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MEDICINE
Research article

LIVER TRANSPLANTATION SURVIVAL IN HEPATOCELLULAR CARCINOMA. FUNDENI CLINICAL INSTITUTE EXPERIENCE

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Accepted August 22, 2018

Hepatocellular carcinoma (HCC) is a major health concern worldwide, resulting from chronic liver injury and inflammation due to viral, non-viral and genetic etiologies. *Background***.** Orthotopic liver transplant (OLT) is a curative treatment for patients with hepatocellular carcinoma (HCC). It is widely practiced around the world, but there is no specific set of recommendations to guide physicians. Milan criteria (MC) is a starting point in selecting optimal candidates for OLT, but no consensus exists for patients whose tumors exceed beyond MC. *Methods***.** We perform a retrospective, non-randomized study and we analyzed 139 patients who were diagnosed with HCC and retrieved liver transplantation in our institute between 2011–2014. Our end-point is Overall Survival based on sex, age, HCC etiology, Milan and UCSF criteria, Edmonson- Steiner classification and AFP. *Results***.** In our group, overall survival was 56.34 months. We obtain mortality rate 1/5 approximate (21.37%). DFS is influenced by Millan and UCSF criteria. Patients with VHB infection has the lowest DFS. Conclusion: Liver transplantation for treatment of hepatocellular carcinoma (HCC) is attractive because resection of the malignant tumor can be achieved while the cirrhotic liver remains at risk for the development of new lesions.

Keywords: Hepatocellular carcinoma, Alpha-fetoprotein, Liver transplantation, Selection criteria.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer[1,11]. It is the most common primary tumor of the liver accounting for 90% of all primary liver tumors[12]. Mean survival is estimated to be 6 to 20 months without intervention.

Liver transplantation offers the most reasonable expectation for curative treatment while simultaneously removing the burden of the diseased liver. Still, advancements in the field have thus far not yet matched its potential, although new immunosuppressive and chemotherapy regimen may allow transplantation to push the envelope once again[3].

Liver Transplant offers the highest rates of long-term survival for patients with hepatocellular carcinoma, the best 5-year survival, with studies demonstrating 70% to 80% survival rates.

Overall survival was 85%, and recurrence-free survival was 92% for patients who met the Milan criteria, dropping to 50% and 59%, respectively, for those who did not.

The most common cause of HCC is chronic hepatitis virus infection. Chronic hepatitis B infection is well defined as an etiology for HCC.[2,15]. Three quarters of the cases of HCC occur in Asian countries where there is a high prevalence of chronic hepatitis B infection[16]. The mechanism remains unclear, but some have postulated that the DNA viral replication plays a role. Chronic hepatitis C infection is a more common etiology in Europe and North America. The distribution of chronic hepatitis C patients varies between regions and ethnic groups within countries where the disease is endemic, suggesting that there is a social or behavioral component to transmission[17].

Alpha fetoprotein (AFP) is highly diagnostic for this tumor. It is present in large quantities during fetal development but decreases rapidly after birth. Normal adult level is typically less than 10 ng. Typically, elevated levels of AFP greater than 400 ng/mL are considered diagnostic. This marker

may return to normal after resection and is useful as a marker for tumor recurrence[4]. Mild elevations in AFP may be found in acute viral hepatitis, chronic liver disease, and some metastatic cancers. Fulminant HBV, teratocarcinomas, yolk sac tumors and metastatic tumors from the stomach or pancreas can also produce markedly elevated levels. As a diagnostic tool, AFP is most helpful in concordance with hepatic imaging confirming the presence of tumor.

In 1996, in a landmark paper published in the New England Journal of Medicine, Dr. Mazzafero published results demonstrating 74% 4 year survival after liver transplantation in patients with solitary lesions less than 5 cm in diameter or up to 3 lesions each less than 3 cm in diameter. This has been designated the Milan criteria[25]. Three years later the Bismuth group published new data suggesting similar survival rates in patients with tumors less than 3 cm[26]. The "Milan Criteria" quickly became the standard. Currently, HCC is the primary indication for liver transplant for 25% of all cases in Europe.

