[c]	31.4±29.3[d]	21.6±25.4

All variables had a significant omnibus test, indicating at least one TTI group had a different distribution for every variable. Percentages represent valid percentages (i.e., denominators exclude cases with unknown values). [a,b,c,d], results of pairwise comparisons; proportions in the same row with the same superscript are not statistically different from one another at alpha =0.05 corrected for multiple comparisons with Bonferroni adjustment; [e], combination therapy = utilization of more than one of the following: surgery, radiation, chemotherapy. SD, standard deviation; CoC, Commission on Cancer.

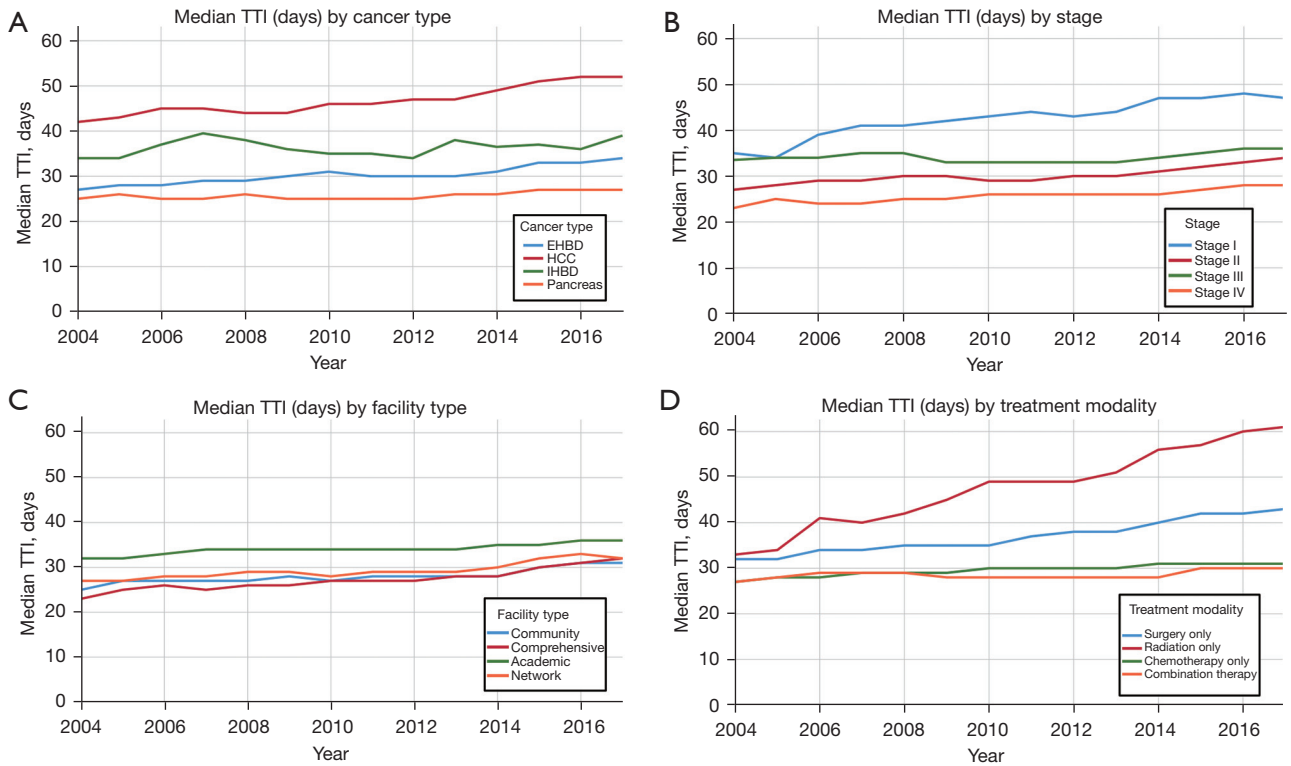

Figure 1 Time to treatment initiation in days from 2004 to 2017 stratified by cancer type (A), cancer stage (B), treatment facility type (C), and treatment modality (D). TTI, time to treatment initiation; EHBD, extrahepatic bile duct; HCC, hepatocellular carcinoma; IHBD, intrahepatic bile duct.

