

Transplant and non-transplant HCC patients at a single institution

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Abstract

Background and Aim: Patients with hepatocellular carcinoma (HCC) are managed in various hospital departments, which complicates the assessment of the overall picture. In our large liver transplant institute, we evaluate all HCC patients in a weekly multi-disciplinary liver tumor board, and their data are prospectively collected in an institutional HCC database to evaluate HCC causes, tumor features, treatments, and survival.

Materials and Methods: Baseline data for patients (n=1322) were prospectively recorded, including hepatitis status, routine clinical serum parameters, radiological assessment of maximum tumor diameter (MTD), tumor number, presence of macroscopic portal vein thrombosis (PVT), and serum alpha-fetoprotein (AFP) levels.

Results: Cirrhosis was found in 81.1% of patients; 58.5% had hepatitis B virus (HBV), 14.9% hepatitis C virus (HCV), 8.9% cryptogenic cirrhosis, and less than 2% had alcoholism. MTD was <5 cm in 61.95% of patients, and 31.9% had PVT. The median overall survival was more than six-fold greater for the 444 liver transplant patients than for those without surgery. Transplanted patients had smaller tumors, whereas larger tumors (MTD >10 cm) were primarily in the no-surgery group. Parallel differences were found for AFP levels (highest in the no-surgery group). PVT was present in similar proportions (25.0% for transplant, 28.0% for no-surgery). The presence of cirrhosis was higher in the transplant group. MTD and levels of serum AFP, gamma-glutamyl transferase (GGT), and blood platelets were prognostic parameters for transplant. Furthermore, AFP and GGT levels were prognostic for transplanted PVT patients. Only albumin was prognostic in the no-surgery patients.

Conclusion: Transplanted HCC patients have longer survival, smaller tumors, and more severe liver damage than no-surgery patients. Prognostic subsets were identified within the surgery and the PVT groups.

Keywords: AFP; HCC; multifocality; PVT; relationships.

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Introduction

Hepatocellular carcinoma (HCC) typically arises against a backdrop of liver cirrhosis, resulting from chronic liver inflammatory disease. The most frequent causes are hepatitis B virus (HBV) or hepatitis C virus (HCV), along with alcoholism, chronic dietary consumption of chemical carcinogens such as aflatoxin B1, or, increasingly, nonalcoholic fatty liver disease. Different etiologies predominate in various countries; broadly, HBV is more common in Asia (excluding Japan), while HCV and obesity are more prevalent in Western countries.^[1,2] The end results are either death from liver failure or HCC, with tumor growth being a leading cause of death. Since the causes of HCC are largely known, it is a potentially preventable cancer.

HCC patients can be referred to and managed by various hospital departments, most commonly including hepatology, medical oncology, gastrointestinal surgery, liver transplant, and interventional radiology departments. Consequently, the overall picture of HCC in any given large institution can be challenging to discern clearly. In our institution, which has been performing liver transplants since 2002, most HCC patients are referred to and evaluated by a weekly interdisciplinary liver tumor board, where decisions regarding surgery or non-surgical options are made. Patients earmarked for surgery remain within the Liver Transplant Institute for management, while those deemed ineligible for transplant, resection, or ablation are referred to appropriate specialties, typically interventional radiology or oncology.

The aim of this report is to describe the tumor causes, extent, and prognosis of patients treated by liver transplant, and, since 2019, the HCC patients who were ineligible for surgical interventions. We found that survival after transplant is significantly greater than for those not undergoing surgery. Additionally, within the transplant group, there are prognostic subsets that may be useful for evaluating future patients.

Materials and Methods

Clinical

A database derived from our weekly liver tumor board was prospectively created to record baseline tumor characteristics. This included 1322 adult patients (Table 1) with HCC, primarily from the Malatya region and surrounding Turkish provinces. The database was interrogated for predisposing hepatic diseases (when known), baseline radiological tumor characteristics, such as maximum tumor diameter (MTD), number of tumor nodules, presence of macroscopic tumor portal vein thrombosis (PVT) from CT scans, baseline serum alpha-fetoprotein (AFP) levels, standard liver function tests, and routine clinical hematology

parameters. Diagnosis was made either from tumor biopsy or according to AASLD/EASL guidelines. Surgical patients were treated by liver transplantation, while the majority, being non-surgical, received systemic therapy (medical oncology with Sorafenib), locoregional therapy (chemoembolization or radioembolization in interventional radiology), or, in a few cases, only best supportive care.

Ethical Approval

Database management adhered to privacy legislation, and this study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for this retrospective study on deceased cases and de-identified patients with HCC was granted by our Institutional Ethics Committee (Institutional Review Board Approval No. 2022-3905). A waiver from obtaining written informed consent was approved for de-identified and mostly deceased patients, in accordance with local guidelines.