Most notably, the 2010 International Consensus for Transplantation for HCC advocates the use of Milan criteria as the benchmark for selection[18].

At the University of California San Francisco, Dr. Yao *et al.* have demonstrated that patients with a single lesions less than 6.5 cm, or up to three lesions each less than 4 cm with a cumulative diameter less than 8 cm have surgical outcomes similar to those transplanted under Milan criteria.

MATERIALS AND METHODS

We perform a retrospective, non-randomized study and we analyzed 139 patients who were diagnosed with HCC and retrieved liver transplantation in our institute between 2011–2014. These subjects are representatives for HCC population diagnosed and treated in a specialized center in multimodal treatment of HCC.

Cases of inflammatory disease or active concomitant infection were excluded. Patients with a diagnosis of HCC made according to radiological or histological criteria were included.

RESULTS

We perform a Kaplan-Meier analysis, our end-point being Overall Survival.

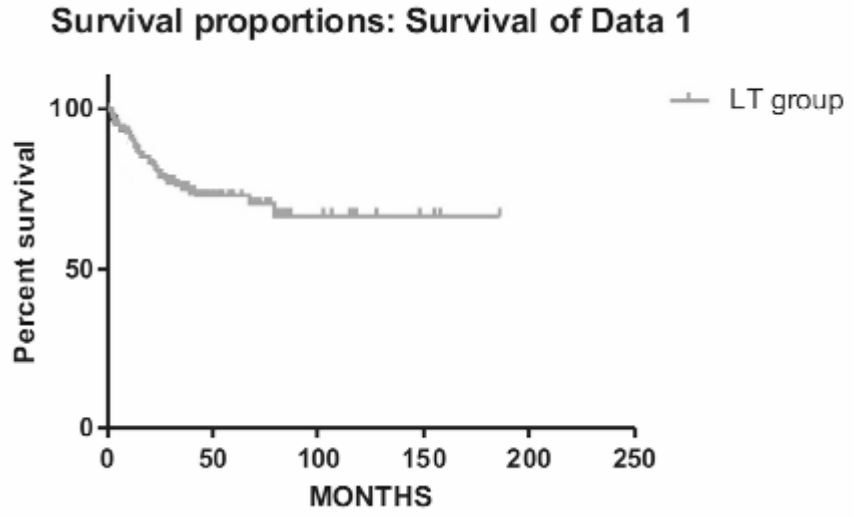


Figure 1. Overall survival in LT group.

Mortality data:

Strata	Deceased	Survivals	Total
Group	15 (21.37)	54 (78.63)	69

We obtain mortality rate1/5 approximate (21.37%) (Fig. 1).

The algorithm for this analysis: first of all, we perform a Kaplan-Meier analysis, followed by univariate Cox regression.

Kaplan–Meier – disease free survival based on sex analysis proved (Fig. 2):