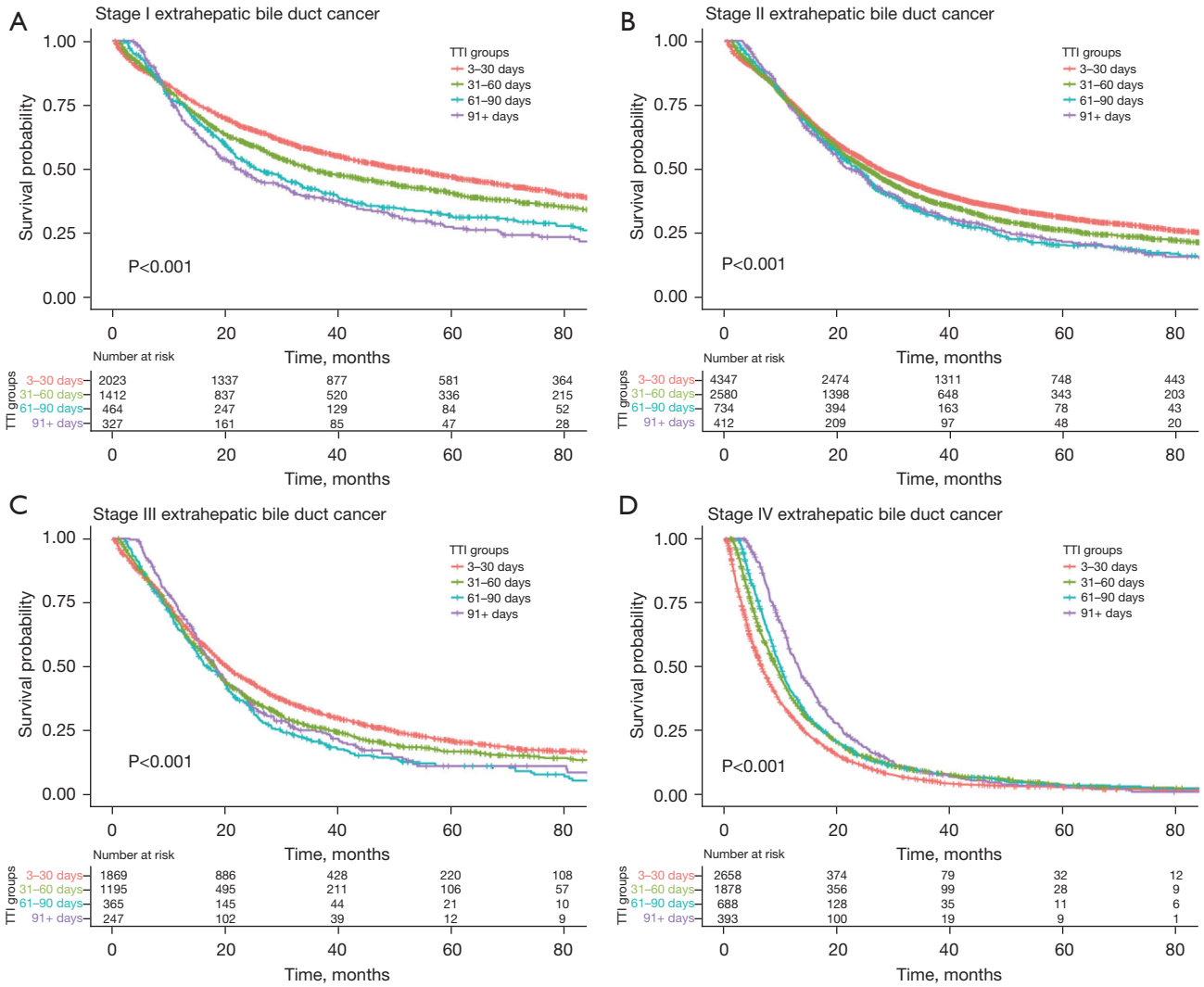

Figure 2 Kaplan-Meier survival analysis for patients with stage I (A), II (B), III (C), and IV (D) extrahepatic bile duct cholangiocarcinoma or adenocarcinoma, stratified by time from diagnosis to initiation of definitive therapy. P values calculated by log-rank test. TTI, time to treatment initiation.

Predictors of TTI

Multivariable linear regression was performed against TTI in days for all cancer types in order to determine clinical and demographic predictors of longer TTI (*Table 3*). Regression coefficient estimates were largest in magnitude for cancer type, with liver cancer associated with the longest TTI (β=+22.2 days *vs.* pancreatic cancer). Treatment modality was the next strongest predictor, with treatment by radiation only associated with the greatest increase in TTI (β=+13.9 days *vs.* treatment with a non-radiation modality or combination therapy). Other factors with significant impacts on TTI were stage IV disease (β=–13.7 days *vs.* stage I), Black race (β=+4.6 days *vs.* White race), Hispanic ethnicity (β=+4.3 days), and treatment at more than one facility (β=+4.1 days).

Discussion

This study in a national cohort investigating the association of TTI with outcomes of patients with HPB cancers found a significant negative association of longer TTI with overall survival for stages I–III EHBD cancer and stages I and II pancreatic cancer. Underscoring this finding, patients with

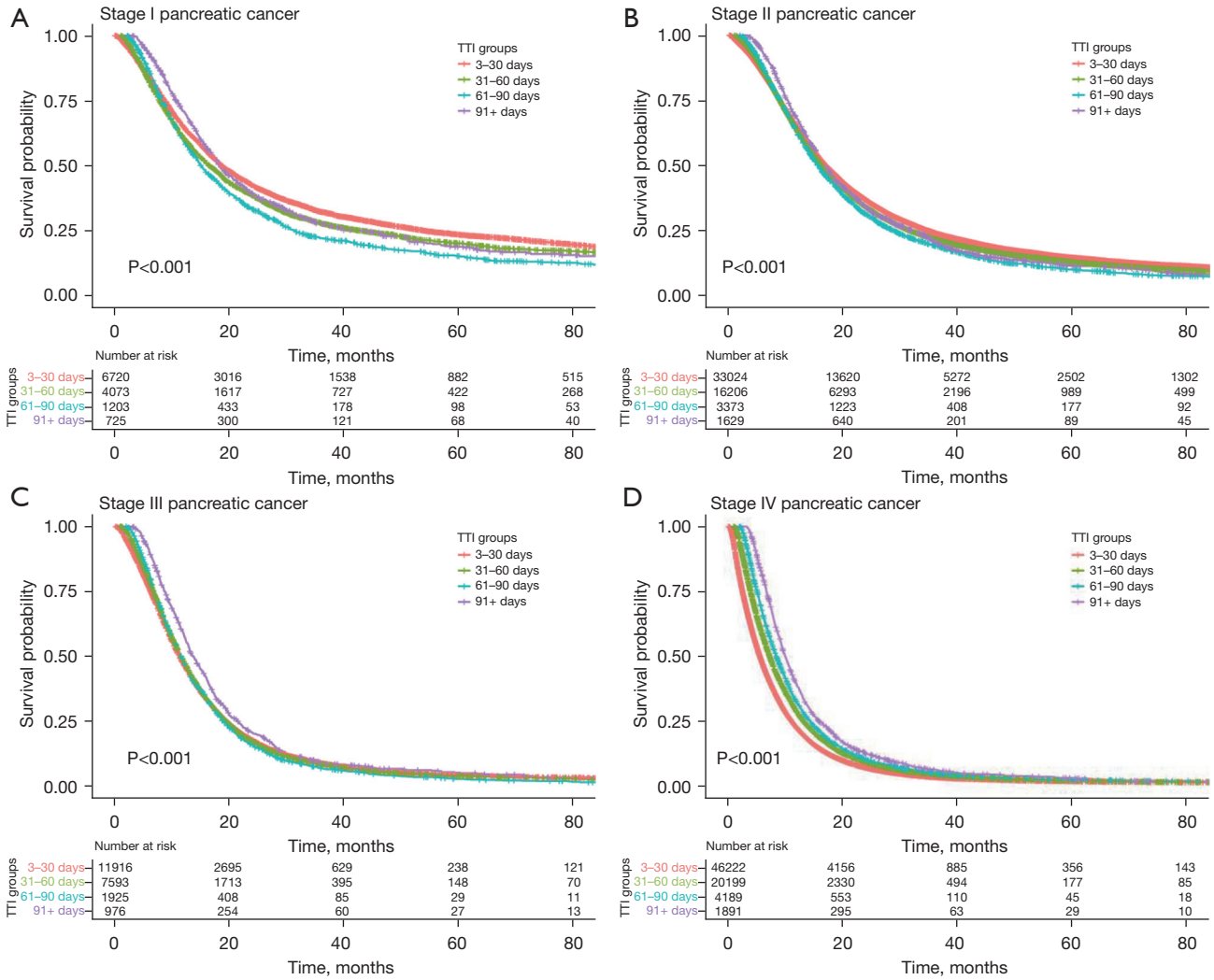

Figure 3 Kaplan-Meier survival analysis for patients with stage I (A), II (B), III (C), and IV (D) pancreatic adenocarcinoma, stratified by time from diagnosis to initiation of definitive therapy. P values calculated by log-rank test. TTI, time to treatment initiation.

stage I EHBD cancer who started treatment within 3 to 30 days had a median survival that was more than twice as long as those treated within 61 to 90 days (51.5 *vs.* 25.4 months, P<0.001). Moreover, TTI and survival exhibited a dose-response relationship for all stages I–III EHBD cancer. Even after adjusting for differences in the populations treated within each time frame, the hazard ratios for mortality associated with longer TTI remained significant for early stage EBHD and pancreatic cancer, and increased with each additional delay.

