



Hepatocellular carcinoma: Impact of academic setting and hospital volume on patient survival

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ARTICLE INFO

Keywords:

Hepatocellular carcinoma
Surgical oncology
Interventional oncology
High volume hospitals
Low volume hospitals

ABSTRACT

Background and objectives: To assess the impact of academic setting and hospital on overall survival in patient with hepatocellular carcinoma (HCC).

Methods: The 2004–2015 NCDB was queried for HCC. First line treatment was stratified as liver transplant, surgical resection, interventional oncology (IO) and chemotherapy. Hospital volume was stratified as high (ranking among top 10% in case numbers) and low volume. Overall survival was assessed via multivariable Cox regressions.

Results: 63,877 patients treated at 1261 hospital systems were included (transplant $n = 10,596$, surgical resection $n = 11,132$, IO $n = 12,286$, chemotherapy $n = 29,863$; academic centers $n = 226$, non-academic $n = 1035$). Younger African American patients with private insurance, high income and education were more likely treated at academic centers. US geographical discrepancies were evident, with highest academic center treatment rates in New England states (83.6%) and lowest in South Atlantic states (48.6%). Overall survival was superior for academic versus non-academic centers (HR = 0.89, 95% CI: 0.87–0.91, $p < 0.001$) and high versus low volume centers (HR = 0.79, 95% CI: 0.77–0.81, $p < 0.001$), after multivariable adjustment for potential confounders. These effects were evident among all HCC treatment modalities.

Conclusions: HCC treatment in academic centers shows distinct patterns according to patient demographics and US geography. Longest patient survival is observed in high-volume academic centers.

1. Introduction

Hepatocellular carcinoma (HCC) is the most frequent hepatic malignancy and ranks second in cancer-related mortality worldwide [1,2]. In the United States, HCC incidence has seen relevant increases from annually 1.6/100,000 in 1975 to 6/100,000 in 2010 [3,4]. In general, HCC carries a poor prognosis with 5-year overall survival rates reported as low as 11–30% [5–8]. Still, in well selected patients undergoing hepatic resection or transplant, 5-year survival rates as high as 74% have been described [9].

Several clinicopathologic prognostic factors that influence HCC survival include cancer size, cancer stage, Child-Pugh score and vascular

invasion [10–12]. Recent studies, however, have focused on the impact of hospital volume and facility type on HCC outcomes, reporting controversial results. While a meta-analysis by Richardson et al. showed an inverse correlation between hospital volume and in-hospital mortality of HCC patients undergoing curative intent hepatic surgery, Epstein et al. and Lin and Lin reported that only surgeons' experience remained as an independent predictor of in-hospital mortality [13–15]. Taking facility type into account, Hyder et al. reported improved survival for HCC patients treated with complex hepatopancreaticobiliary surgery at teaching hospitals [16].

The current literature tends to focus on specific surgical procedures, not taking into account interventional oncology and systemic therapy,

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<https://doi.org/10.1016/j.suronc.2019.10.009>

Received 19 April 2019; Received in revised form 4 August 2019; Accepted 10 October 2019

Available online 12 October 2019

0960-7404/© 2019 Published by Elsevier Ltd.

Table 1
Baseline characteristics of included patients.