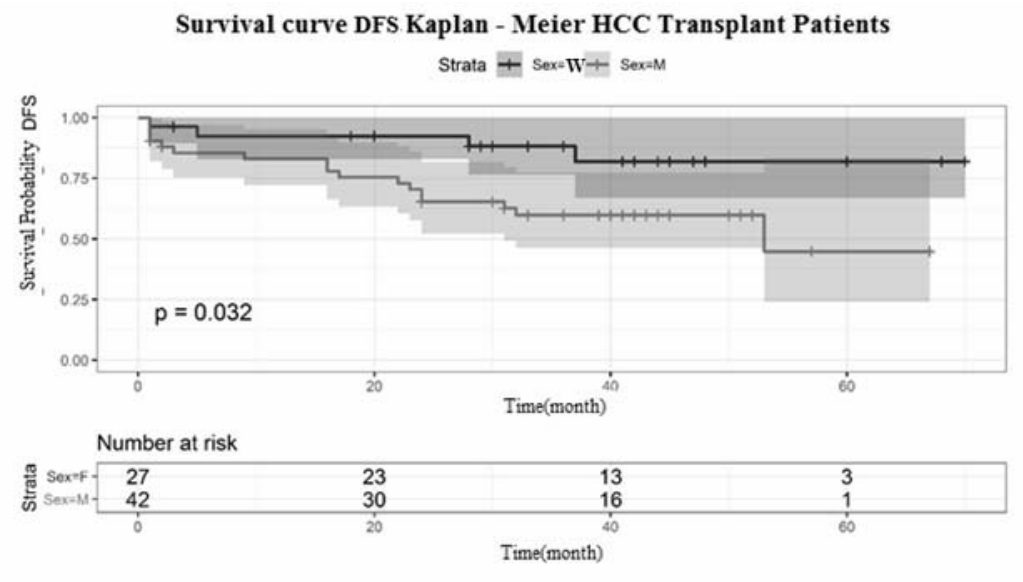


Figure 2. DFS based on sex in LT group.

In our population, DFS is better for women (up to 15 months), with statistically significant. ($p < 0.05$, at log-rank test).

Strata Sex	Restrictive Media	Mediana	IC95% Mediana
W	59.90	N/A	N/A la N/A
M	44.40	53.00	31.00 la N/A

Events analysis showed that the risk is 3.09 higher in male population, this effect has statistical significance ($p < 0.05$) (fig. 3):

Strata Sex	Event	Non-Event	Total
W	4 (14.81)	23 (85.19)	27
M	17 (40.47)	25 (59.53)	42

Cox regression:

Sex	Coefficient	Wald z	P value	HR [IC95%]
W	REFERENCE	-	-	-
M	1.131	2.034	0.042	3.09 [1.04 la 9.21]

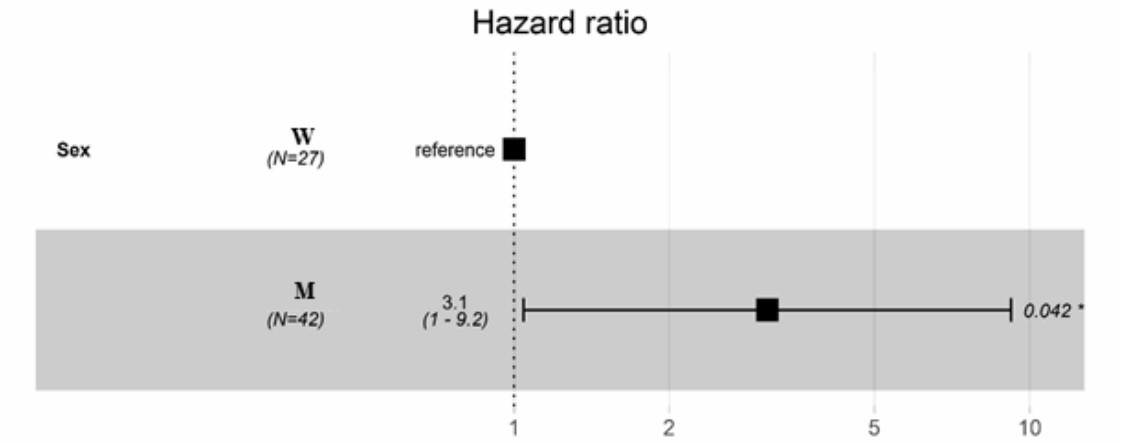
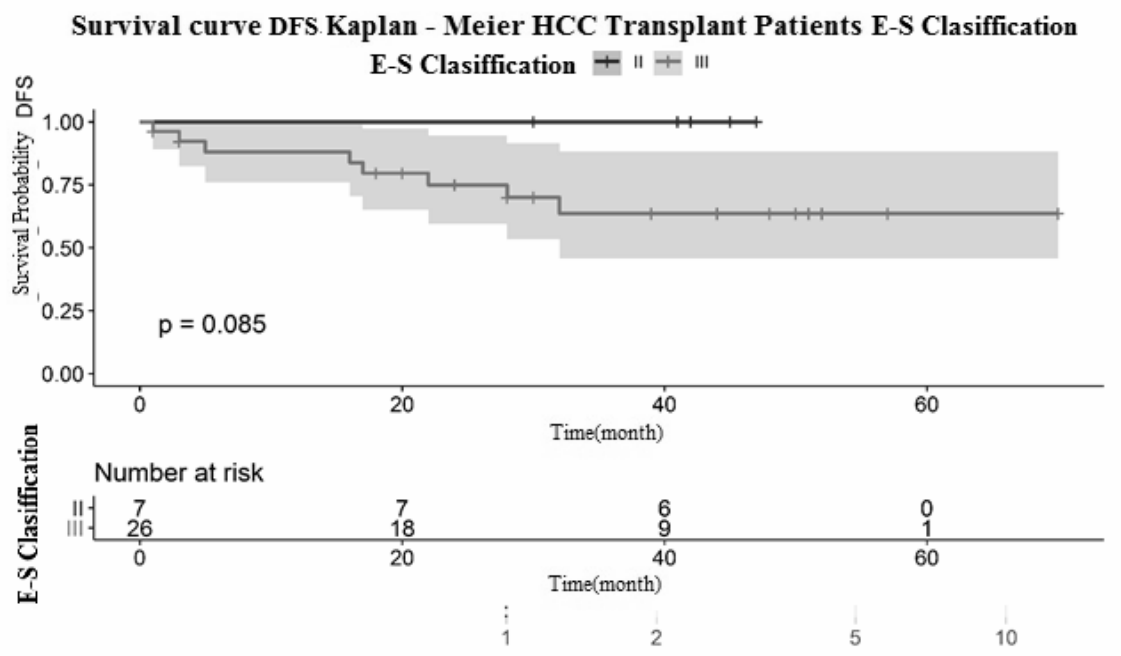