To our knowledge, this is the first study to describe the association of delay in treatment with worse survival for EHBD cancer patients. As we hypothesized, this may be attributable to the aggressiveness of the cancer's biology, such that even a month's delay in care leads to progression of disease and worsening of outcomes. It is also possible that a subset of poor prognosis patients, such as those with refractory obstructive jaundice, see longer treatment delays due to prolonged efforts to optimize the patient prior to surgery. For example, patients with complex disease extending into the intrahepatic ducts may require repeated endoscopic and percutaneous biliary tract interventions and referral to an academic center. Data from this study support coordination of complex care as a contributing factor to delayed treatment for at least the subset of patients treated between 31 and 90 days, given that this group had a higher rate of treatment at more than one facility compared to those treated within 30 days or after 90 days. These patients

Table 2 Cox proportional hazard ratios for overall survival with 95% confidence intervals associated with each TTI group

Cancer type and stage	Time to treatment initiation (days)			
	3–30	31–60	61–90	91+
EHBD				
Stage I	REF	1.17 (1.07–1.29)*	1.39 (1.21–1.59)*	1.63 (1.40–1.90)*
Stage II	REF	1.07 (1.00–1.14)*	1.17 (1.06–1.29)*	1.14 (1.00–1.29)
Stage III	REF	1.12 (1.02–1.22)*	1.37 (1.20–1.57)*	1.21 (1.03–1.42)*
Stage IV	REF	0.79 (0.74–0.84)*	0.74 (0.67–0.81)*	0.61 (0.54–0.68)*
Pancreas				
Stage I	REF	1.08 (1.03–1.13)*	1.19 (1.11–1.28)*	0.99 (0.90–1.09)
Stage II	REF	1.05 (1.02–1.07)*	1.09 (1.04–1.13)*	1.02 (0.97–1.09)
Stage III	REF	0.98 (0.94–1.01)	0.98 (0.92–1.03)	0.81 (0.75–0.87)
Stage IV	REF	0.81 (0.79–0.82)*	0.70 (0.67–0.72)*	0.60 (0.57–0.63)*
Liver				
Stage I	REF	0.93 (0.90–0.97)*	0.94 (0.90–0.99)*	0.89 (0.85–0.93)*
Stage II	REF	0.92 (0.88–0.96)*	0.91 (0.86–0.95)*	0.82 (0.78–0.86)*
Stage III	REF	0.81 (0.78–0.84)*	0.68 (0.65–0.72)*	0.58 (0.55–0.61)*
Stage IV	REF	0.69 (0.66–0.73)*	0.55 (0.52–0.59)*	0.45 (0.42–0.49)*
IHBD				
Stage I	REF	0.94 (0.81–1.09)	0.94 (0.89–1.12)	1.18 (0.98–1.41)
Stage II	REF	0.78 (0.69–0.89)*	0.84 (0.72–0.98)*	0.68 (0.56–0.81)*
Stage III	REF	0.88 (0.77–1.00)*	0.98 (0.82–1.16)	0.67 (0.54–0.83)*
Stage IV	REF	0.77 (0.73–0.82)*	0.68 (0.62–0.74)*	0.64 (0.56–0.72)*

*, P value <0.05. Covariates included in hazard regression: age (<65 *vs.* ≥65), sex, year of diagnosis (before or after 2013), race, Hispanic ethnicity, geographic region, facility urbanicity, patient insurance, facility type, and Charlson-Deyo score. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

can also be expected to be more surgically challenging and may be less likely to have an R0 resection, more likely to suffer a complication of treatment, and more likely to die. Moreover, any progression in these patients with complex disease is likely to have an outsized impact on their outcome, and may make a negative margin resection even more challenging.

With respect to the current literature, our EHBD cancer results stand in contrast to a study in a related population, which retrospectively reviewed 355 patients with periampullary adenocarcinoma and found that timing of resection was not associated with survival (9). Regarding pancreatic adenocarcinoma, the results of our study corroborate existing evidence that prompt treatment of early stage disease is associated with slightly improved survival, on the order of 1–3 months (1,38), while timing of treatment for late-stage disease is of lesser or no importance (1,10,12). This finding is possibly attributable to low overall survival rates for patients with late-stage pancreatic cancer regardless of therapy (25).

Notably, for metastatic EHBD and pancreatic cancer—in addition to all stages of HCC and IHBD cancer—longer TTI was largely associated with longer survival. This seemingly paradoxical finding of lower mortality with longer delay in treatment has been retrospectively demonstrated before in non-small cell lung cancer (39,40). This observation is likely due to a selection bias amongst clinicians favoring expedited treatment for patients with

Table 3 Predictors of time to treatment for all cancers (Linear regression)

Patient or facility characteristic	B coefficient (days)	95% CI	P value
Age, ≥65	–2.9	–3.2 to –2.6	<0.001
Sex, female	–0.3	–0.5 to 0.02	0.074
Year of diagnosis, 2013–2017	+0.7	0.4 to 1.0	<0.001
Race			
White	REF	REF	REF
Black	+4.6	4.2 to 5.1	<0.001
Other	–1.5	–2.1 to –0.9	<0.001
Hispanic ethnicity	+4.3	3.8 to 4.8	<0.001
Location			
Northeast	REF	REF	REF
South	–1.7	–2.0 to –1.3	<0.001
Midwest	–3.2	–3.6 to –2.8	<0.001
West	+4.0	3.6 to 4.5	<0.001
Urbanicity			
Metropolitan	REF	REF	REF
Urban	+0.2	–0.2 to 0.6	0.252
Rural	–0.2	–1.3 to 0.8	0.672
Insurance			
None	REF	REF	REF
Private	–1.8	–2.6 to –1.0	<0.001
Government	+1.9	1.1 to 2.7	<0.001
Facility			
Community	REF	REF	REF
Comprehensive	–1.7	–2.3 to –1.1	<0.001
Academic	+3.1	2.5 to 3.7	<0.001
Network	–1.3	–2.0 to –0.6	<0.001
Charlson-Deyo score			
0	REF	REF	REF
1	+0.3	–0.0 to 0.6	0.052
2	+1.7	1.2 to 2.2	<0.001
3+	+2.9	2.4 to 3.5	<0.001
Stage			
I	REF	REF	REF
II	–5.7	–6.1 to –5.3	<0.001
III	–8.6	–9.1 to –8.2	<0.001
IV	–13.7	–14.2 to –13.2	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Patient or facility characteristic	B coefficient (days)	95% CI	P value
Cancer type			
Pancreas	REF	REF	REF
Liver	+22.2	21.8 to 22.6	<0.001
IHBD	+12.6	11.9 to 13.2	<0.001
EHBD	+5.5	4.9 to 6.0	<0.001
Treatment >1 CoC facility	+4.1	3.7 to 4.4	<0.001
Primary surgery only	+1.0	–0.1 to 2.2	0.075
Radiation only	+13.9	12.7 to 15.1	<0.001
Chemotherapy only	+3.7	2.6 to 4.8	<0.001
Combination therapy[a]	–1.4	–2.5 to –0.3	0.014