	Total No. 63,877	high volume academic center No. 33,606	high volume non-academic center No. 7198	low volume academic center No. 8548	low volume non-academic center No. 14,525	P-value
age	46.8 (±9.9)	45.8 (±9.3)	46.3 (±9.4)	46.2 (±10.0)	49.8 (±10.6)	<0.0001
Gender						0.14
female	15,517 (24.3%)	8160 (24.3%)	1776 (24.7%)	1999 (23.4%)	3582 (24.7%)	
male	48,360 (75.7%)	25,446 (75.7%)	5422 (75.3%)	6549 (76.6%)	10,943 (75.3%)	
Race						<0.0001
african american	8892 (13.9%)	4650 (13.8%)	904 (12.6%)	1445 (16.9%)	1893 (13.0%)	
white	47,304 (74.1%)	24,553 (73.1%)	5312 (73.8%)	6164 (72.1%)	11,275 (77.6%)	
others	7681 (12.0%)	4403 (13.1%)	982 (13.6%)	939 (11.0%)	1357 (9.3%)	
comorbidities [Charlson Comorbidity Index]						<0.0001
0	29,022 (45.4%)	15,319 (45.6%)	3097 (43.0%)	3656 (42.8%)	6950 (47.8%)	
1	18,583 (29.1%)	9669 (28.8%)	2165 (30.1%)	2570 (30.1%)	4179 (28.8%)	
2	7290 (11.4%)	3817 (11.4%)	797 (11.1%)	1039 (12.2%)	1637 (11.3%)	
3	8982 (14.1%)	4801 (14.3%)	1139 (15.8%)	1283 (15.0%)	1759 (12.1%)	
tumor grade						<0.0001
Grade I	10,441 (16.3%)	4748 (14.1%)	1001 (13.9%)	1768 (20.7%)	2924 (20.1%)	
Grade II	14,787 (23.1%)	7232 (21.5%)	1552 (21.6%)	2367 (27.7%)	3636 (25.0%)	
Grade III	5445 (8.5%)	2446 (7.3%)	531 (7.4%)	811 (9.5%)	1657 (11.4%)	
Grade IV	532 (0.8%)	373 (1.1%)	30 (0.4%)	37 (0.4%)	92 (0.6%)	
Grade unknown	32,672 (51.1%)	18,807 (56.0%)	4084 (56.7%)	3565 (41.7%)	6216 (42.8%)	
tumor stage						<0.0001
Stage I	24,655 (38.6%)	13,433 (40.0%)	3061 (42.5%)	3469 (40.6%)	4692 (32.3%)	
Stage II	16,318 (25.5%)	9557 (28.4%)	1931 (26.8%)	2276 (26.6%)	2554 (17.6%)	
Stage III	11,695 (18.3%)	5649 (16.8%)	1215 (16.9%)	1371 (16.0%)	3460 (23.8%)	
Stage IV	5547 (8.7%)	2112 (6.3%)	446 (6.2%)	647 (7.6%)	2342 (16.1%)	
Stage unknown	5662 (8.9%)	2855 (8.5%)	545 (7.6%)	785 (9.2%)	1477 (10.2%)	
treatment modality						<0.0001
chemotherapy	29,863 (46.8%)	15,581 (46.4%)	3629 (50.4%)	2366 (27.7%)	8287 (57.1%)	
interventional oncology	12,286 (19.2%)	6824 (20.3%)	1289 (17.9%)	1550 (18.1%)	2623 (18.1%)	
surgical resection	11,132 (17.4%)	5498 (16.4%)	1087 (15.1%)	1781 (20.8%)	2766 (19.0%)	
transplant	10,596 (16.6%)	5703 (17.0%)	1193 (16.6%)	2851 (33.4%)	849 (5.8%)	
30d unplanned hospital readmission						<0.0001
no unplanned readmission	62,068 (97.2%)	32,643 (97.1%)	7005 (97.3%)	8201 (95.9%)	14,219 (97.9%)	
unplanned readmission	1809 (2.8%)	963 (2.9%)	193 (2.7%)	347 (4.1%)	306 (2.1%)	
30d mortality						<0.0001
alive	63,042 (98.7%)	33,277 (99.0%)	7112 (98.8%)	8344 (97.6%)	14,309 (98.5%)	
dead	835 (1.3%)	329 (1.0%)	86 (1.2%)	204 (2.4%)	216 (1.5%)	
90d mortality						<0.0001
alive	62,423 (97.7%)	32,990 (98.2%)	7046 (97.9%)	8218 (96.1%)	14,169 (97.5%)	
dead	1454 (2.3%)	616 (1.8%)	152 (2.1%)	330 (3.9%)	356 (2.5%)	
overall survival						<0.0001
alive	23,817 (37.3%)	13,806 (41.1%)	2739 (38.1%)	3719 (43.5%)	3553 (24.5%)	
dead	40,060 (62.7%)	19,800 (58.9%)	4459 (61.9%)	4829 (56.5%)	10,972 (75.5%)	

thereby lacking a generalizable conclusion encompassing all HCC treatment approaches. We hypothesized that both hospital volume and facility type influence survival in HCC patients undergoing hepatic transplant, resection, interventional oncology procedures or chemotherapy.

2. Material and methods

This study was approved by the Yale University Internal Review Board and is Health Insurance Portability and Accountability Act compliant. Written informed consent was not necessary due to anonymized reporting in the National Cancer Database (NCDB).

The United States based NCDB is jointly sponsored by the American College of Surgeons and the American Cancer Society. It contains 34 million cancer records from over 1500 participating institutions and covers approximately 70% of the annually diagnosed cancer cases in the United States.

The NCDB was retrospectively searched for HCC diagnosed between 2004 and 2015. Only patients with HCC diagnosed via histopathology or radiological imaging were included. Exclusion criteria were unknown tumor size, age <18 years, unknown survival status and follow-up time.

Main comparators were academic versus non-academic institutions

and high volume versus low volume centers. Primary outcome of interest was overall survival, defined as time from cancer diagnosis to death from any cause or censoring.

2.1. Variables

The NCDB classified contributing institutions as “academic” if they participate in postgraduate medical education in at least 4 program areas (including internal medicine and general surgery) and provided the full range of diagnostic and treatment services on site or via referral. For assessment of hospital volume, the absolute number of cases submitted to the NCDB was calculated and institutions were ranked in ascending order. This was done separately for each treatment modalities. Institutions ranked in the top 10% were considered “high volume” centers and those ranked in the lower 90% “low volume centers”.