Figure 3. Events risk based on sex in LT group.

Kaplan-Meier DFS analysis, for Edmonson-Steiner classification showed in our population, the DFS seems to be better for the patients with E-S II grade with 15 months. But the significance is

marginal (p = 0.08, at log-rank test). We consider that a high grade of E-S classification is unfavourable prognostic factor for these patients (Fig. 4).



Strata E-S Clasiffication	Restrictive Media	Mediana	IC95% Mediana
II	58.50	N/A	N/A la N/A
III	43.40	N/A	32.00 la N/A

Figure 4. DFS based on E-S classification in LT group.

In Kaplan-Meier DFS analysis, based on HCC etiology, we found that the patients with VHB infection has the lowest disease free survival rate, even if p > 0.05 (Fig. 5):

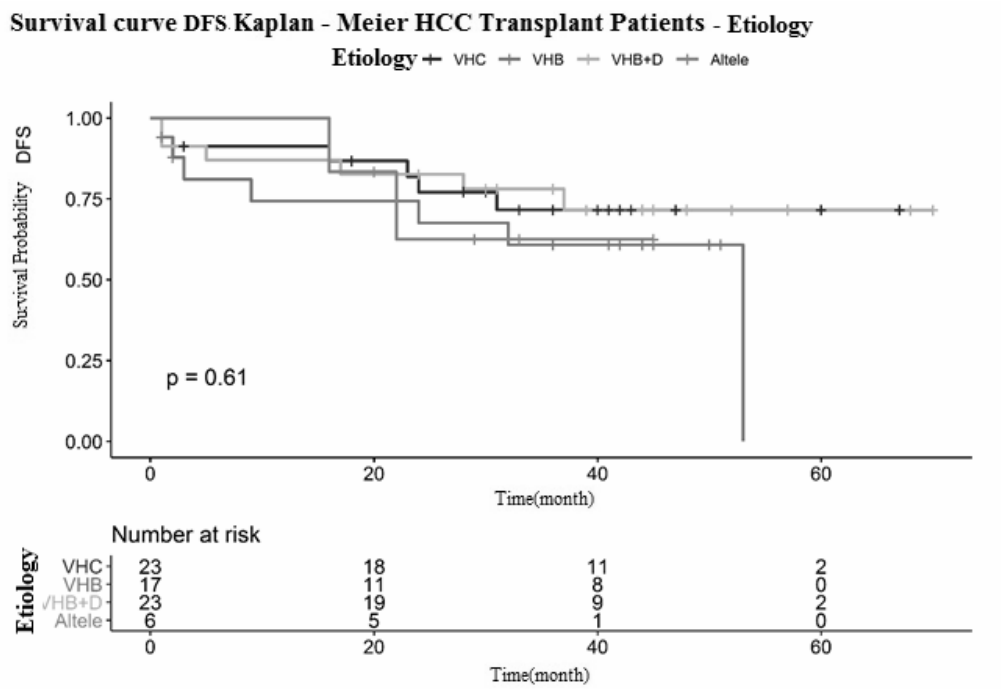


Figure 5. DFS based on HCC etiology in LT group.

