JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.03164
J Inonu Liver Transpl Inst 2024;2(2):72–77

Original Research

Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience

Volkan Ince,[1] Sertac Usta,[1] Brian Carr,[1] Ramazan Kutlu,[2] Mustafa Dikilitas,[3] Murat Harputluoglu,[4] Aysegul Sagir Kahraman,[2] Oztun Temelli,[5] Ayse Nur Akatli,[6] Ersoy Kekilli,[7] Burak Isik,[1] Sezai Yilmaz[1]

[1]Department of General Surgery, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[2]Department of Radiology, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[3]Department of Medical Oncology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[4]Department of Gastroenterology and Hepatology, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
[5]Department of Radiation Oncology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[6]Department of Pathology, Inonu University, Faculty of Medicine, Malatya, Türkiye
[7]Department of Nuclear Medicine, Inonu University, Faculty of Medicine, Malatya, Türkiye

Abstract

Objectives: The aim of this study is to present updated data on liver transplantation (LT) for hepatocellular carcinoma (HCC) of Inonu University, Liver Transplantation Institute, one of the largest volume liver transplant centers in the world.

Methods: The data of 492 LT patients with HCC were analyzed retrospectively from the databank which is recorded prospectively and sequentially. Post-transplant recurrence rates and patient survival according to Milan, Malatya and Expanded Malatya criteria were calculated. Milan Expansion rate of the Malatya and Expanded Malatya criteria were also calculated.

Results: Median follow-up period of the total cohort was 11.1±1.6 years (8.0–14.2, 95% CI) and the recurrence rate was 18.5 % (91/492). 5-year OS according to Milan, Malatya and Expanded Malatya criteria in our cohort were 80%, 79.3% and 78.4%, respectively. Post-transplant recurrence rates within these criteria were 3.2%, 3.8%, and 4.7%, respectively. Milan expansion rates were 25.2% for Malatya criteria and 35.2% for Expanded Malatya criteria.

Conclusion: Milan criteria can be expanded reasonably by Expanded Malatya criteria. Low GGT and low AFP are good prognostic biomarkers that predict survival following LT in patients with HCC. Patients within Expanded Malatya Criteria had 78.4% 5-year OS, 4.7% post-transplant recurrence rate and Expanded Malatya criteria expanded the Milan criteria by 35.2%. Thus, 88 patients were beyond Milan criteria and were within Expanded Malatya criteria and so had an opportunity for LT.

Keywords: Liver tumor, live donor, hepatic transplantation

Please cite this article as "Ince V, Usta S, Carr B, Kutlu R, Dikilitas M, Harputluoglu M, et al. Liver Transplantation for Hepatocellular Carcinoma with Expanded Criteria: Malatya Experience. J Inonu Liver Transpl Inst 2024;2(2):72–77".

Hepatocellular carcinoma (HCC) is the 6th commonest cancer globally with 866.136 new cases and the 3rd global cause for cancer related deaths, with 758.725 deaths in the world.[1] It seems that it will continue to be one of the leading cancers in the future with an estimated number of annual new HCC cases of 1.52 million and deaths of 1.37 million by 2050.[2] Liver transplantation (LT) has an important role in the treatment of HCC patients by providing a chance of cure by removing both the underlying liver disease and as well as the tumor.

Address for correspondence: Volkan Ince, MD. Department of General Surgery, Inonu University, Liver Transplantation Institute, Malatya, Türkiye
Phone: +90 505 326 04 62 **E-mail:** volkanince@outlook.com

Submitted Date: 22.09.2024 **Revised Date:** 27.09.2024 **Accepted Date:** 30.09.2024 **Available Online Date:** 09.10.2024

Milan criteria were the first to be accepted globally for HCC patients for LT. We defined Malatya and Expanded Malatya criteria from Türkiye. In Türkiye, one of the countries with a cadaveric organ shortage, the patient selection criteria for deceased donor liver transplantation (DDLT) in patients with HCC are still the Milan criteria.[3] On the other hand, the search for criteria that will predict the best outcomes in LT for HCC continues.

In this study, we aimed to share the outcomes of patients with HCC who underwent LT in our institute, which is one of the largest transplantation centers in the world.

Methods

Inonu University Ethics Committee approved this study by approval no: 2024/6410. No informed consent was requested from patients since this is a retrospectively designed study.