[a], combination therapy = utilization of more than one of the following: surgery, radiation, chemotherapy. REF, reference group; CI, confidence interval; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct; CoC, Commission on Cancer.

features of more aggressive disease, such as high symptom burden, such that patients triaged for early treatment may be those with the most concerning presentations and worst prognoses. In this setting, any negative survival impact due to a delay in care must necessarily overcome the survival disparity introduced by clinician triage in order to be retrospectively observed. Although more detailed clinical information would be helpful in further clarifying the impact of TTI on survival in HCC and IHBD cancer, the results of this study demonstrate that clinicians currently triage these patients effectively such that those treated in a delayed fashion have outcomes comparable to patients with similar disease burden treated more expeditiously. This also appears to be the case for metastatic EHBD and pancreatic cancer—but for earlier stages of these two diseases, the patients who are treated first have the best outcomes; thus, TTI in early stages of these cancers may have a sufficiently strong impact on survival to overcome the effect of clinician triage. This finding warrants further investigation.

With respect to the current literature, these findings are novel. The association of treatment timing with outcomes has not been previously studied in IHBD cancer. In liver cancer, a single retrospective analysis of 267 patients found a TTI of greater than 3 months to be associated with worse survival (18).

Trends and predictors of TTI

Our study also draws attention to national trends in TTI and to factors associated with longer TTI for patients with HPB cancer. One major finding from our study is that time to treatment differs significantly by patient race and ethnicity, with Black race and Hispanic ethnicity associated with delays in care. In fact, Hispanic patients represented more than 1 in 8 patients starting treatment after 90 days, compared to less than 1 in 16 patients starting treatment within 30 days. This finding reinforces previous observations of racial and ethnic disparities in the presentation, treatment, and survival of patients with HPB cancer (41-43), and identifies a possible target for interventions aimed at combating outcomes disparities in cancer care. Cancer treatment centers should work to study and address obstacles to expedient care that disproportionately affect the minority patient populations seeking treatment at their institution.

Early stage disease was also associated with significantly longer TTI than late stage disease. This finding is intuitively explained by the typical treatment pathways for these populations: work up and management decisions for early stage disease often require multidisciplinary evaluation and planning, whereas treatment options for late stage disease tend to be limited and management directed primarily by one specialist. Furthermore, patients with later stage disease may be more symptomatic, thereby adding a level of urgency to their therapy.

To a lesser degree, insurance status and facility type were also found to be predictors of TTI. Private insurance was found to be associated with significantly shorter TTI than

not having insurance. This reflects previously described insurance-related disparities in quality of cancer care (44,45), and represents another possible target population for access interventions. Last, treatment at an academic center was associated with longer TTI, but this is likely attributable to referral patterns and differences in patient population: academic institutions may serve as the treating facility for patients diagnosed at other hospitals, particularly the most complex patients, given the highly specialized care required for the treatment of many HPB tumors.

In examining national trends, one noteworthy finding of our study is that time to initiation of radiation monotherapy increased by nearly 80% between 2004 and 2017. This finding may represent a deprioritization of radiation in the management of HPB cancers over time, as gemcitabine- and FOLFIRINOX-based chemotherapy regimens have increased response rates to systemic therapy and taken center stage. Given the lesser role of radiation in the curative treatment of HPB cancers, this observation may also represent a trend related to longer postponements of palliative intervention.

Limitations

Our study has several limitations. First, this was a retrospective study, and the timeline for initiation of definitive oncologic care is influenced by a wide variety of individual patient and facility factors, many of which were not possible to control for in this analysis. For example, a delay in treatment initiation may be facility-driven due to limited resources such as operating room availability; provider-driven to allow time for optimization of patient comorbidities; or patient-driven due to difficulty with transportation, receiving time off work, low health literacy, scheduling conflicts, or other health circumstances. Some of these factors affecting timing of care might also be independent predictors of outcome and therefore bias our results. Intrinsic limitations to the NCDB also apply to our study, including inability to assess for non-reported outcomes (e.g., cancer-specific survival) and control for non-reported variables (e.g., patient symptoms, prior surgery, serum albumin). The NCDB also does not capture all cancer diagnoses in the United States, but does capture more than two-thirds, allowing for inclusion in this study of men and women and a wide range of ages, geographic location, income, and types of treatment facilities, increasing the external validity of these results. Last, the data analyzed in this study are from prior to the COVID-19 pandemic, and therefore conclusions about delays in treatment in this cohort may not be generalizable to delays in treatment due to the COVID-19 pandemic.

Conclusions

Longer time to initiation of definitive therapy is associated with increased mortality in stage I–III EHBD and stage I and II pancreatic cancer. Some patients, including those with early stage disease, Blacks, and Hispanics, are more likely to experience delayed care. Efforts should be made to better understand these disparities and mitigate them through targeted outreach to those at highest risk for treatment delay. While this retrospective study is unable to support a causative association, the strong and clinically-significant risk-adjusted relationship between delay in care and increased mortality in EHBD cancer compels further investigation. Overall, the findings underscore the importance of timely multidisciplinary evaluation and coordination of care for patients with these high-risk malignancies, and propose TTI as a possible quality metric for HPB cancer centers.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.