Statistical Analysis

The normal distribution of quantitative variables was tested using the Shapiro-Wilk test and summarized by median, minimum, and maximum values. For comparisons of two independent groups, the Mann-Whitney U test was used. The distribution of qualitative variables was presented by count (percentage), and chi-square tests (Pearson or continuity-corrected, where appropriate) were used for comparisons. Different superscript letters indicate significant differences between column proportions in tables as appropriate. Survival analyses were performed using the Kaplan-Meier method, Log-Rank test, and Cox regression analysis. The two-tailed significance level was set at 0.05. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Results

Patient Demographics

The patient demographics are presented in Table 1. Males predominated (82.5%), and most patients had cirrhosis (81.1%). The predominant etiological predisposing cause was HBV (58.8%), followed by HCV (14.9%) and cryptogenic cirrhosis (8.9%), with minimal cases associated with alcoholism. Most patients had small HCC tumors <5 cm (61.9%), and low serum alpha-fetoprotein (AFP) levels (69.3%). Macroscopic portal vein thrombosis (PVT) was present in 31.9% of the total cohort, and approximately half of the total cohort had multifocal HCC. Median serum parameters were as follows: total bilirubin 1.1 mg/dL, albumin 3.3 g/dL, aspartate aminotransferase (AST) 48 IU/L, gamma-glutamyl transferase (GGT) 82 IU/L, and AFP 12.95 IU/mL with a wide range (0.1–118883), C-reactive protein (CRP) level 11.7 mg/dL, and erythrocyte sedimentation rate (ESR) 24 mm/hr (Table 1).

Patient Survival in Transplant and No-Surgery Patients

Survival was analyzed after dividing patients into a surgical group (majority undergoing liver transplant) and a no-surgery group who received locoregional therapies, sorafenib, or best supportive care (BSC). The median survival of the transplant group (n=434) was 88.73 months, whereas the median survival of the no-surgery group (n=548) was 12.93 months (Table 2 and cumulative survival Figure 1). The patient numbers in this table total only 1092, as many no-surgery patients were lost to follow-up once referred elsewhere for care.

Table 1. Characteristics of the total HCC cohort (n=1322)

	n	%
Gender		
Female	231	17.5
Male	1091	82.5
Cirrhosis		
No	251	18.9
Yes	1071	81.1
HBV		
No	545	41.2
Yes	777	58.8
HCV		
No	1125	85.1
Yes	197	14.9
Alcoholic		
No	1297	98.2
Yes	25	1.8
Cryptogenic		
No	1204	91
Yes	118	8.9
MTD (cm)		
<5 cm	818	61.9
>5 cm	502	38.1
AFP IU/mL		
<100	845	69.3
≥100	495	37.4
PVT # (%)		
No	899	68.1
Yes	423	31.9
Number of tumors		
<2	551	50.9
≥2	532	49.1

	n	Median (Min–Max)
Age	1322	59 (1–89)
NE# (2.1–6.1)	1322	3.72 (0.4–24.69)
LY# (1.3–3.5)	1322	1.32 (0.12–18.3)
CRP (0–0.35)	608	11.7 (3.0–129)
ESR (0–20)	231	24 (0.15–119)
WBC (4.3–10.3)	1322	6.2 (0.7–15)
HGB (13.6–17.2)	1322	13 (3.6–18)
Platelets (150–400)	1322	144 (2.64–934)
T. Bil (0.5–1.2)	1322	1.1 (0.03–19.6)
Alb. (3.4–4.8)	1322	3.3 (0.9–5.4)
Na (136–145)	1181	138 (4.31–149)
Creat (0.72–1.25)	1322	0.8 (0.2–62)
AST (0–34)	1322	48 (9–489)
ALT (0–55)	1322	38 (0.28–446)
GGT (9–64)	1322	82 (8–975)
ALKP (40–150)	1322	117 (1.2–980)
Cholesterol (0–199)	1002	155 (11–617)
LDL (0–100)	975	92 (1–437.4)
HDL (>40)	934	40 (3–131)
AFP (0–8)	1222	12.95 (0.1–118883)
MTD (cm)	1222	3.5 (0.3–38)
NLR	1313	2.75 (0.15–35.25)
APRI	1322	0.93 (0.06–31.63)
GPR	1322	67.57 (3.81–4763.64)

NE: Neutrophils; LY: Lymphocytes; HCC: Hepatocellular carcinoma; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell; HGB: Hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALKP: Alkaline phosphatase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; AFP: Alpha-fetoprotein; maximum tumor diameter; MTD: Maximum tumor diameter; NLR: Neutrophil lymphocyte ratio; APRI: AST to platelet ratio; GPR: Glutamyl transpeptidase-to-platelet ratio.

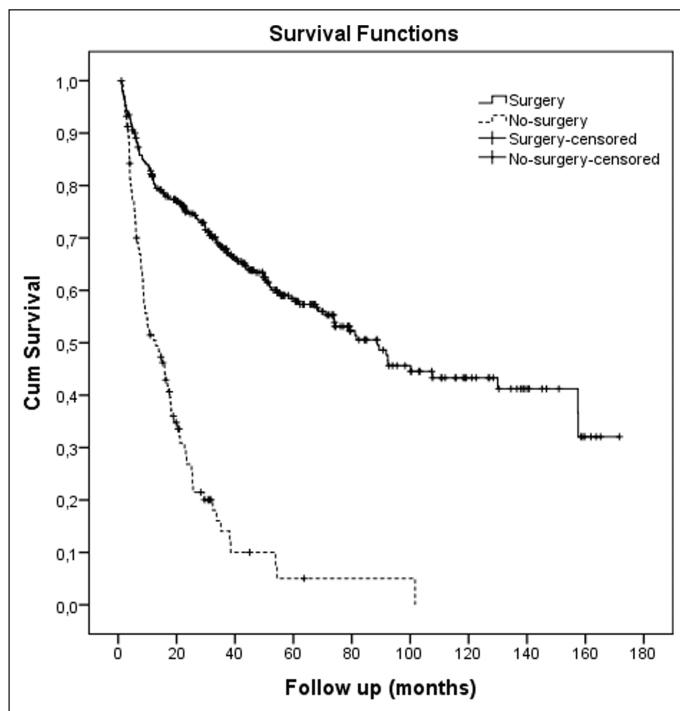


Figure 1. Kaplan-Meier survival graph: transplant vs. no-surgery.