Study Population

Between March 2002 and July 2024, 3784 LTs were performed at the Liver Transplantation Institute of Inonu University. We retrospectively analyzed the data of LT patients from the database which is recorded prospectively and sequentially. Patient demographics, tumor morphology (according to explant pathology report), etiology of the underlying liver disease, pre-transplant laboratory values, CHILD-Pugh class, MELD Na score, graft to recipient weight ratio (GRWR), overall (OS) and disease-free survival (DFS) years post-transplant and recurrence rate were recorded. Patient survivals were then calculated according within or beyond Milan criteria,[4] Malatya[5] and Expanded Malatya criteria.[6] Finally, the rate of expansion which the Malatya and Expanded Malatya criteria expanded the Milan criteria, were calculated.

Patient Inclusion and Exclusion Criteria

- Inclusion criteria
- Patients whose HCC was confirmed pathologically at the explant specimen
- Exclusion criteria
- Patients who had combined HCC and cholangio carcinoma
- Patients with post-transplant follow up period of less than 90 days

Definition of Milan Criteria[4]

- Patients with HCC who had no macrovascular invasion, no extrahepatic disease, for single nodule, maximum tumor diameter should be less than 5 cm; for multiple nodules, number of nodules should be less than 3 nodules and maximum tumor diameter of all nodules should be less than 3 cm.

Definition of Malatya Criteria[5]

- Patients with HCC should not have macrovascular invasion and extrahepatic metastasis
- If patient is within Milan criteria, its accepted as also within Malatya criteria
- If patient is beyond Milan criteria, should meet all the following 4 parameters
    - o Largest tumor diameter ≤ 6 cm
    - o AFP ≤ 200 ng/ml
    - o GGT ≤ 104 IU/ml
    - o Well or moderately tumor differentiation

Definition of Expanded Malatya Criteria[6]

- Patients with HCC should not have macrovascular invasion and extrahepatic metastasis
- If patient is within Milan criteria, its accepted as also within Expanded Malatya criteria
- If patient is beyond Milan criteria, should meet all the following 3 parameters
    - o Largest tumor diameter ≤ 10 cm
    - o AFP ≤ 200 ng/ml
    - o GGT ≤ 104 IU/ml

Surgical Technique and Management of Immunosuppressive Treatment

- Our patient selection criteria, surgical method in LT for HCC, and immunosuppressive treatment protocol have been described in our previous studies.[5, 7-10]

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.
- Overall survival defined as the time between the transplant day and death and calculated as years and death patients were censored by Kaplan-Meier method.
- Disease-free survival defined as the time between the

transplant day and the recurrence day and calculated as years and recurred patients and death patients were censored by Kaplan-Meier method.

- All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp, Armonk, NY).

Between March 2002 and July 2024, 3784 LTs were performed at the Liver Transplantation Institute of Inonu University, of which 592 (15.6%) were due to HCC. Following the inclusion and exclusion criteria, data of remaining 492 HCC patients were analyzed.

Annual LT numbers for HCC patients at our institute were shown at Figure 1. We thus perform an average of 35 to 40 LT for patients with HCC annually.

Median age was 56 (1–72 years), rate of male gender was 86.6% (n=426). Median AFP 12.3 (0.2–55.000 ng/ml), MELD/PELD 13 (6–41), Largest tumor diameter 3 (0.1–26 cm), number of nodules 2 (1–36). Demographics, laboratory parameters, and tumor data were summarized at Table 1.

Median follow-up period of the total HCC cohort was 11.1±1.6 years (8.0–14.2, 95% CI) and recurrence rate was 18.5% (91/492) (Table 1).

Survivals of the Total HCC Cohort (n=492)

1-, 5- and 10-year overall and disease-free survivals of the total cohort were 87.6%, 65% and 52.9% and 82.8 %, 62.3 %, and 51.4 % respectively, and recurrence rate in total cohort was 18.5 % (n=91).