amegroups.com/article/view/10.21037/jgo-22-1067/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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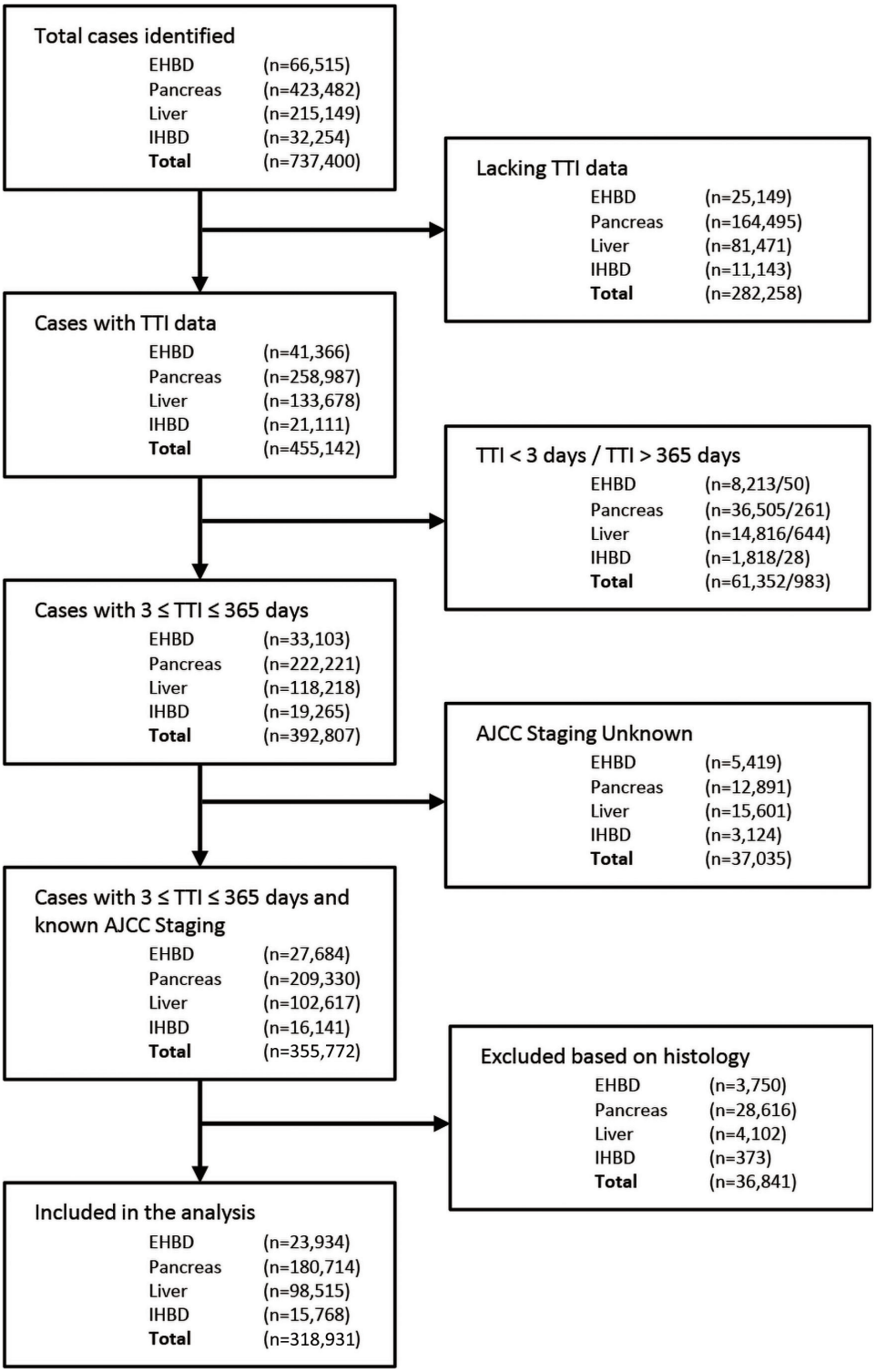

Figure S1 Flow diagram for the inclusion and exclusion of patients in the study.

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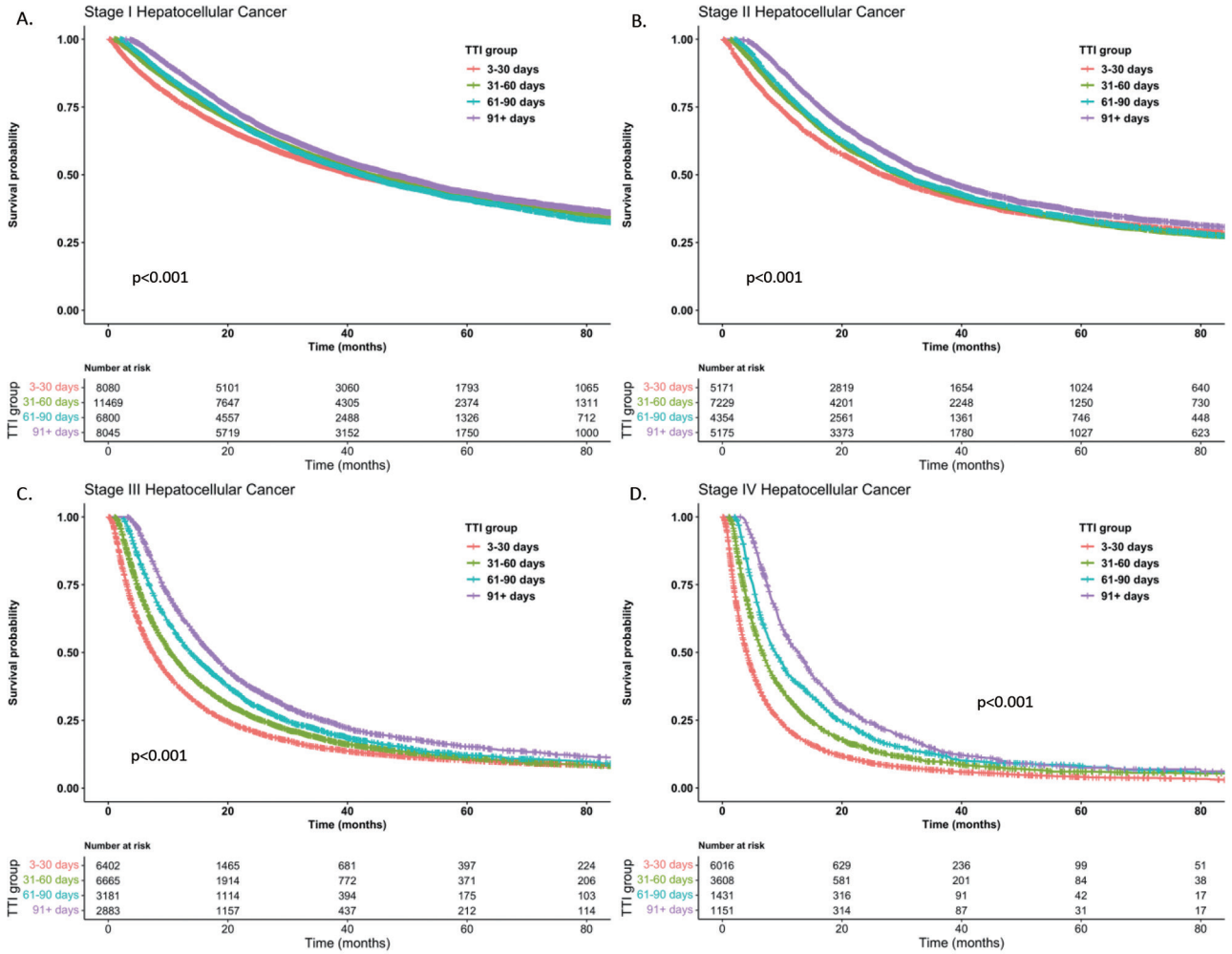

Figure S2 Kaplan-Meier survival analysis for patients with stage I (A), II (B), III (C), and IV (D) hepatocellular carcinoma, stratified by time from diagnosis to initiation of definitive therapy. P values calculated by log-rank test. TTI, time to treatment initiation.