Etiology	Coefficient	Wald z	P value	HR [IC95%]
VHB	Reference	-	-	-
VHC	-0.597	-1.071	0.284	0.55 [0.18 la 1.64]
VHB + VHD	-0.631	-1.131	0.258	0.53 [0.17 la 1.58]
Others	-0.176	-0.218	0.827	0.83 [0.17 la 4.06]

Cox analysis reveals that HCC etiology has no effect on events hazard (p > 0.05) (Fig. 6):

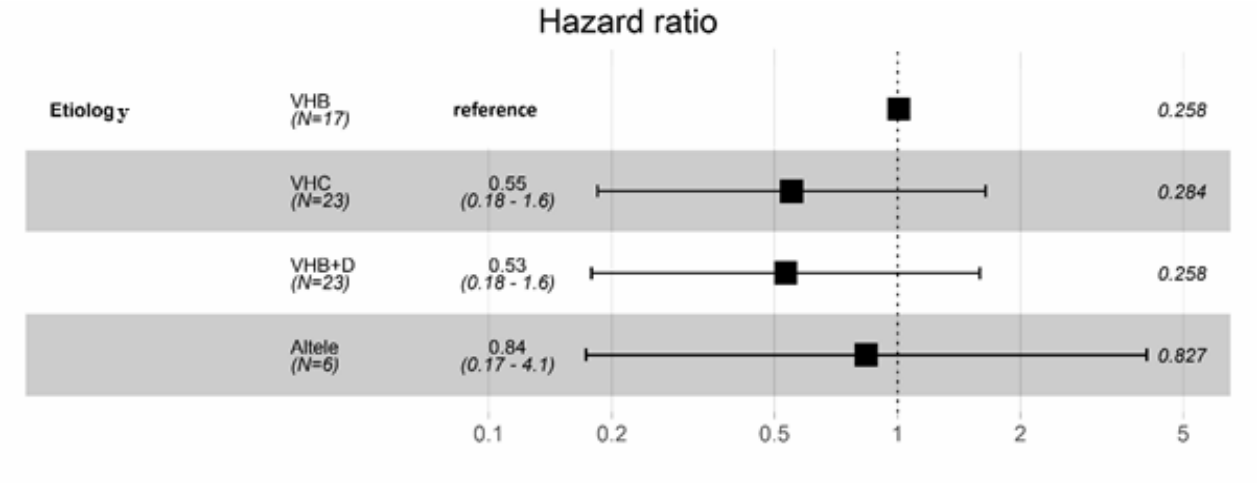


Figure 6. Events risk based on HCC etiology.

Kaplan-Meier DFS analysis for Milan classification demonstrated that DFS is influenced by Milan classification (p > 0.05 at log-rank test) (Fig. 7):