Survivals According to Milan Criteria (Figs. 2a, 3a)

When we dichotomized the total cohort according to Milan criteria by pathology report, 250 patients were within Milan and 242 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Milan criteria were 91.3%, 80% and 66.1 % for overall and 90.9 %, 78.5 %, and 63.8 % for disease-free, respectively, and the recurrence rate in patients within Milan

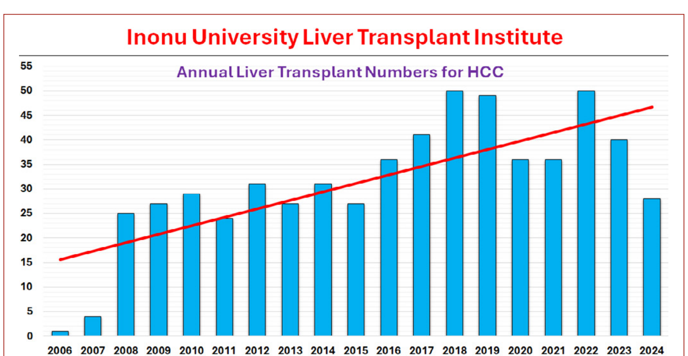

Figure 1. Annual liver transplant numbers for HCC at Inonu University, Liver Transplantation Institute.

Table 1. Demographics, tumor features, and laboratory parameters of all cohort

Parameters	Median	Minimum	Maximum
Age, years	56	1	72
AFP, ng/ml	12.3	0.2	55000
LTD, cm	3.0	0.1	26,00
NN	2.00	1	36
BSA	1.92	0.38	2.54
BMI	26.0	14.80	46.90
NLR	2.6	0.10	35.30
PLR	81.8	2.60	1092.30
Platelets, $x10^3$/uL	96	15	701
INR	1.31	0.82	4.10
Albumin g/dl	3.0	1.20	5.20
Total Bilirubin, mg/dl	1.87	0.23	44.70
Creatinine, mg/dl	0.8	0.22	13.8
AST, U/L	59	9	7789
ALT, U/L	42	10	3535
ALP, U/L	118	28	2327
GGT, IU/L	73	11	1396
MELD Na	13	6	41
	n	**%**	
Recurrence			
Yes	91	18.5	
No	401	81.5	
Milan criteria			
In	250	50.8	
Out	242	49.2	
Malatya criteria			
In	313	63.6	
Out	179	36.4	
Malatya criteria			
In	338	68.7	
Out	154	31.3	
Gender			
Male	426	86.6	
Female	66	13.4	
CHILD class			
A	175	35.6	
B	205	41.7	
C	112	22.8	
AFP, ng/ml			
≤200	410	83.3	
>200	77	15.7	
Missed	5	1.0	
GGT, ng/ml			
≤104	318	64.6	
>104	172	35	
Missed	2	0.4	
Differentiation			
Well	210	42.7	
Moderate	208	42.3	
Poor	73	14.8	
Missed	1	0.2	

Table 1. Demographics, tumor features, and laboratory parameters of all cohort (Cont.(

	n	%
Venous invasion		
None	270	54.9
Microvascular	165	33.5
Macrovascular	57	11.6
Etiology		
Viral hepatitis	374	76.0
Cyrptogenic	74	15.0
Budd-Chiari	12	2.4
Ethanol	10	2.0
Metabolic	8	1.6
Others	14	2.8
GRWR		
≥0.8	428	87
<0.8	51	10.6
Missed	13	2.6

criteria was 3.2 % (n=8).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Milan criteria were 83.7 %, 49.2 % and 38.9 % and 74.2 %, 45.1 %, and 38.1 % respectively, and recurrence rate in patients beyond Milan criteria was 34.3 % (n=83).

Survivals According to Malatya Criteria (Figs. 2b, 3b)

When we dichotomize the whole cohort according to Malatya criteria by pathology report, 313 patients were within Malatya and 179 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Malatya criteria were 91.6%, 79.3 % and 67.6 % and 91.3 %, 77.8 %, and 65.6 % respectively, and recurrence rate in patients within Malatya criteria was 3.8 % (n=12).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Malatya criteria were 80.7 %, 40 % and 26.7 % and 68 %, 35.1 %, and 26 % respectively, and recurrence rate in patients beyond Malatya criteria was 44.1 % (n=79).

The rate of expansion which Malatya criteria expanded the Milan by 25.2% (n=63 beyond Milan patients were within Malatya criteria).

Survivals According to Expanded Malatya Criteria (Figs. 2c, 3c)

When we dichotomized the total cohort according to Expanded Malatya criteria by pathology report, 338 patients were within Expanded Malatya and 154 were beyond.