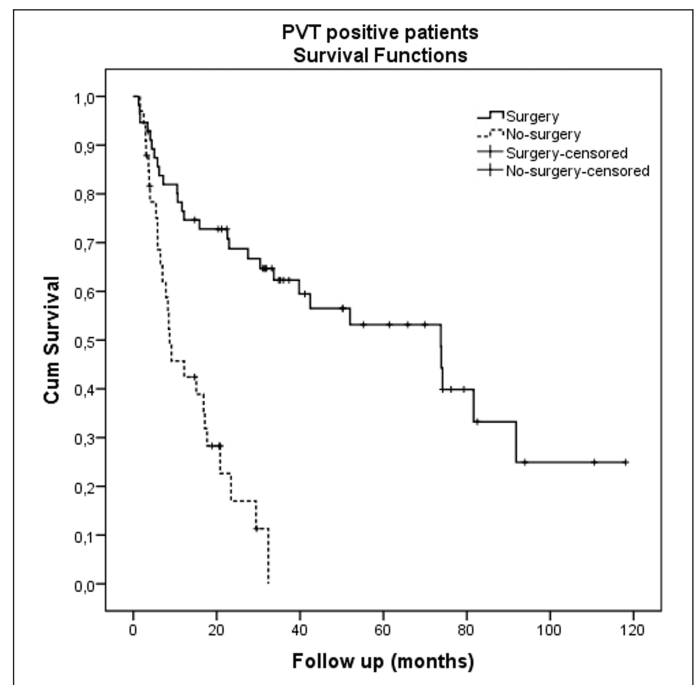


Figure 2. Kaplan-Meier survival graph of PVT positive patients: transplant vs. no-surgery.

Table 2. Survival analysis: transplant versus no-surgery

Treatment group	Kaplan-Meier analysis			Univariate Cox regression	
	Survival (mo.) Mean±SE	Survival (mo.) Median±SE	Log-rank p	HR (95% CI)	HR p
Transplant (n=434)	93.58±4.61	88.73±9.50	<0.001	Reference	
No surgery (n=548)	20.39±2.75	12.93±2.93		4.243 (3.171–5.678)	<0.001

SE: Standard error; HR: Hazard ratio; CI: Confidence interval.

Baseline clinical features of the transplant and no-surgery groups were then compared, as shown in Table 3. Notably, the transplant group had a significantly higher proportion of patients with HBV (transplant 70.9% vs. no-surgery 19%), while the no-surgery group had more HCV (no-surgery 44.6% vs. transplant 17.4%). There were major differences in maximum tumor diameter (MTD) between the two groups, with 80.9% of the transplant group having small tumors with MTD <5 cm compared to 54.0% for the no-surgery group (Table 3a). Conversely, 17.7% of the no-surgery patients had massive HCCs (>10 cm) versus only 0.3% for the transplant patients. These differences were mirrored in the percentages of patients in the three AFP groups, with the majority (78.8%) of transplant patients having low serum AFP <100 IU/mL compared to 67.3% of the no-surgery patients. Patients with very high serum AFP levels >1000 IU/mL were predominantly in the no-surgery group (no-surgery 18.1% vs. transplant 5.8%). Interestingly, the two groups were similar with regard to the percentage of patients with PVT (25.0% transplant vs. 28.0% no-surgery) and tumor multifocality (47.7% vs. 48%). Evidence of portal hypertension (thrombocytopenia) and liver dysfunction (elevated serum total bilirubin, AST, alanine aminotransferase [ALT], alkaline phosphatase [ALKP] levels, and decreased albumin levels) was greater in the trans-

plant group (Table 3b), as liver transplantation is a curative treatment for liver failure. The systemic inflammation markers, platelet-to-lymphocyte ratio (PLR), gamma-glutamyl transpeptidase-to-platelet ratio (GPR), and aspartate aminotransferase-to-platelet ratio index (APRI), yielded conflicting results.

Transplant Patients and Survival

Factors associated with survival in the transplant group were analyzed. Tumor and liver factors were dichotomized according to previously established receiver operating characteristic curve (ROC) cutoffs,^[3] and the associated survivals were then calculated (Table 4). Table 4a shows the effects on survival of various parameters using both Kaplan-Meier and univariate Cox regression analysis. Four parameters—MTD and serum AFP, GGT, and blood platelet levels—had significant Log-Rank p-values and Hazard Ratio (HR) p-values, while the presence of PVT and elevated AST levels adversely influenced survival, but not significantly.

A similar approach was taken for patients with elevated serum AFP levels (Table 4b), but no factor had a significant p-value, although large MTD came close (p=0.062).