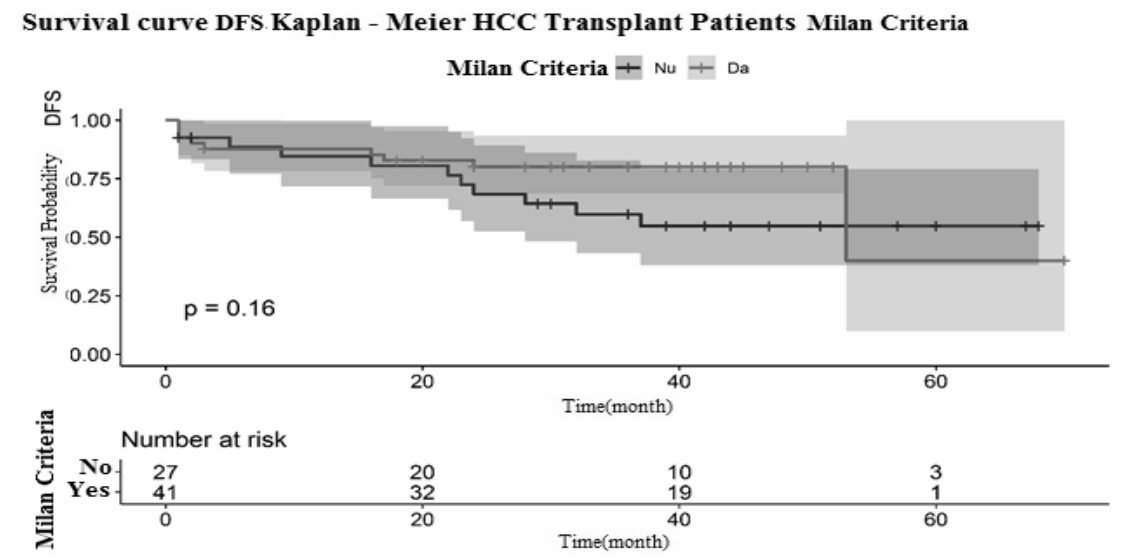


Figure 7. DFS based on Milan Criteria in LT group.

Events analysis:

Strata Milan Criteria	Events	Non-Events	Total
No	11 (40.74)	16 (59.26)	27
Yes	9 (21.95)	32 (78.05)	41

Cox regression demonstrated that patients in Milan criteria has the risk less than ½ compared with the patients out of Milan criteria (p = 0.17) (Fig. 8):

Milan Criteria	Coefficient	Wald z	P value	HR [IC95%]
No	REFERENCE	-	-	-
Yes	-0.620	-1.37	0.171	0.53 [0.22 la 1.30]

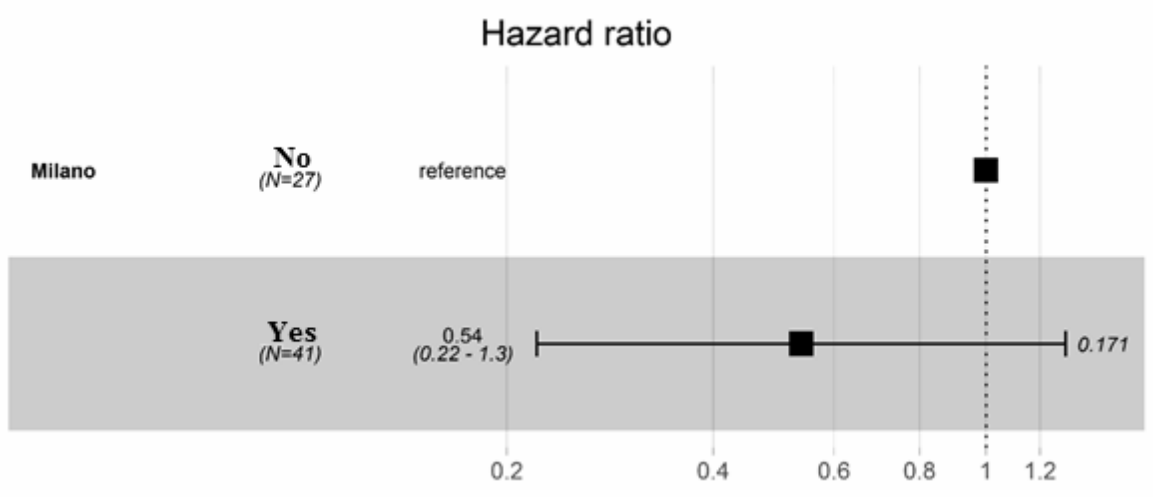


Figure 8. Events risk based on Milan Criteria in LT group.