1-, 5- and 10-year overall and disease-free survivals of patients within Expanded Malatya criteria were 91.3%, 78.4 % and 65.6 %, and 90.7 %, 76.4 %, and 63.9 % respectively,

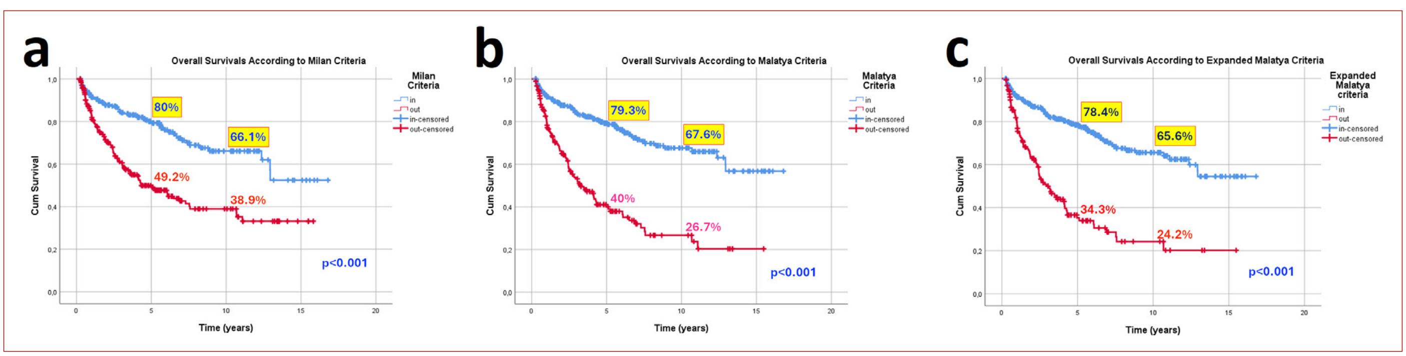

Figure 2. (a) Overall survivals according to Milan criteria, **(b)** Overall survivals according to Malatya criteria, **(c)** Overall survivals according to Expanded Malatya criteria.

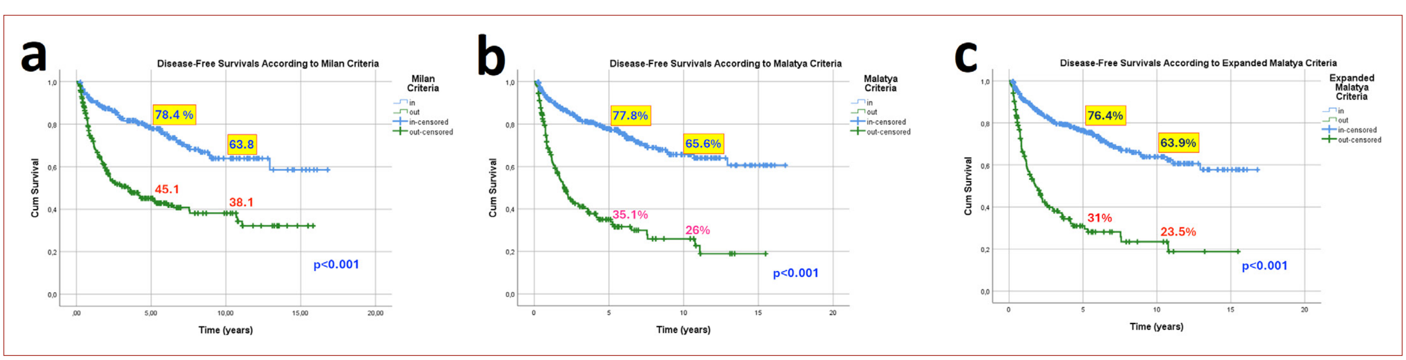

Figure 3. (a) Disease-free survivals according to Milan criteria, **(b)** Disease-free survivals according to Malatya criteria, **(c)** Disease-free survivals according to Expanded Malatya criteria.

and recurrence rate in patients within Expanded Malatya criteria was 4.7 % (n=16).

1-, 5- and 10-year overall and disease-free survivals of patients beyond Expanded Malatya criteria were 79.7 %, 35.3 % and 24.2 % and 65.5 %, 31 %, and 23.5 % respectively, and recurrence rate in patients beyond Expanded Malatya criteria was 48.7 % (n=75).

The rate of expansion which Expanded Malatya criteria expanded the Milan by 35.2% (n=88 beyond Milan patients were within Expanded Malatya criteria).

The OS and DFS, recurrence rates, and Milan criteria expansion rates of patients within the criteria are summarized in Figure 4.