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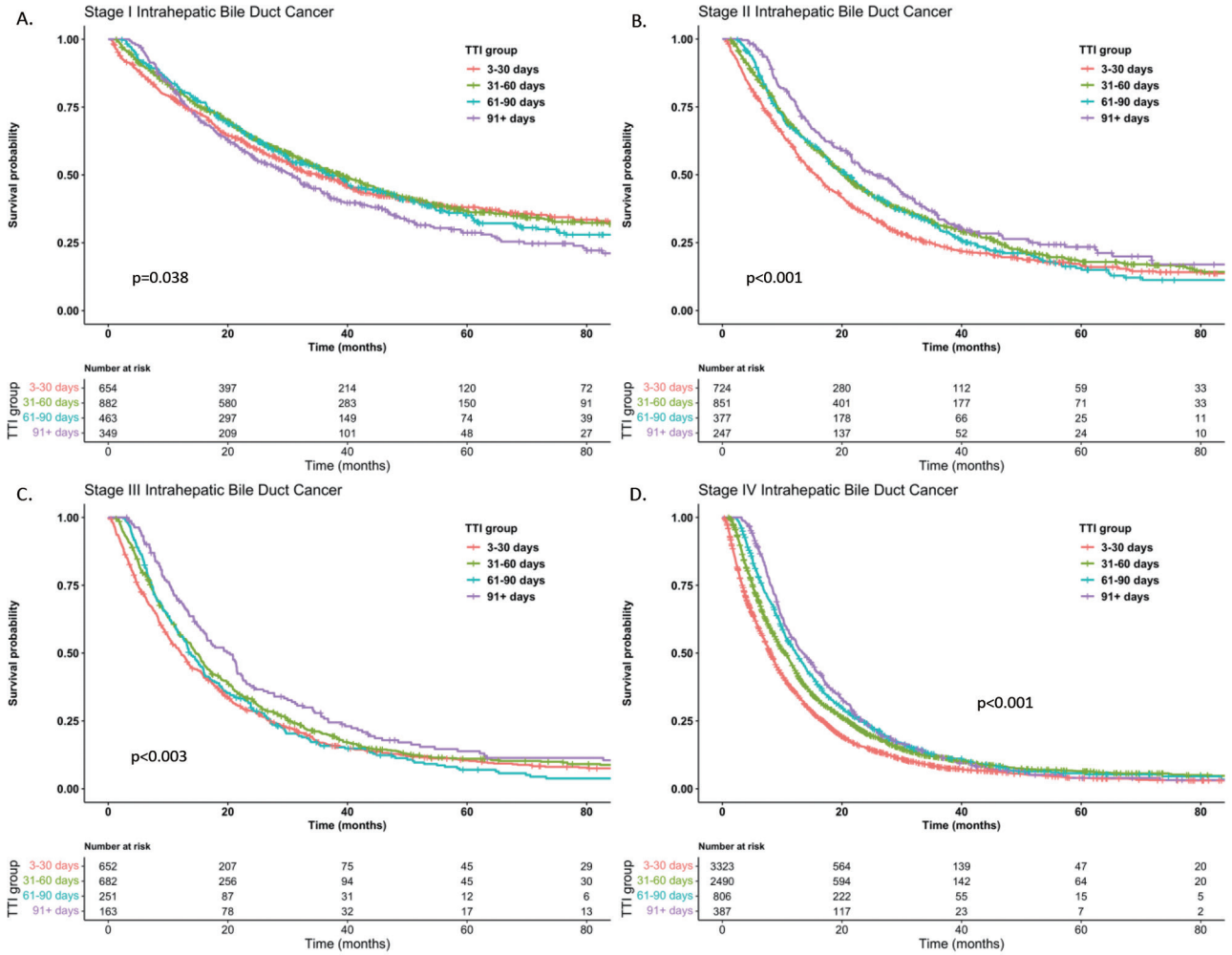

Figure S3 Kaplan-Meier survival analysis for patients with stage I (A), II (B), III (C), and IV (D) intrahepatic bile duct cholangiocarcinoma or adenocarcinoma, stratified by time from diagnosis to initiation of definitive therapy. P values calculated by log-rank test. TTI, time to treatment initiation.

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Table S1 Histology and ICD-10 codes included in each cancer cohort

Cancer type	Included histology codes (SEER ICD-0-3)		Included ICD-10 codes
Extrahepatic bile duct	8140–8147		C24.0 - Malignant neoplasm of extrahepatic bile duct
	8160–8163		C24.1 - Malignant neoplasm of ampulla of Vater
			C24.8 - Malignant neoplasm of overlapping sites of biliary tract
			C24.9 - Malignant neoplasm of biliary tract, unspecified
Pancreas	8450-8455	8140-8148	C25.0 - Malignant neoplasm of head of pancreas
	8470-8471	8210-8211	C25.1 - Malignant neoplasm of body of pancreas
	8480-8481	8260-8263	C25.2 - Malignant neoplasm of tail of pancreas
	8500	8310	C25.3 - Malignant neoplasm of pancreatic duct
	8503	8323	C25.4 - Malignant neoplasm of endocrine pancreas
	8570-8576	8440-8441	C25.7 - Malignant neoplasm of other parts of pancreas
			C25.8 - Malignant neoplasm of overlapping sites of pancreas
			C25.9 - Malignant neoplasm of pancreas, unspecified
Liver	8170-8175		C22.0 - Liver cell carcinoma
Intrahepatic bile duct	8140-8147		C22.1 - Intrahepatic bile duct carcinoma
	8160-8163		

Table S2 Time to treatment initiation by cancer stage

Cancer type and stage	Median TTI in days (IQR)	Number treated in each time frame, n (%)			
		3-30 d	31-60 d	61-90 d	91+ d
EHBD					
Stage I	32 (20–53)	2,202 (47)	1,574 (34)	534 (11)	373 (8)
Stage II	29 (17–46)	4,782 (53)	2,915 (33)	821 (9)	456 (5)
Stage III	30 (17–49)	2,025 (50)	1,323 (33)	409 (10)	270 (7)
Stage IV	32 (20–53)	2,919 (47)	2,095 (34)	789 (13)	447 (7)
All	31 (18–49)	11,928 (50)	7,907 (33)	2,553 (11)	1,546 (7)
Pancreas					
Stage I	29 (19–47)	7,709 (52)	4,794 (32)	1,404 (10)	871 (6)
Stage II	26 (16–40)	36,626 (61)	18,312 (30)	3,778 (6)	1,812 (3)
Stage III	29 (19–44)	13,181 (53)	8,363 (34)	2,080 (8)	1,061 (4)
Stage IV	24 (15–38)	51,287 (64)	22,706 (28)	4,670 (6)	2,060 (3)
All	26 (16–40)	108,803 (60)	54,175 (30)	11,932 (7)	5,804 (3)
Liver					
Stage I	54 (33–87)	8,891 (23)	13,160 (34)	7,843 (20)	9,065 (23)
Stage II	55 (33–88)	5,652 (23)	8,143 (33)	4,962 (20)	5,848 (24)
Stage III	43 (25–70)	6,917 (33)	7,460 (35)	3,628 (17)	3,209 (15)
Stage IV	32 (16–55)	6,674 (49)	4,112 (30)	1,644 (12)	1,307 (10)
All	48 (28–79)	28,134 (29)	32,875 (33)	18,077 (18)	19,429 (20)
IHBD					
Stage I	47 (29–72)	761 (27)	1,038 (37)	557 (20)	423 (15)
Stage II	42 (27–65)	861 (33)	1,028 (39)	446 (17)	304 (12)
Stage III	38 (23–58)	687 (37)	740 (40)	263 (14)	173 (9)
Stage IV	33 (21–50)	3,952 (47)	3,086 (36)	960 (11)	489 (6)
All	37 (22–58)	6,261 (40)	5,892 (37)	2,226 (14)	1,389 (9)