The NCDB provided information on first line HCC treatment only, except for chemotherapy which was detailed in addition to any other treatment. HCC treatment was stratified as hepatectomy with liver transplant, surgical resection (including wedge resection, segmental resection and lobectomy), interventional oncology (IO; local tissue destruction and radioembolization) and chemotherapy (systemic chemotherapy and transarterial chemoembolization). The NCDB did not

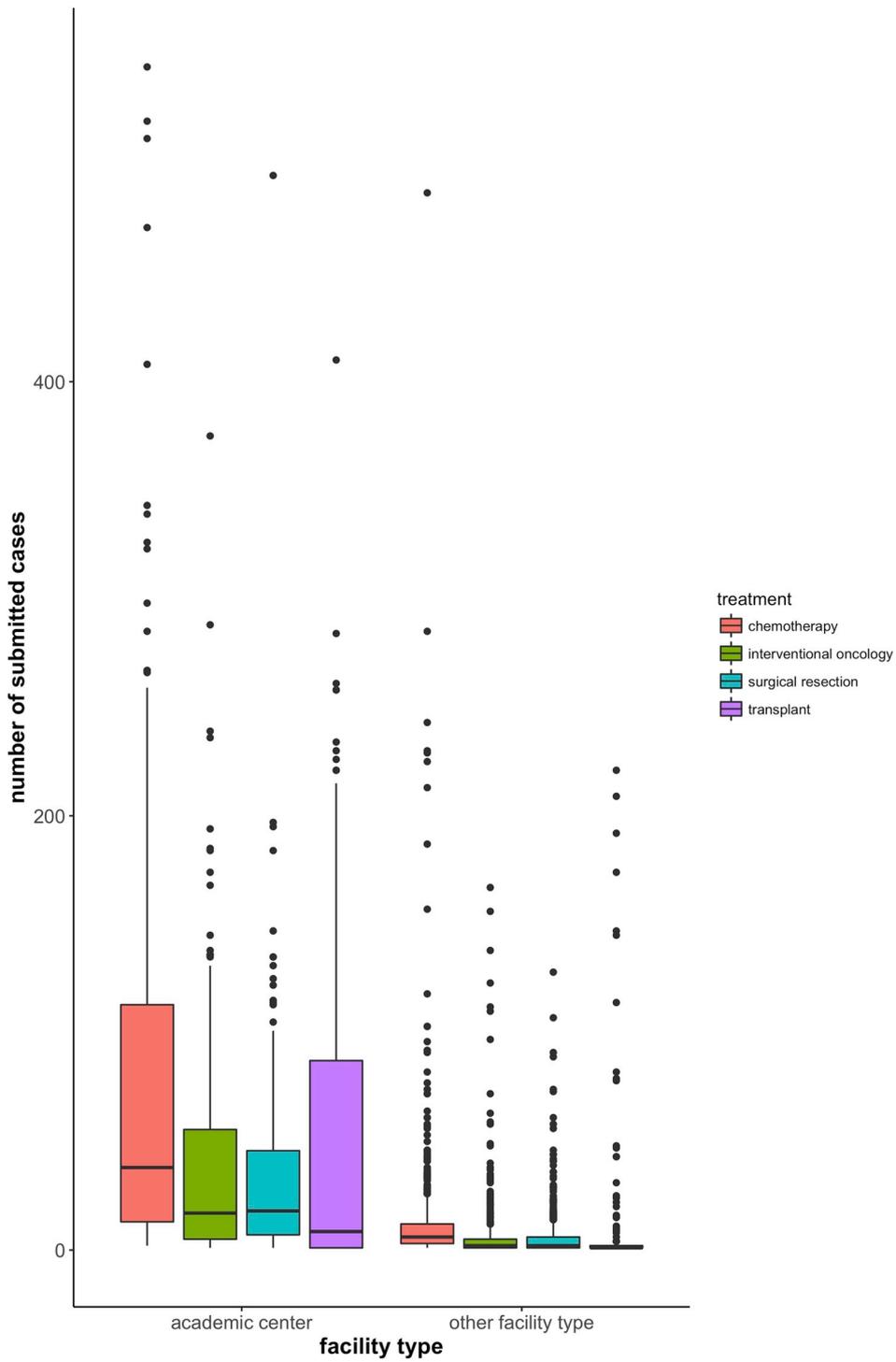


Fig. 1. Number of submitted hepatocellular carcinoma cases stratified by facility type and treatment modality.

Table 2
Details on number of performed treatments.

	Transplant	Surgical resection	Interventional oncology	Chemotherapy
Total number of centers	348	838	801	1232
Mean case numbers	30.6	13.5	15.4	24.4
Mean case numbers in academic/research programs	55.2	34.6	40.7	79.9
Mean case numbers in other facility types	10.7	6.25	6.6	11.9
Cutoff for high volume centers (90% percentile of submitted cases)	103	36	40	52.7
Number of high volume centers	36	88	82	124

provide separate categories to distinguish systemic chemotherapy and transarterial chemoembolization.

The American Joint Committee on Cancer 7th edition staging system was used to stage HCC in the NCDB. The Charlson Deyo Comorbidity Index (CCI) was used to measure comorbidities, stratified as CCI 0, CCI 1, CCI 2 and CCI ≥ 3.

2.2. Statistical analyses

For descriptive statistics, continuous variables were given as median with inter-quartile-range (IQR) and categorical variables as absolute number and percent. Continuous variables were compared via Wilcoxon rank sum tests and categorical variables using χ^2 tests.

Multivariable Cox proportional hazards models were used to assess overall survival. Variables with p-values less than 0.1 were considered for inclusion on multivariable models. To avoid overfitting, the final parsimonious multivariable model only included variables with $p < 0.05$. The Kaplan-Meier method was used to visualize overall

survival. For survival curve plotting of multivariable adjusted Cox models, a conditional approach was chosen that weighted individual strata based on individual patients' probability of being in the respective stratum given the variables in the multivariable Cox model.