Discussion

Efforts are ongoing to increase the donor pool through living donor liver transplantation and swap liver transplantation procedures in countries with organ shortage, such as Türkiye.[11, 12] However, the demand for organs is overwhelmingly higher than the donor organ supply. Therefore, using a valuable resource for patients with malignancy should be performed in accord with very strict criteria to choose patients who will benefit the most from transplantation. In patients with HCC, a 5-year overall survival more than 50 – 61% is considered as a target survival by LT,[13-16] but there is not any recommended data on the post-transplant recurrence rate.

Although 28 years have passed since its publication, Milan criteria which is very strict, is still used in cadaver organ distribution in Türkiye. As shown in many studies, when LT was performed in a group of patients beyond Milan criteria, survival outcomes were similar to Milan criteria.[3] In the present study, the 5-year overall survival rates of patients within Milan, within Malatya and within Expanded Malatya criteria were similar by LT, 80%, 79% and 78%, respectively (p=0.903). Additionally, the tumor recurrence rates after LT

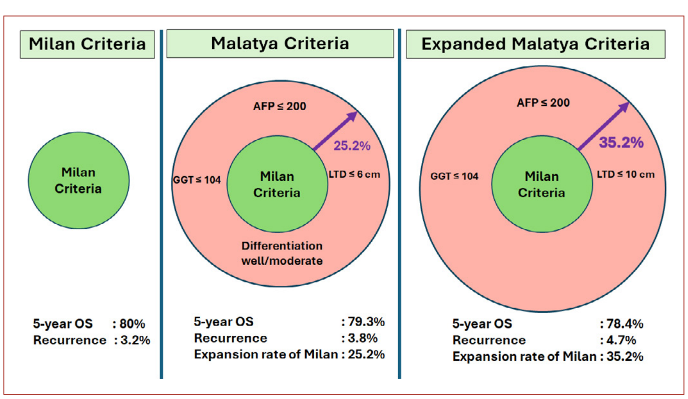

Figure 4 . Summary of OS and DFS, recurrence rates, and Milan criteria expansion rates of patients within the criteria.

in patients within these criteria were quite low, being 3.2%, 3.6% and 4.7%, respectively. On the other hand, the 5-year OS of patients with beyond Milan in our study is 49.2%. It is very close to the acceptable survival recommended in the guidelines. Thus, almost half of the patients with beyond Milan had a 5-year survival according to our study. These results are also evidence that the Milan criteria should be expanded reasonably.

There are more than 25 transplant criteria which are published in the literature from 10 different countries.[3] These criteria were called the expanded Milan criteria and each of them expanded the Milan criteria in different rates. Two of them were published from our institute in Türkiye, which are called Malatya criteria[5] and Expanded Malatya criteria.[6] The current study revealed that there were 250 patients within Milan, 313 patients within Malatya, 338 patients within Expanded Malatya criteria with similar 5-year OS. When we focused on the Milan expansion rates of the Malatya and Expanded Malatya criteria, Malatya criteria expanded the Milan by 25.2 % (n=63 beyond Milan patients had a chance to LT), while expanded Malatya criteria expanded Milan by 35.2 % (n=88 beyond Milan patients had a chance to LT).

Tumor morphological features such as number of nodules and largest tumor diameter as a selection criteria for LT in patients with HCC were insufficient to predict post-transplant survival. In addition to tumor morphology, biomarkers that predict tumor biological behavior are needed. We used low serum levels of alpha-fetoprotein (AFP) plus low serum levels of gamma glutamyl transpeptidase (GGT) as a good prognostic biomarker, in addition to largest tumor diameter in Expanded Malatya criteria and we expanded the Milan criteria by 35.2% with a similar 5-year OS 78.4%.

There are many studies on the diagnostic and prognostic usefulness of GGT and GGT-II which is its hepatoma-specific isoform. Several studies have also shown the prognostic usefulness of GGT in various treatments of HCC, including chemoembolization, radiofrequency ablation, resection, and LT.[17] We also have an ongoing study on GGT-II in our institute.

The retrospective design of the study and the fact of 80% of the cases being caused by viral hepatitis are among the limitations of the study. The strength of this study are the prospectively collected data and the relatively large number of patients.