Table 3a. Patient characteristics in the surgery and no-surgery groups. Demographics: Transplant versus no-surgery

	Surgery (%)	No-surgery (%)	p
Gender			
Female	13.1	22.6	<0.001
Male	86.9	77.3	
HCV			
No	82.4	55.3	<0.001
Yes	17.4	44.6	
HBV			
No	29.0	81	<0.001
Yes	70.9	19	
Alcoholic			
No	100	97.0	0.163
Yes	0	2.8	
Cryptogenic			
No	88.2	88.7	0.219
Yes	11.7	9.2	
MTD			
≤5 cm	80.9 ^a	54.0 ^b	<0.001
>5–10 cm	18.9 ^a	28.3 ^b	
>10 cm	1(0.2) ^a	17.7 ^b	
AFP			
<100	78.8 ^a	67.3 ^b	<0.001
100–1000	15.3 ^a	14.6 ^a	
>1000	5.8 ^a	18.1 ^b	
PVT			
No	75.0	72.0	0.247
Yes	25.0	28.0	
Number of tumors			
1	52.2	52.0	0.542
>1	47.7	48.0	
Platelets			
<100	48.6 ^a	19.8 ^b	<0.001
100–250	40.8 ^a	50.0 ^b	
>250	10.6 ^a	30.2 ^b	

a, b: Superscript letters indicate the difference between the column proportions. HCV: Hepatitis C virus; HBV: Hepatitis B virus; MTD: Maximum tumor diameter; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis.

Given that the presence of PVT is considered the worst prognostic factor for HCC patients, yet is present in 25% of the transplant patients in this study, we explored whether there might be prognostic subsets within the PVT-associated transplant patient group (Table 4c). Serum GGT and AFP levels were found to be significant for survival within this PVT-associated group. Patients with lower levels of either GGT or AFP had more than double the median survival of patients with elevated levels of these two parameters; PVT patients with the combination of low AFP plus low GGT levels had a five-fold greater median survival compared to patients with elevated AFP plus GGT levels (81.63 mo. vs 15.87 mo).

Table 3b. Patient characteristics in the surgery and no-surgery groups. Laboratory characteristics: Surgery versus no-surgery

	Transplant Median (Min–Max)	No-surgery Median (Min–Max)	p
Age	56 (1–82)	61 (6–87)	<0.001
NE# (2.1–6.1)	3.2 (0.4–14.1)	4.1 (0.4–24.7)	<0.001
LY# (1.3–3.5)	1.2 (0.2–18)	1.5 (0.1–18.3)	<0.001
CRP (0–0.35)	1.3 (0.2–129)	1 (0.1–127)	0.076
ESR	18.5 (1–109)	28.5 (0.2–119)	0.034
WBC (4.3–10.3)	5.4 (0.7–15)	6.6 (1–14.9)	<0.001
HGB (13.6–17.2)	13 (6.3–18)	13.1 (3.6–18)	0.066
Platelets (150–400)	101.5 (16–640)	176.5 (2.6–934)	<0.001
T. Bil (0.5–1.2)	1.6 (0.1–17.3)	0.9 (0–14.5)	<0.001
Albumin (3.4–4.8)	3 (1–5.2)	3.5 (0.9–5.4)	<0.001
Sodium (136–145)	136 (19–149)	138 (4.3–148)	<0.001
Creat (0.72–1.25)	0.8 (0.3–13.8)	0.8 (0.4–62)	0.055
AST (0–34)	54 (9–489)	41 (9–470)	<0.001
ALT (0–55)	39 (5–446)	34 (0.3–321)	0.001
GGT (9–64)	67.5 (11–719)	91 (8–975)	<0.001
ALKP (40–150)	113.5 (24–810)	119 (1.2–980)	0.008
AFP (0–8)	11.1 (0.2–29528)	11.9 (0.1–118883)	0.115
MTD (cm)	3 (0.3–12)	5 (0.4–58)	<0.001
PVT # (%)	116 (26.1)	200 (22.8)	0.247
PLR	86.79 (2.61–610)	115.63 (1.66–1061.36)	<0.001
APRI	1.4 (0.08–31.63)	0.67 (0.06–29.36)	<0.001
GPR	75.3 (4.36–700)	59.23 (3.81–4763.64)	0.004

NE: Neutrophils; LY: Lymphocytes; HCC: Hepatocellular carcinoma; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood cell; HGB: Hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALKP: Alkaline phosphatase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; AFP: Alpha-fetoprotein; maximum tumor diameter; MTD: Maximum tumor diameter; NLR: Neutrophil lymphocyte ratio; APRI: AST to platelet ratio; GPR: Glutamyl transpeptidase-to-platelet ratio.

An identical analytical approach was applied to patients with both PVT and large tumors (Table 4d). However, significant prognostic subsets could not be identified, likely due to small patient numbers. Nevertheless, patients with low levels of serum GGT had a two-fold increase in median survival, though not significantly, while patients with low serum AFP levels had a seven-fold increase in median survival, again without statistical significance due to low patient numbers.

Patients with PVT in the Transplant versus No-Surgery Groups

The percentage of patients with PVT was similar in the transplant and no-surgery groups (Table 3), despite a large survival difference between the two groups. To examine this observation further, PVT-positive transplant and PVT-positive no-surgery groups were compared (Table 5). The majority of patients in each subgroup had small tumors <5 cm (76.8% transplant vs. 59.4% no-surgery, p=0.234), although there were more in the transplant group. AFP levels were significantly different, with more patients having low serum AFP <100 IU/mL in the transplant group (72.7% transplant vs. 54.6% no-surgery, p=0.007). Furthermore, there were significantly more patients in the no-surgery group with very high AFP levels >1000 IU/mL (33.3% no-surgery vs. 7.3% transplant). Thus, transplant patients with PVT also had less aggressive tumors than

Table 4a. Survival analysis of transplant group. Transplant cohort survival subsets