TTI, time to treatment initiation; IQR, interquartile range; d, days; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

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Table S3 Cox proportional hazards regression for overall survival sensitivity analysis: unadjusted model

Cancer type and stage	Time to treatment initiation (days)			
	3-30	31-60	61-90	>90
EHBD				
Stage I	REF	1.19 [1.08–1.30]*	1.44 [1.27–1.63]*	1.61 [1.39–1.86]*
Stage II	REF	1.11 [1.04–1.17]*	1.25 [1.14–1.37]*	1.22 [1.09–1.38]*
Stage III	REF	1.15 [1.06–1.25]*	1.32 [1.17–1.50]*	1.19 [1.02–1.38]*
Stage IV	REF	0.78 [0.73–0.83]*	0.73 [0.67–0.80]*	0.61 [0.54–0.68]*
Pancreas				
Stage I	REF	1.12 [1.07–1.17]*	1.25 [1.16–1.33]*	1.02 [0.94–1.12]
Stage II	REF	1.06 [1.04–1.08]*	1.14 [1.10–1.18]*	1.03 [0.98–1.09]
Stage III	REF	0.99 [0.96–1.02]	1.02 [0.97–1.07]	0.84 [0.79–0.90]*
Stage IV	REF	0.81 [0.80–0.82]*	0.72 [0.70–0.74]*	0.62 [0.59–0.65]*
Liver				
Stage I	REF	0.96 [0.92–0.99]*	0.97 [0.93–1.02]	0.87 [0.84–0.91]*
Stage II	REF	0.95 [0.91–0.99]*	0.93 [0.88–0.98]*	0.82 [0.78–0.86]*
Stage III	REF	0.82 [0.79–0.85]*	0.69 [0.66–0.73]*	0.59 [0.56–0.62]*
Stage IV	REF	0.70 [0.67–0.73]*	0.56 [0.53–0.60]*	0.46 [0.43–0.49]*
IHBD				
Stage I	REF	0.93 [0.81–1.06]	0.99 [0.85–1.16]	1.17 [0.99–1.37]
Stage II	REF	0.83 [0.74–0.92]*	0.86 [0.74–0.99]*	0.70 [0.59–0.83]*
Stage III	REF	0.88 [0.79–0.99]*	0.97 [0.83–1.13]	0.72 [0.60–0.86]*
Stage IV	REF	0.79 [0.75–0.84]*	0.71 [0.65–0.77]*	0.66 [0.59–0.74]*

*, P value <0.05. Covariates included in hazard regression: none. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

Table S4 Cox proportional hazards regression for overall survival sensitivity analysis: adjusted for patient factors only

Cancer type and stage	Time to treatment initiation (days)			
	3-30	31-60	61-90	>90
EHBD				
Stage I	REF	1.13 [1.03–1.24]*	1.34 [1.17–1.53]*	1.54 [1.33–1.79]*
Stage II	REF	1.06 [1.00–1.13]	1.18 [1.07–1.30]*	1.13 [1.00–1.29]*
Stage III	REF	1.12 [1.03–1.22]*	1.31 [1.15–1.50]*	1.19 [1.02–1.39]*
Stage IV	REF	0.77 [0.72–0.82]*	0.72 [0.65–0.78]*	0.59 [0.52–0.66]*
Pancreas				
Stage I	REF	1.08 [1.03–1.13]*	1.19 [1.11–1.28]*	0.98 [0.90–1.08]
Stage II	REF	1.04 [1.02–1.06]*	1.10 [1.06–1.15]*	1.01 [0.95–1.07]
Stage III	REF	0.99 [0.96–1.02]	1.01 [0.96–1.06]	0.84 [0.78–0.90]*
Stage IV	REF	0.80 [0.79–0.82]*	0.71 [0.68–0.73]*	0.61 [0.58–0.64]*
Liver				
Stage I	REF	0.93 [0.89–0.96]*	0.94 [0.90–0.98]*	0.88 [0.84–0.92]*
Stage II	REF	0.92 [0.88–0.96]*	0.89 [0.85–0.94]*	0.81 [0.77–0.85]*
Stage III	REF	0.81 [0.78–0.84]*	0.68 [0.65–0.71]*	0.58 [0.55–0.61]*
Stage IV	REF	0.69 [0.66–0.73]*	0.55 [0.52–0.59]*	0.45 [0.42–0.49]*
IHBD				
Stage I	REF	0.91 [0.79–1.04]	0.92 [0.78–1.08]	1.11 [0.94–1.32]
Stage II	REF	0.80 [0.71–0.90]*	0.82 [0.70–0.95]*	0.65 [0.55–0.78]*
Stage III	REF	0.84 [0.74–0.95]*	0.90 [0.76–1.06]	0.66 [0.54–0.80]*
Stage IV	REF	0.77 [0.73–0.82]*	0.68 [0.63–0.74]*	0.63 [0.56–0.71]*

*, P value <0.05. Covariates included in hazard regression: age (<65 *vs.* ≥65), sex, race, Hispanic ethnicity, patient insurance, and Charlson-Deyo score. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

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Table S5 Cox proportional hazards regression for overall survival sensitivity analysis: adjusted for facility factors only