Conclusion

Milan criteria can be expanded reasonably by Expanded Malatya criteria. Low GGT and low AFP are good prognostic biomarkers that predict survival following LT in patients with HCC. Patients Within Expanded Malatya Criteria had 78.4% 5-year OS, 4.7% post-transplant recurrence rate and Expanded Malatya criteria expanded the Milan by 35.2% which means 88 patients beyond Milan criteria were within Expanded Malatya criteria, giving them an opportunity for LT.

Disclosures

Ethics Committee Approval: Inonu University Ethics Committee approved this study by approval no: 2024/6410.

Informed Consent: Due to this study having a retrospective design, informed consent from patients was not necessary.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – V.I., S.U.; Design – V.I., S.U., B.I.C., S.Y.; Supervision – B.I.C., B.I., S.Y.; Funding – None; Materials – R.K., A.S.K., M.D., M.H., A.N.A.; Data Collection and/or Processing – O.T., E.K.; Analysis and/or Interpretation – V.I., S.U., E.K.; Literature Review – V.I.,A.S.K, A.N.A.; Writing – V.I., S.U.; Critical Review –B.I.C., B.I., S.Y.

References

1. Global Cancer Observatory: GLOBOCAN 2022. https://gco.iarc.who.int/media/globocan/factsheets/cancers/11-liver-and-intrahepatic-bile-ducts-fact-sheet.pdf
2. Global Cancer Observatory: Cancer Tomorrow https://gco.iarc.fr/tomorrow/en/dataviz/isotype?cancers=11&single_unit=50000&years=2050&types=1
3. Ince V, Sahin TT, Akbulut S, Yilmaz S. Liver transplantation for hepatocellular carcinoma: Historical evolution of transplantation criteria. World J Clin Cases 2022;10(29):10413-10427.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
5. Ince V, Akbulut S, Otan E, Ersan V, Karakas S, Sahin TT, et al. Liver Transplantation for Hepatocellular Carcinoma: Malatya Experience and Proposals for Expanded Criteria. J Gastrointest Cancer 2020;51:998–1005.
6. Ince V, Carr BI, Bag HG, Ersan V, Usta S, Koc C, et al. Liver transplant for large hepatocellular carcinoma in Malatya: The role of gamma glutamyl transferase and alpha-fetoprotein, a retrospective cohort study. World J Gastrointest Surg 2020;12:520–533.
7. Karakaş S, İnce V, Elkıran ET, Yılmaz S. Hepatoselüler Karsinomada Cerrahi ve Transplantasyonun yeri. Turk Klin Hepato-Pankreato Biliyer Sist Kanserleri 2021;1:23 31.
8. Kayaalp C, Ince V, Ersan V, Karakas S, Kahraman AS, Yilmaz S. Liver transplantation for hepatocellular carcinoma at Inonu University. J Gastrointest Cancer 2017;48(3):268-271.
9. Carr BI, Ince V, Bag HG, Ersan V, Usta S, Yilmaz S. Microscopic vascular invasion by hepatocellular carcinoma in liver transplant patients. Clin Pract (Lond) 2020;17(3):1497-1505.
10. Yilmaz S, Ince V. The importance of the immunosuppressive regime on hepatocellular carcinoma recurrence after liver transplantation. J Gastrointest Cancer 2021;1:1 6.
11. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Isik B, Emre S. The first 4-way liver paired exchange from an interdisciplinary collaboration between health care professionals and design economists. Am J Transplant 2023;23(10):1612-1621.
12. Yilmaz S, Sönmez T, Ünver MU, Ince V, Akbulut S, Sarici KB, Isik B. Enhanced role of multipair donor swaps in response to size incompatibility: The first two 5-way and the first 6-way liver paired exchanges. Am J Transplant 2024:S1600-6135(24)00338-1.
13. Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. Lancet 1999;354(9190):1636-9.
14. Bruix J, Fuster J, Llovet JM. Liver transplantation for hepatocellular carcinoma: Foucault pendulum versus evidence-based decision. Liver Transpl 2003;9(7):700-2.
15. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 2008;8(4):839-46.
16. Mehta N, Bhangui P, Yao FY, Mazzaferro V, Toso C, Akamatsu N, et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020;104(6):1136-1142.
17. Ince V, Carr BI, Bag HG, Koc C, Usta S, Ersan V, Baskiran A, Sahin TT, Yilmaz S. Gamma glutamyl transpeptidase as a prognostic biomarker in hepatocellular cancer patients especially with >5 cm tumors, treated by liver transplantation. Int J Biol Markers 2020;35(2):91-95.