	Kaplan-Meier analysis			Univariate Cox regression	
	*Survival Mean±SE	*Survival Median±SE	Log-rank p	HR (95% CI)	HR p
MTD					
<5 cm (n=340)	94.94±5.12	89.37±13.58	0.006	Reference	0.007
≥5 cm (n=94)	72.67±9.35	37.30±10.13		1.701 (1.159–2.498)	
PVT					
No (n=352)	95.76±4.98	100.20±20.75	0.073	Reference	0.075
Yes (n=82)	61.18±3.78	73.77±20.94		1.465 (0.962–2.231)	
Number of nodules					
1 (n=223)	92.62±6.43	89.37±NA	0.944	Reference	0.944
>1(n=211)	88.81±6.25	81.63±9.92		0.988 (0.701–1.392)	
AFP					
<100 (n=334)	101.10±5.23	100.20±19.26	0.002	Reference	0.002
≥100 (n=100)	63.43±7.79	38.97±12.06		1.815 (1.238–2.661)	
T. Bil					
<1.5 (n=183)	94.29±6.39	91.83±25.65	0.972	Reference	0.972
≥1.5 (n=251)	91.15±6.29	81.63±9.06		1.006 (0.725–1.396)	
GGT					
<50 (n=280)	104.94±5.67	157.43±28.97	0.001	Reference	0.001
≥50 (n=154)	67.24±5.98	51.97±6.93		1.740 (1.250–2.423)	
AST					
<40 (n=331)	96.48±4.93	107.63±20.10	0.066	Reference	0.067
≥40 (n=103)	73.89±9.31	52.53±10.06		1.414 (0.973–2.048)	
Albumin					
≥3.5 (n=111)	87.18±8.29	67.97±12.04	0.388	Reference	0.388
<3.5 (n=323)	94.93±5.33	89.37±9.81		0.852 (0.591–1.227)	
Platelets					
<125 (n=282)	99.60±5.52	92.37±20.18	0.025	Reference	0.026
≥125 (n=152)	77.63±7.51	55.40±12.17		1.470 (1.046–2.066)	

*: Survival, months. MTD: Maximum tumor dimension; PVT: Portal vein thrombosis; GGT: Gamma glutamyl transpeptidase; AST: Aspartate amino transferase; AFP: Alpha-fetoprotein; T. Bili: Total bilirubin; NA: Not available; HR: Hazard ratio; CI: Confidence interval.

the no-surgery patients (Tables 5a, b). As noted in the transplant versus no-surgery cohorts of Tables 3b and 5b, cirrhosis (thrombocytopenia) and liver dysfunction (elevated total bilirubin and AST, lower albumin) were more severe in the transplant group. The median survival of these PVT-positive patients was significantly better in the surgery (55 liver transplant) compared to the no-surgery group (73.7 months vs. 8.7 months, $p<0.001$), as shown in Table 5c and Figure 2.

No-Surgery Patients and Survival

Table 2 illustrates the markedly decreased survival for patients not treated by transplant. The accompanying graph shows a significant decline in cumulative survival within the first 12 months, and no prognostic subsets could be identified among them (data not shown). For those no-surgery patients who survived beyond 12 months, the only significant survival differences were observed in the albumin groups (Table 6a and Figure 3). Additionally, no significant survival effects were found when comparing different locoregional medical therapies, such as chemoembolization or radioembolization (Table 6b).

Discussion

The results presented provide a snapshot of HCC seen in a major tertiary referral center in our part of Turkiye (Table 1). The 4:1 gender ratio is typical for this region, and 81.1% of the patients had cirrhosis. The most common predisposing disease was HBV, followed by HCV, with little alcoholism (reflecting the Muslim country) and 8.9% of patients had cryptogenic cirrhosis, although a large portion of that is likely previously unrecognized metabolic-associated cirrhosis. The majority of the patients had relatively small (<5 cm) tumors at baseline presentation (61.9%) and low AFP levels (69.3%). PVT was present in 31.9%, consistent with other series,^[4] and half the patients had unifocal tumors. Serum parameters included median total bilirubin and alanine aminotransferase (ALT) levels within the normal range, but slightly elevated median aspartate aminotransferase (AST), alkaline phosphatase (ALKP), and gamma-glutamyl transferase (GGT) levels, and slightly low albumin levels.

Although this is a major liver transplant center, the clinical data for no-surgery patients were also documented at baseline, as well as their

Table 4b. Survival analysis of transplant group. Survival analysis for Transplant group surviving >30 days, AFP≥100 IU/mL patients

	Kaplan-Meier analysis			Univariate Cox regression	
	*Survival Mean±SE	*Survival Median±SE	Log-rank p	HR (95% CI)	HR p
MTD					
<5 cm (n=60)	71.03±9.72	61.80±20.28	0.058	Reference	0.062
≥5 cm (n=34)	43.45±11.61	22.97±8.58		1.885 (0.968–3.670)	
GGT					
<50 (n=57)	71.16±10.60	38.97±17.76	0.300	Reference	0.302
≥50 (n=37)	52.70±10.75	21.97±18.93		1.413 (0.733–2.724)	
AST					
<40 (n=65)	68.69±9.28	51.97±20.32	0.376	Reference	0.378
≥40 (n=29)	37.48±6.11	29.73±5.95		1.386 (0.671–2.862)	

*: Survival, months. MTD: Maximum tumor dimension; GGT: Gamma glutamyl transpeptidase; AST: Aspartate; amino transferase; HR: Hazard ratio; CI: Confidence interval.