Cancer type and stage	Time to treatment initiation (days)			
	3-30	31-60	61-90	>90
EHBD				
Stage I	REF	1.23 [1.13–1.35]*	1.52 [1.34–1.74]*	1.74 [1.50–2.02]*
Stage II	REF	1.11 [1.04–1.18]*	1.25 [1.13–1.37]*	1.25 [1.10–1.41]*
Stage III	REF	1.14 [1.05–1.25]*	1.39 [1.22–1.58]*	1.22 [1.05–1.42]*
Stage IV	REF	0.80 [0.75–0.85]*	0.76 [0.69–0.83]*	0.63 [0.56–0.70]*
Pancreas				
Stage I	REF	1.12 [1.07–1.18]*	1.25 [1.16–1.34]*	1.04 [0.95–1.14]
Stage II	REF	1.07 [1.05–1.09]*	1.13 [1.08–1.17]*	1.05 [1.00–1.11]
Stage III	REF	0.98 [0.95–1.01]	0.99 [0.94–1.04]	0.82 [0.77–0.88]*
Stage IV	REF	0.82 [0.81–0.83]*	0.71 [0.69–0.74]*	0.61 [0.58–0.64]*
Liver				
Stage I	REF	0.96 [0.92–1.00]*	0.98 [0.93–1.02]*	0.89 [0.86–0.93]*
Stage II	REF	0.94 [0.90–0.99]*	0.94 [0.89–0.99]*	0.84 [0.80–0.88]*
Stage III	REF	0.83 [0.79–0.86]*	0.69 [0.66–0.73]*	0.60 [0.57–0.63]*
Stage IV	REF	0.69 [0.66–0.72]*	0.56 [0.52–0.59]*	0.46 [0.43–0.49]*
IHBD				
Stage I	REF	0.97 [0.84–1.11]	1.02 [0.87–1.19]	1.23 [1.04–1.46]*
Stage II	REF	0.80 [0.71–0.90]*	0.87 [0.75–1.00]	0.71 [0.60–0.85]*
Stage III	REF	0.91 [0.81–1.02]	1.02 [0.87–1.20]	0.73 [0.60–0.89]*
Stage IV	REF	0.79 [0.75–0.84]*	0.70 [0.65–0.77]*	0.67 [0.59–0.75]*

*, P value <0.05. Covariates included in hazard regression: year of diagnosis (before or after 2013), geographic region, facility urbanicity, and facility type. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

Table S6 Cox proportional hazards regression for overall survival sensitivity analysis: fully-adjusted model with age and year of diagnosis as continuous variables

Cancer type and stage	Time to treatment initiation (days)			
	3-30	31-60	61-90	>90
EHBD				
Stage I	REF	1.14 [1.04–1.25]*	1.33 [1.16–1.53]*	1.55 [1.33–1.81]*
Stage II	REF	1.06 [0.99–1.13]	1.15 [1.05–1.27]*	1.09 [0.96–1.24]
Stage III	REF	1.11 [1.02–1.21]*	1.35 [1.19–1.55]*	1.21 [1.04–1.42]*
Stage IV	REF	0.79 [0.74–0.84]*	0.74 [0.67–0.81]*	0.60 [0.53–0.68]*
Pancreas				
Stage I	REF	1.05 [1.00–1.11]*	1.24 [1.14–1.35]*	0.95 [0.86–1.04]
Stage II	REF	1.03 [1.01–1.06]*	1.06 [1.02–1.11]*	1.01 [0.95–1.07]
Stage III	REF	0.96 [0.93–0.99]*	0.95 [0.90–1.00]	0.79 [0.73–0.85]*
Stage IV	REF	0.81 [0.79–0.82]*	0.69 [0.67–0.72]*	0.59 [0.56–0.62]*
Liver				
Stage I	REF	0.93 [0.90–0.97]*	0.94 [0.90–0.99]*	0.91 [0.87–0.95]*
Stage II	REF	0.92 [0.88–0.96]*	0.91 [0.86–0.95]*	0.82 [0.78–0.86]*
Stage III	REF	0.81 [0.78–0.84]*	0.68 [0.65–0.72]*	0.58 [0.55–0.61]*
Stage IV	REF	0.69 [0.66–0.73]*	0.55 [0.52–0.59]*	0.45 [0.42–0.49]*
IHBD				
Stage I	REF	0.92 [0.80–1.06]	0.92 [0.77–1.08]	1.15 [0.96–1.37]
Stage II	REF	0.78 [0.69–0.88]*	0.82 [0.71–0.96]*	0.67 [0.55–0.80]*
Stage III	REF	0.87 [0.77–0.99]*	0.98 [0.82–1.16]	0.66 [0.53–0.82]*
Stage IV	REF	0.76 [0.72–0.81]*	0.67 [0.61–0.73]*	0.61 [0.54–0.69]*

*, P value <0.05. Covariates included in hazard regression: age (continuous), sex, year of diagnosis (continuous), race, Hispanic ethnicity, geographic region, facility urbanicity, patient insurance, facility type, and Charlson-Deyo score. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

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Table S7 Cox proportional hazards regression for overall survival sensitivity analysis: fully-adjusted model with time to treatment initiation as a binary variable, split points at 30 and 60 days

Cancer type and stage	Time to treatment initiation (days)			
	3-30	>30	3-60	>60
EHBD				
Stage I	REF	1.27 [1.17–1.39]*	REF	1.39 [1.25–1.54]*
Stage II	REF	1.09 [1.03–1.16]*	REF	1.13 [1.05–1.22]*
Stage III	REF	1.17 [1.08–1.27]*	REF	1.25 [1.12–1.38]*
Stage IV	REF	0.75 [0.71–0.79]*	REF	0.76 [0.71–0.82]*
Pancreas				
Stage I	REF	1.09 [1.04–1.14]*	REF	1.08 [1.02–1.14]*
Stage II	REF	1.05 [1.03–1.07]*	REF	1.05 [1.02–1.09]*
Stage III	REF	0.96 [0.93–0.99]*	REF	0.92 [0.88–0.96]*
Stage IV	REF	0.77 [0.76–0.78]*	REF	0.71 [0.69–0.73]*
Liver				
Stage I	REF	0.92 [0.89–0.96]*	REF	0.95 [0.93–0.98]*
Stage II	REF	0.88 [0.85–0.92]*	REF	0.90 [0.87–0.93]*
Stage III	REF	0.72 [0.69–0.74]*	REF	0.71 [0.68–0.73]*
Stage IV	REF	0.60 [0.58–0.63]*	REF	0.59 [0.56–0.62]*
IHBD				
Stage I	REF	0.98 [0.86–1.12]	REF	1.08 [0.96–1.21]
Stage II	REF	0.78 [0.70–0.87]*	REF	0.89 [0.79–1.00]*
Stage III	REF	0.86 [0.77–0.97]*	REF	0.90 [0.79–1.03]
Stage IV	REF	0.73 [0.69–0.77]*	REF	0.75 [0.70–0.81`]*

*, P value <0.05. Covariates included in hazard regression: age (<65 *vs.* ≥65), sex, year of diagnosis (before or after 2013), race, Hispanic ethnicity, geographic region, facility urbanicity, patient insurance, facility type, and Charlson-Deyo score. REF, reference group; TTI, time to treatment initiation; IHBD, intrahepatic bile duct; EHBD, extrahepatic bile duct.

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