All statistical analyses were performed via R version 3.4.3 and RStudio version 1.1.414 [17,18]. An alpha-level of 0.05 was chosen to indicate statistical significance. All p-values are two-sided.

3. Results

3.1. Patient cohort

A total of 63,877 patients fulfilled the inclusion criteria of which 10,596 received transplant (16.6%), 11,132 surgical resection (17.4%), 12,286 interventional oncology (19.2%) and 29,863 chemotherapy (46.8%). A study flow chart is provided in Supplemental Fig. 1 and patient characteristics are detailed in Table 1 and Supplemental Table 1.

3.2. Academic setting and hospital volume

A total of 1261 distinct institutions submitted HCC cases to the NCDB between 2004 and 2015. Of these, 226 (17.9%) were academic/research programs and 1035 (82.1%) other facility types, including comprehensive cancer programs and community cancer programs. As shown in Table 2, 1232 centers (97.7%) provided chemotherapy, 838 centers provided surgical HCC resection (66.5%), 801 interventional oncology (63.5%), and 349 hepatectomy with liver transplant (27.6%). A total of 293 centers (23.2%, 150 academic/research programs, 143 other facility types) provided all 4 treatment modalities.

Fig. 1 and Table 2 further detail that case numbers for each treatment modality were larger in academic/research programs when compared to other facility types ($p < 0.001$ for treatment via chemotherapy, surgical resection, interventional oncology and transplant, respectively). High volume centers (top 10%) were considered those performing at least 103 liver transplantations, 36 surgical resections, 40 interventional oncology procedures or 52.7 chemotherapies.

As shown in Table 1, patients treated at academic centers were younger and more often African Americans compared to non-academic centers ($p < 0.001$, respectively). Similarly, patients with private insurance, high income and education were more often treated at academic centers. Higher HCC stage and grade were more frequent in low-volume non-academic centers, which also administered chemotherapy

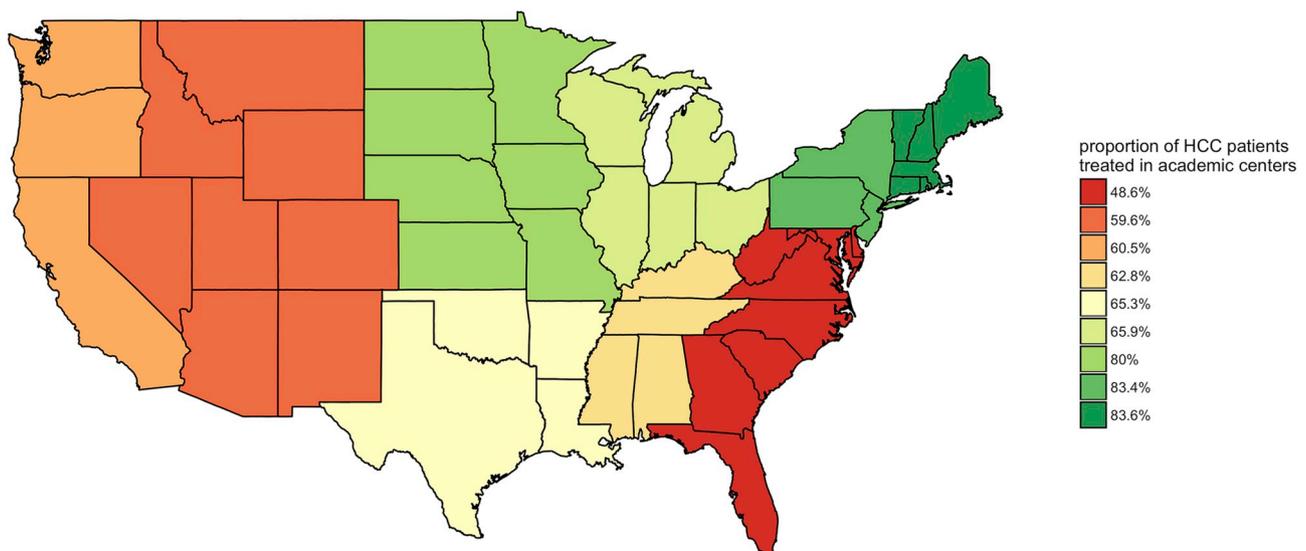


Fig. 2. Proportion of HCC patients treated in academic centers by United States region.