Kaplan-Meier DFS analysis, based on UCSF classification explained that patients who are not included in UCSF criteria has o low disease free survival rate than the patients who fulfill these criteria $p < 0.01$ at log-rank test) (Fig. 9):

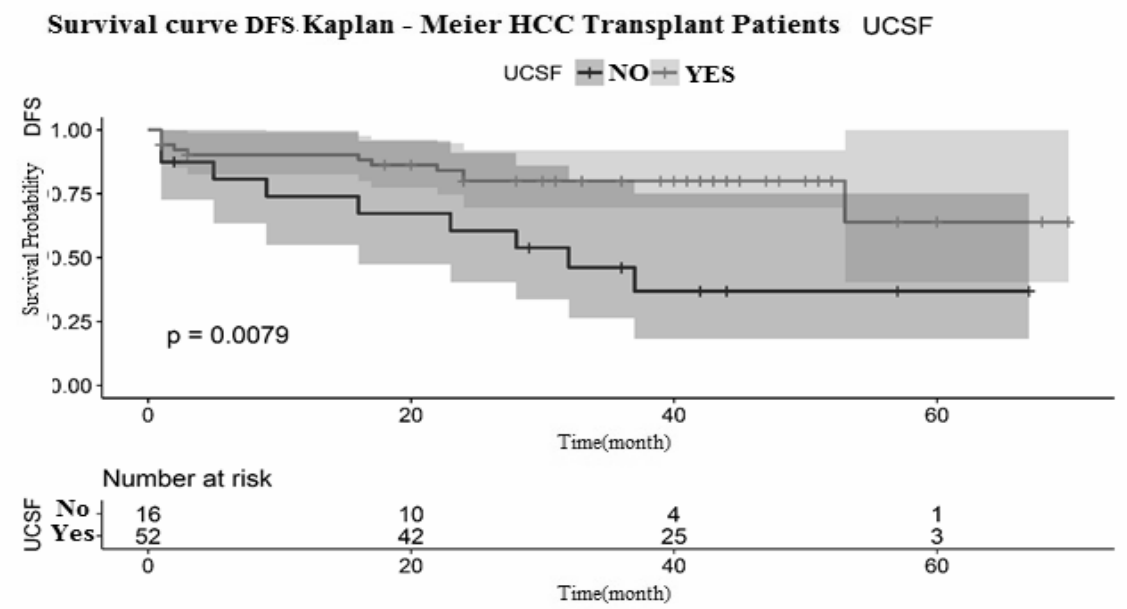


Figure 9. DFS based on UCSF criteria in LT group.

Strata UCSF	Events	Non-Events	Total
No	9 (56.25)	7 (43.75)	16
Yes	11 (21.15)	41 (78.85)	52

Cox regression:

Clasa UCSF	Coefficient	Wald z	P value	HR [IC95%]
No	REFERINTA	-	-	-
Yes	-1.133	-2.514	0.0119	0.32 [0.13 la 0.77]

Our analysis demonstrated that UCFS patients has the risk ratio 3 times lower than non-UCSF patients, with an important statistical significance ($p < 0.05$) (Fig. 10):

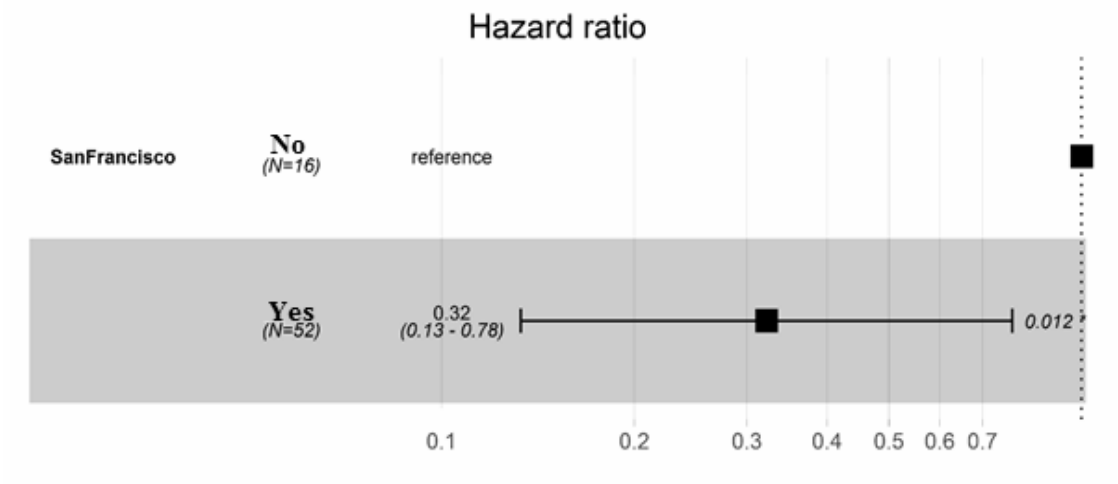


Figure 10. Events risk based on UCSF criteria in LT group.