Table 4c. Survival analysis of transplant group. Survival analysis for PVT+ve Transplant patients surviving >30 days

	Kaplan-Meier analysis			Univariate Cox regression	
	*Survival Mean±SE	*Survival Median±SE	Log-rank p	HR (95% CI)	HR p
MTD					
<5 cm (n=41)	59.69±7.55	73.77±17.60	0.681	Reference	0.681
≥5 cm (n=15)	65.44±12.41	81.63±47.87		0.837 (0.359–1.952)	
GGT					
<50 (n=34)	72.27±8.24	81.63±5.18	0.028	Reference	0.033
≥50 (n=22)	44.58±8.84	33.70±11.53		2.265 (1.069–4.800)	
AST					
<40 (n=47)	60.37±7.50	73.77±19.42	0.977	Reference	0.977
≥40 (n=9)	53.44±11.81	74.17±24.40		0.986 (0.374–2.597)	
AFP					
<100 (n=40)	71.49±8.50	81.63±5.79	0.022	Reference	0.026
≥100 (n=15)	38.68±8.61	30.40±12.79		2.370 (1.109–5.067)	
AFP & GGT					
<100 & <50 (n=29)	76.72±8.68	81.63±8.22	0.011	Reference	0.016
≥100 & ≥50 (n=10)	39.05±10.90	15.87±21.82		3.179 (1.246–8.109)	

*: Survival, months. PVT: Portal vein thrombosis; MTD: Maximum tumor dimension; GGT: Gamma glutamyl transpeptidase; AST: Aspartate amino transferase; AFP: Alpha-fetoprotein; HR: Hazard ratio; CI: Confidence interval.

survival, when follow-up was feasible, as shown in Tables 2 and 3. A major finding of this paper was the seven-fold survival difference between the transplant group and all other patients, which is unsurprising and consistent with the literature.^[5] It is hoped that the large number of newly approved drugs, especially immune checkpoint inhibitor agents, might narrow this gap in the coming years. The sequencing and possible combinations of the newer (kinase inhibitors, immune checkpoint inhibitors, cell signaling inhibitors) and older (chemoembolization, radioembolization) no-surgery agents are the subject of intense current clinical trial activity.

The transplant and no-surgery patients were then compared for their clinical characteristics (Table 3), in view of the large survival dif-

ferences seen in Table 2. The main differences related to etiology, with more HBV in the transplant group (70.9% vs. 19%) and more HCV in the no-surgery group (44.6% vs. 16.4%). Perhaps this related to maximum tumor diameter (MTD), but the percentages of patients with PVT and multifocality were similar in the two treatment groups. Small tumors of <5 cm constituted 80.9% of the transplant patients (consistent with the Milan criteria), but only 54% of the no-surgery patients, whereas very large tumors were almost entirely confined to the no-surgery group. Similarly, patients with low serum AFP levels constituted 78.8% of the transplant group vs. 67.3% of the no-surgery group, and as with MTD, patients with extremely high AFP levels were mainly in the no-surgery group (18.1% vs. 5.8%). Surprisingly, the incidence of both PVT and multifocality

Table 4d. Survival analysis of transplant group. Survival analysis for Transplant patients surviving >30 days, PVT+ve and MTD \geq 5 cm

	Kaplan-Meier analysis			Univariate Cox regression	
	*Survival Mean \pm SE	*Survival Median \pm SE	Log-rank p	HR (95% CI)	HR p
GGT					
<50 (n=8)	68.69 \pm 12.03	81.63 \pm 43.56	0.349	Reference	0.358
\geq 50 (n=7)	51.71 \pm 17.52	39.77 \pm 43.56		1.975 (0.463-8.431)	
AST					
<40 (n=11)	58.46 \pm 13.38	39.77 \pm 33.04	0.367	Reference	0.384
\geq 40 (n=4)	73.11 \pm 18.04	NA		0.393 (0.048-3.209)	
AFP					
<100 (n=11)	79.24 \pm 14.66	81.63 \pm NA	0.078	Reference	0.095
\geq 100 (n=4)	34.28 \pm 19.39	11.67 \pm 6.17		3.307 (0.811-13.477)	
AFP & GGT					
<100 & <50 (n=6)	87.78 \pm 4.35	81.63 \pm NA	0.259	Reference	0.289
\geq 100 & \geq 50 (n=2)	51.75 \pm 40.08	11.67 \pm NA		3.766 (0.324-43.719)	

*: Survival, months. PVT: Portal vein thrombosis; MTD: Maximum tumor dimension; GGT: Gamma glutamyl transpeptidase; AST: Aspartate amino transferase; AFP: Alpha-fetoprotein; HR: Hazard ratio; CI: Confidence interval.

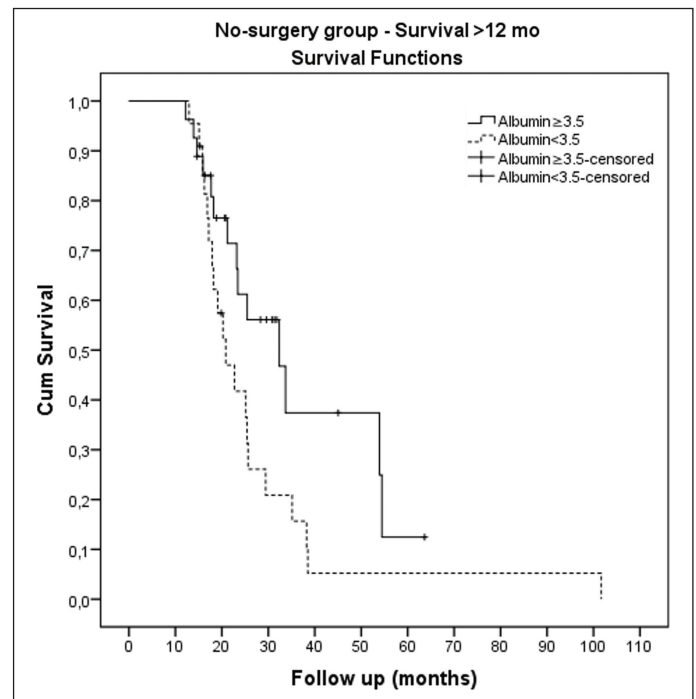
Table 5a. PVT positive patients in surgery and no-surgery groups. PVT positive patients, transplant versus no-surgery: demographics