Table 3
Multivariable Cox proportional hazards model predicting overall survival.

predictor	HR	lower 95% CI	upper 95% CI	p value
facility type				
other facility type (reference)				
academic/research program	0.891	0.869	0.912	<0.001
hospital volume				
low volume (reference)				
high volume	0.789	0.771	0.808	<0.001
treatment modality				
chemotherapy (reference)				
interventional oncology	0.717	0.698	0.737	<0.001
surgical resection	0.413	0.401	0.426	<0.001
transplant	0.207	0.199	0.215	<0.001
cancer stage				
Stage I (reference)				
Stage II	1.317	1.281	1.353	<0.001
Stage III	1.959	1.902	2.018	<0.001
Stage IV	2.802	2.701	2.906	<0.001
Stage unknown	1.449	1.396	1.504	<0.001
tumor size [mm]				
	1.004	1.004	1.004	<0.001
age [years]				
	1.006	1.005	1.008	<0.001
sex				
female (reference)				
male	1.074	1.049	1.099	<0.001
comorbidities [Charlson Comorbidity Index]				
0 (reference)				
1	1.067	1.042	1.092	<0.001
2	1.128	1.092	1.165	<0.001
3 or more	1.267	1.228	1.307	<0.001
income				
<\$37,999				
\$38,000 - \$47,999	1.004	0.975	1.034	0.777
\$48,000 - \$62,999	0.951	0.924	0.978	<0.001
\$63,000 +	0.862	0.837	0.887	<0.001
insurance				
private insurance (reference)				
govt insurance	1.09	1.011	1.175	0.025
insurance unknown and no insurance	1.131	1.081	1.182	<0.001
Medicaid	1.182	1.144	1.222	<0.001
Medicare	1.171	1.141	1.202	<0.001
year of diagnosis [since 2004]				
	0.964	0.961	0.968	<0.001

more often than other institutions ($p < 0.001$, respectively). Surgical resection was more often provided in low-volume centers, whereas liver transplant was more common in academic centers.

Further, there were geographical discrepancies: as shown in Fig. 2, the highest proportion of patients treated in academic centers was observed in New England States (83.6%), and the lowest in South Atlantic States (48.6%).

3.3. Survival analyses

Median follow-up was 58.2 months (IQR: 34.5–88.4 months).

On univariate survival analyses, academic/research programs showed superior survival to other facility types (HR = 0.64, 95% CI: 0.63–0.66, $p < 0.001$), and high volume centers superior survival to low volume centers (HR = 0.72, 95% CI: 0.71–0.74, $p < 0.001$). These effects were seen in univariate analyses across all treatment modalities, as demonstrated in Supplemental Fig. 2.

Using multivariable Cox regression models, both academic setting

and hospital volume were confirmed as independent survival predictors (Table 3), although their influence was diminished compared to the univariate analyses. Survival was superior for academic/research programs versus other facility types (HR = 0.89, 95% CI: 0.87–0.91, $p < 0.001$), and for high volume versus low volume centers (HR = 0.79, 95% CI: 0.77–0.81, $p < 0.001$), after adjustment for cancer variables and patient demographics. Fig. 3 details overall survival differences by academic setting and hospital volume.

These discrepancies also proved independent from treatment modality, as shown in Fig. 4: for all treatment modalities, the influence of academic setting and hospital volume on overall survival was evident. Subgroup analyses demonstrated that our results were consistent across all HCC stages and treatment modalities (Supplemental Figs. 3–6).

4. Discussion

Several recent HCC studies have focused on the impact of hospital volume and type but reported controversial results and lacked long-term follow-up [13–16]. Our study shows that improved long-term overall survival in HCC independently correlated with high hospital volume and academic setting, irrespective of the administered treatment and after adjustment for potential confounders. Several potential mechanisms may explain these findings. Physicians working in high volume facilities might treat HCC more frequently and are thus more experienced. Interestingly, the positive effect of this experience seems to extend beyond surgical procedures, such as HCC resection or interventional oncology, as the beneficial effect of high volume facilities was seen even in patients treated with chemotherapy. Academic centers may further provide well-coordinated HCC patient care in interdisciplinary teams that positively affect clinical outcome. Optimal periprocedural management, follow-up schemes and management of HCC-associated chronic liver disease may attribute to the superior outcomes in academic centers as well.

Our study further demonstrated that access to academic centers varied considerably according to US region: while up to 83.6% of patients in New England states were treated in academic centers, access to academic centers was lowest in South Atlantic states at 48.6%. In light of our findings on superior survival seen in academic centers, healthcare providers should be aware of these geographical discrepancies and their potential effect on HCC outcomes.

Moreover, we showed that there is a certain patient selection according to hospital volume and facility type: high-volume academic centers tended to select younger patients with private insurance, high income and education as well as lower HCC stage and grade as compared to other institutions. There might be concerns that this patient selection introduces biases to our results regarding superior HCC outcomes in high volume academic centers – still, our findings proved independent from potential confounders after statistical adjustment in multivariable survival models. Due to missing data from the NCDB, we could however not control for underlying liver disease or HCC etiology. Given the overall low number of surgical resections performed by the majority of included centers, there are also concerns about the surgical experience in these centers, which in turn might affect HCC outcomes. Further, treatment patterns observed in our study, i.e. the higher number of surgical resections in low-volume centers, might be biased by patient selection.