	Surgery (%)	No-surgery (%)	p
Gender			
Female	8 (14.3)	10 (30.3)	0.123
Male	48 (85.7)	23 (69.7)	
MTD			
\leq 5 cm	43 (76.8)	19 (59.4)	0.234
>5–10 cm	12 (21.4)	12 (37.5)	
>10 cm	1 (1.8)	1 (3.1)	
AFP			
<100	40 (72.7) ^a	18 (54.6) ^a	0.007
100–1000	11 (20.0) ^a	4 (12.1) ^a	
>1000	4 (7.3) ^a	11 (33.3) ^b	
PLT			
<100	25 (44.6) ^a	4 (12.1) ^b	<0.001
100–250	28 (50.0) ^a	17 (51.5) ^a	
>250	3 (5.4) ^a	12 (36.4) ^b	

a, b: Superscript letters indicate the difference between the column proportions. PVT: Portal vein thrombosis; MTD: Maximum tumor dimension; AFP: Alpha-fetoprotein; PLT: Platelet.

was similar in the two treatment groups. As shown in the results section, liver function was worse in the transplant group (higher total bilirubin, AST, and ALT, with lower albumin levels), but their survival was much better than for no-surgery patients, as liver transplantation is curative for liver failure.

The transplant patients were further examined. Their tumor and liver function parameters were dichotomized, and four parameters showed significantly different survival within their parameter pairs.

**Figure 3.** Kaplan-Meier survival graph of no-surgery patients. Albumin \geq 3.5 vs <3.5.

These were serum AFP, GGT, MTD, and platelets (Table 4a), with all four having significant hazard ratios, the highest being for AFP, followed closely by GGT. The reason for the significance of platelets is unclear (Tables 3 and 4), although they had the lowest of the significant hazard ratios, and thrombocytopenia is regarded as a cirrhosis surrogate.^[6,7] Probably the advanced cirrhosis and associated portal hypertension caused these patients to get diagnosed earlier with resulting definitive therapy by liver transplantation. Given the

Table 5b. PVT positive patients in surgery and no-surgery groups. Laboratory characteristics in PVT positive patients: transplant versus no-surgery.

	Surgery		No-surgery		p
	n	Median (Min–Max)	n	Median (Min–Max)	
Platelets (150–400)	56	102.5 (34–528)	33	212.5 (24–691)	<0.001
T. Bil. (0.5–1.2)	56	1.71 (0.3–12.5)	33	0.7 (0.28–2.45)	<0.001
Albumin (3.4–4.8)	56	2.9 (1.6–4.5)	33	3.6 (1.7–4.9)	<0.001
AST (0–34)	56	57.5 (24–248)	33	34 (13–128)	<0.001
ALT (0–55)	56	36.5 (5–165)	33	32 (0.28–128)	0.079
GGT (9–64)	56	76 (17–719)	33	126 (17–681)	0.120
ALKP (40–150)	56	133.5 (37–810)	33	128 (39–385)	0.538
AFP (0–8)	55	10.1 (0.68–14560)	33	59.8 (0.2–19211.6)	0.461
MTD (cm)	56	2.8 (1–12)	32	4.4 (1–12)	0.081

PVT: Portal vein thrombosis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ALKP: Alkaline phosphatase; AFP: Alpha-fetoprotein; maximum tumor diameter; MTD: Maximum tumor diameter.

Table 5c. Survival analysis of transplant group. Survival analysis: PVT positive transplant versus no-surgery (patients surviving >30 days)

Treatment group	Kaplan-Meier analysis			Univariate Cox regression	
	*Survival (mo.) Mean±SE	*Survival (mo.) Median±SE	Log-rank p	HR (95% CI)	HR p
Surgery (n=56)	61.18±6.78	73.77±20.94	<0.001	Reference	
No-surgery (n=33)	13.65±1.89	8.70±2.68		4.313 (2.310–8.054)	<0.001

*: Survival, months; HR: Hazard ratio; CI: Confidence interval.

prognostic importance for liver transplantation of high AFP levels, we looked for survival subsets in this group (Table 4b), but only MTD <5 cm came close.