Our study’s findings on long-term HCC outcomes are supported by several trials reporting low perioperative mortality in several surgical fields, including lung and cardiac surgery, although most of the studies only reported short term outcomes [19–21]. For patients undergoing liver surgery, a recent meta-analysis reported a strong inverse correlation between hospital volume and perioperative morbidity, although the impact of facility types was not evaluated [13]. On the other hand,

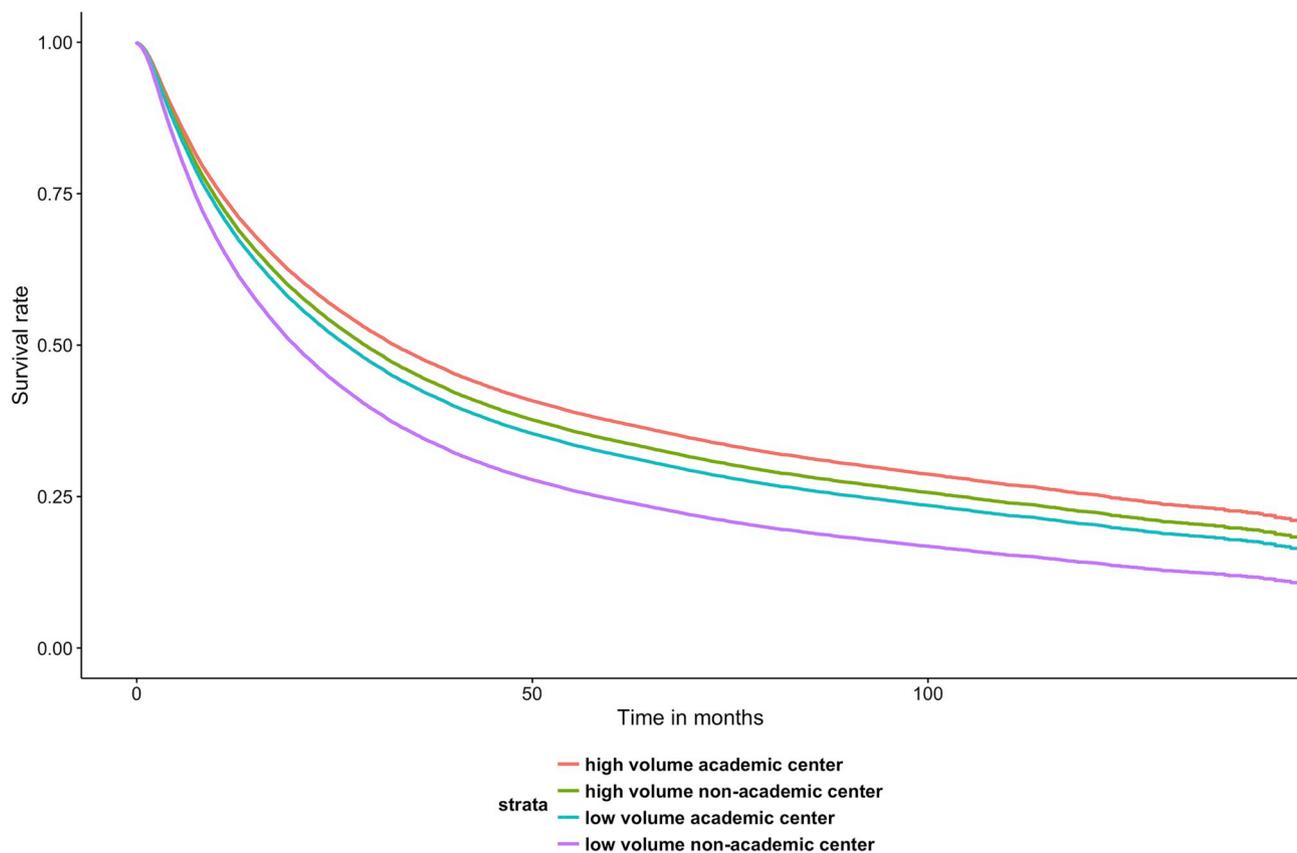


Fig. 3. Kaplan Meier curve from a multivariable adjusted Cox model showing the independent influence of academic setting and hospital volume on overall survival in HCC ($p < 0.001$).

Hyder et al. demonstrated that teaching hospital status was associated with lower in-hospital mortality in patients undergoing hepatobiliary surgery, although they did not account for hospital volume [16]. Interestingly, our study reports controversial results to a recent study by Chapmann et al. evaluating both the influence of hospital volume as well as facility type [22]. Using outdated NCDB data from 1998 to 2011, the authors concluded that hospital volume rather than the facility type affected overall survival in HCC patients. These discrepancies might be attributable to different definitions of “high volume” centers and a smaller patient cohort in the study by Chapmann et al. that could limit statistical power.

Our study is not devoid of limitations, which are mostly inherent to the NCDB as its datasource. First, our analyses were limited to variables reported in the NCDB and thereby lacked information on hepatic cirrhosis and portal hypertension, as well as disease recurrence, chemotherapeutic agents, repetitive treatments and patients’ clinical performance. Our findings might be biased if high volume and academic centers tended to select healthier patients, although our results’ reproducibility across all treatment strata and independency from comorbidities makes this less probable. Further, the NCDB does not provide details on specific chemotherapy approaches, which might be imbalanced across hospital settings and thus bias our results. Furthermore, each hospital system was assessed at the time of first NCDB participation and thus changes in facility type might not be covered. Finally, due to the blinded data provided by the NCDB, we were unable to further evaluate “academic centers” based on multi-disciplinary tumor board meetings or their HCC research output.

5. Conclusion

HCC treatment in academic centers shows distinct patterns according to patient demographics and US geography. Among all treatment modalities, both academic setting and hospital volume seem to independently affect HCC outcomes, with highest patient survival observed in high-volume academic centers, although residual confounding by cirrhosis and liver function might have biased our results. Given these results, HCC patients should preferably be treated at high-volume academic centers.

Funding

HSK is supported by the United States Department of Defense (CA160741). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability

The NCDB data analyzed in this study is available from the American College of Surgeons upon request.

Declaration of competing interest

No authors have competing interests. The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript. Hyun S. Kim served on Advisory boards for Boston Scientific and SIRTex.

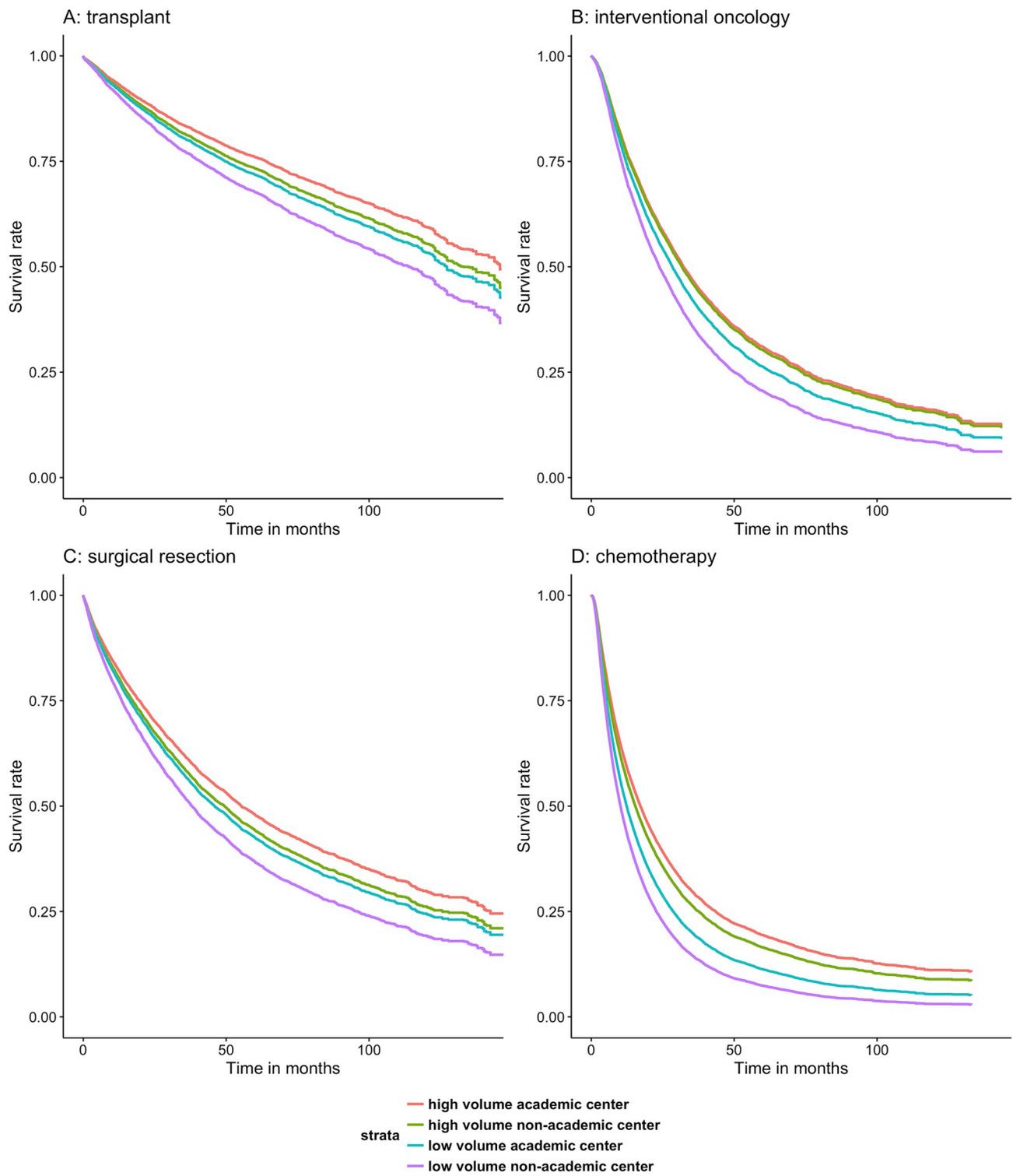


Fig. 4. (A–D): Kaplan Meier curves from a multivariable adjusted Cox model showing the independent influence of academic setting and hospital volume on overall survival in HCC, stratified by treatment modality ($p < 0.001$).

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2019.10.009>.