The other major prognostic factor for liver transplantation for HCC is the presence of PVT.^[8] Parameter dichotomization (Table 4c) showed that both AFP and GGT were significant for survival, and especially the combination of these two parameters, which revealed a five-fold survival difference in these PVT patients (81.63 months for low parameter levels vs. 15.87 months for high parameter levels, hazard ratio of 3.179). These observations have potential usefulness in the selection for liver transplantation of appropriate HCC patients with PVT in the future. A further subgroup analysis of HCC patients with PVT was then made, focusing on PVT-positive patients with large tumors (Table 4d). Although the combination of AFP plus GGT again showed survival differences, the very small patient numbers in this sub-subgroup precluded statistical significance. PVT-positive patients were then compared with respect to transplant versus no-surgery treatment groups. There was a nine-fold survival difference in favor of the transplant surgery group, with a hazard ratio of 4.313, p<0.001 (Table 4c). The transplant patients had smaller tumors and lower AFP levels, which likely helped explain the big survival advantage, in addition to the fact of the treatment itself being the major cause of the survival advantage. These findings suggest that HCC patients with PVT and low serum AFP and GGT levels might be suitable for treatment with liver transplantation. In a large series of transarterial radioembolization (TARE) treatment for PVT-positive HCC patients, the median overall survival was 7–13 months, depending

on liver and tumor factors.^[9] Others have also shown significantly increased survival of these PVT patients with surgery compared to no-surgery treatments.^[10]

The no-surgery group was approached similarly, using parameter dichotomization, but only serum albumin levels were found to be significant (Table 6a and Figure 3). The no-surgery group included patients treated with sorafenib, regional interventional therapies of transarterial chemoembolization (TACE) or TARE, or best supportive care (Table 6b). Patients with regional interventional therapies were compared to the rest of the no-surgery group, but neither appeared to offer a particular survival advantage (15.93 months for TACE and 10.1 months for TARE) compared to the other no-surgery patients at the time of writing (median survival of 12.93 months as shown in the graph within Table 2). Although survival rates for non-surgical management have been increasing in recent years, none of them approaches the results of surgery. TACE and TARE seem to offer similar survival on meta-analysis,^[11] and survival of 17–18 months on direct comparison.^[12] The median overall survival after Sorafenib was 10.7 months,^[13] while the median overall survival was recently reported to be 19 months for the combination of atezolizumab plus bevacizumab,^[14] which has now become an approved first-line therapy for no-surgery HCC patients. However, the median survivals continue to increase, as new combinations emerge, such as the recently published combination of immune checkpoint inhibitor camrelizumab plus tyrosine kinase inhibitor rivoceranib yielding overall survival of 22.1 months versus sorafenib of 15.2 months,^[15] although sorafenib appears increasingly outmoded.

Table 6a. Survival analysis of the no-surgery group. Survival analysis (survivals>12 mo) for no-surgery group

	Kaplan-Meier analysis		
	*Survival time Mean±SE	Survival time Median±SE	Log-rank p
MTD			0.709
<5 cm	36.79±6.60	23.43±3.25	
≥5 cm	28.48±3.56	25.47±4.98	
PVT			0.129
No	38.12±5.87	25.47±6.16	
Yes	23.18±2.21	20.83±3.57	
Number of nodules			0.171
1	28.10±3.70	21.17±2.00	
>1	38.12±6.56	35.13±7.46	
AFP			0.809
<100	30.52±3.38	23.43±3.35	
≥100	39.46±11.55	25.43±4.03	
T. Bil			0.981
<1.2	32.12±4.96	25.47±1.83	
≥1.2	30.15±5.22	18.17±4.56	
GGT			0.673
<100	29.44±2.71	25.43±1.89	
≥100	40.99±10.99	25.17±7.39	
Albumin			0.047
≥3.5	36.04±4.25	32.37±5.44	
<3.5	27.07±4.41	20.83±2.54	
Platelets			0.769
<125	30.95±4.00	23.43±1.84	
≥125	34.71±6.48	25.43±2.60	

*: Survival, months; MTD: Maximum tumor dimension; PVT: Portal vein thrombosis; GGT: Gamma glutamyl transpeptidase; AFP: Alpha-fetoprotein; T. Bili: Total bilirubin.

Conclusion

Some strengths of this study include the large patient number from a single institution and the ability to evaluate both transplant and no-surgery patients who were evaluated by the same team and conditions. Disadvantages include the large loss to follow-up and thus survival data in the no-surgery cohort and the non-randomized nature of the treatment groups. Indeed, other than noting the large survival differences and thus stressing once again the importance of liver transplantation in this disease, the two groups are non-comparable. Notwithstanding these considerations, this analysis reinforces the idea that when transplant is possible, it produces much better survival results than any no-surgery therapies so far, despite our non-inclusion of patients treated with immune checkpoint inhibitors, which are not yet covered by insurance for HCC in this country. Also, the 80 plus months of survival in transplant patients with PVT and having low serum levels of AFP or GGT might suggest a future controlled study of the inclusion of such PVT patients for liver transplant eligibility. The results also suggest the importance of downstaging efforts to get more of the advanced-stage patients to be within the (slowly expanding)^[16] criteria for liver transplantation.

Table 6b. Survival analysis of the no-surgery group. Survival analysis (survivals >30 days) for no-surgery group by treatment

	Kaplan-Meier analysis		
	Survival time Mean±SE	Survival time Median±SE	Log-rank p
Medical+TARE (n=89)	17.41±1.89	10.73±2.78	0.259
TACE (n=14)	29.72±9.57	15.93±0.86	
Medical+TACE (n=29)	28.00±6.73	15.87±2.94	0.170
TARE (n=74)	16.03±1.70	10.10±3.08	

Medical includes Sorafenib plus Best Supportive Care; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Ethics Committee Approval: The Inonu University Clinical Research Ethics Committee granted approval for this study (date: 04.10.2022, number: 2022- 3905).

Author Contributions: Concept – BIC; Design – BIC; Supervision – BIC; Fundings – BIC; Materials – SY, BI, VI, AB; Data Collection and/or Processing – SY, BI, VI, AB; Analysis and/or Interpretation – HB; Literature Search – BIC; Writing – BIC, SY; Critical Reviews – BIC, SY, VI.

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