Abbreviations

CCI	Charlson comorbidity index
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IO	Interventional oncology
NCDB	National Cancer Database
OS	Overall survival

References

- [1] H.B. El-Serag, Hepatocellular carcinoma, *N. Engl. J. Med.* 365 (12) (2011) 1118–1127.
- [2] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, *CA A Cancer J. Clin.* 61 (2) (2011) 69–90.
- [3] H.B. El-Serag, F. Kanwal, Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* 60 (5) (2014) 1767–1775.
- [4] S.F. Altekruse, K.A. McGlynn, M.E. Reichman, Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005, *J. Clin. Oncol.* 27 (9) (2009) 1485–1491.
- [5] E. Villa, A. Moles, I. Ferretti, P. Buttafoco, A. Grottola, M. Del Buono, et al., Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival, *Hepatology* 32 (2) (2000) 233–238.
- [6] R. Lerosé, R. Molinari, E. Rocchi, F. Manenti, E. Villa, Prognostic features and survival of hepatocellular carcinoma in Italy: impact of stage of disease, *Eur. J. Cancer* 37 (2) (2001) 239–245.
- [7] C.-H. Chen, W.-W. Su, S.-S. Yang, T.-T. Chang, K.-S. Cheng, H.H. Lin, et al., Long-term trends and geographic variations in the survival of patients with hepatocellular carcinoma: analysis of 11 312 patients in Taiwan, *J. Gastroenterol. Hepatol.* 21 (10) (2006) 1561–1566.
- [8] J.F. Perry, B. Charlton, D.J. Koorey, R.C. Waugh, P.J. Gallagher, M.D. Crawford, et al., Outcome of patients with hepatocellular carcinoma referred to a tertiary centre with availability of multiple treatment options including cadaveric liver transplantation, *Liver Int. : Off. J. Int. Assoc. Stud. Liver* 27 (9) (2007) 1240–1248.
- [9] J.M. Llovet, J. Fuster, J. Bruix, Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation, *Hepatology* 30 (6) (1999) 1434–1440.
- [10] F. Trevisani, G. Magini, V. Santi, A.M. Morselli-Labate, M. Chiara Cantarini, M. Anna Di Nolfo, et al., Impact of etiology of cirrhosis on the survival of patients diagnosed with hepatocellular carcinoma during surveillance, *Am. J. Gastroenterol.* 102 (2007) 1022.
- [11] K.W. Park, J.-W. Park, J.I. Choi, T.H. Kim, S.H. Kim, H.S. Park, et al., Survival analysis of 904 patients with hepatocellular carcinoma in a hepatitis B virus-endemic area, *J. Gastroenterol. Hepatol.* 23 (3) (2008) 467–473.
- [12] U. Gelatti, F. Donato, A. Tagger, C. Fantoni, N. Portolani, M.L. Ribero, et al., Etiology of hepatocellular carcinoma influences clinical and pathologic features but not patient survival, *Am. J. Gastroenterol.* 98 (4) (2003) 907–914.
- [13] A.J. Richardson, T.C.Y. Pang, E. Johnston, M.J. Hollands, V.W.T. Lam, H.C. C. Pleass, The volume effect in liver surgery—a systematic Review and meta-analysis, *J. Gastrointest. Surg.* 17 (11) (2013) 1984–1996.
- [14] R.W. Eppsteiner, N.G. Csikesz, J.P. Simons, J.F. Tseng, S.A. Shah, High volume and outcome after liver resection: surgeon or center? *J. Gastrointest. Surg.* 12 (10) (2008) 1709–1716.
- [15] H.-C. Lin, C.-C. Lin, Surgeon volume is predictive of 5-year survival in patients with hepatocellular carcinoma after resection: a population-based study, *J. Gastrointest. Surg.* 13 (12) (2009) 2284–2291.
- [16] O. Hyder, T. Sachs, A. Ejaz, G. Spolverato, T.M. Pawlik, Impact of hospital teaching status on length of stay and mortality among patients undergoing complex hepatopancreaticobiliary surgery in the USA, *J. Gastrointest. Surg.* 17 (12) (2013) 2114–2122.
- [17] R Development Core Team R, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2008. <https://www.r-project.org>.
- [18] RStudio Team, RStudio: integrated development for R. Boston, MA, USA. <https://www.rstudio.com2015>.
- [19] E.L. Hannan, H. Kilburn Jr., H. Bernard, J.F. O'Donnell, G. Lukacik, E.P. Shields, Coronary artery bypass surgery: the relationship between inhospital mortality rate and surgical volume after controlling for clinical risk factors, *Med. Care* 29 (11) (1991) 1094–1107.
- [20] E.L. Hannan, M. Radzyner, D. Rubin, J. Dougherty, M.F. Brennan, The influence of hospital and surgeon volume on in-hospital mortality for colectomy, gastrectomy, and lung lobectomy in patients with cancer, *Surgery* 131 (1) (2002) 6–15.
- [21] J.D. Birkmeyer, T.A. Stukel, A.E. Siewers, P.P. Goodney, D.E. Wennberg, F.L. Lucas, Surgeon volume and operative mortality in the United States, *N. Engl. J. Med.* 349 (22) (2003) 2117–2127.
- [22] B.C. Chapman, A. Panizza, P.W. Hosokawa, W.G. Henderson, D.M. Overbey, W. Messersmith, et al., Impact of facility type and surgical volume on 10-year survival in patients undergoing hepatic resection for hepatocellular carcinoma, *J. Am. Coll. Surg.* 224 (3) (2017) 362–372.