Kaplan-Meier DFS analysis, based on AFP (cut-off value => 100 Ui) proved (fig 11):

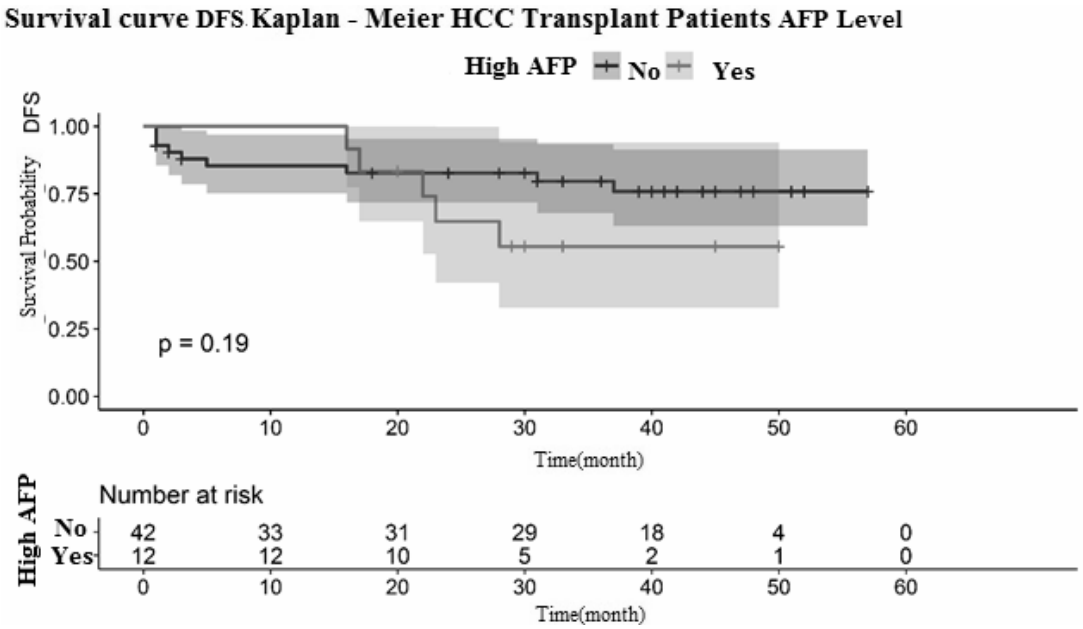


Figure 11. DFS based on AFP in LT group.

DFS data:

Strata high AFP	Restrictive Media	Mediana	IC95% Mediana
No	43.70	N/A	N/A la N/A
Yes	39.20	N/A	23.00 la N/A

We found differences between these 2 groups of patients, patients with higher AFP has a worst DFS rate ($p > 0.05$, at log-rank test).

Events analysis:

Strata high AFP	Events	Non-Events	Total
No	9 (21.42)	33 (78.58)	42
Yes	5 (41.66)	7 (58.34)	12

This analysis revelead that the effect is statistical significant 1.002.
Cox regression for age:

Variable	Coefficient	Wald z	P Value	HR [IC95%]
Age	0.031	1.103	0.270	1.03 [0.97 la 1.09]

In our group, age seems to influence event risk ratio (p > 0.05).

Variable	Coefficient	Wald z	P Value	HR [IC95%]
AFP	0.002	2.502	0.0123	1.002 [1.001 la 1.004]

The final model revealed AFP as independent predictor, this affirmation demonstrated different AFP value between sex and UCSF classification.

	UCSF Criteria (+)	UCSF Criteria (-)
AFP – Media ± D.S.	76.23 ± 154.31	185.90 ± 301.23

We can see that patients out of UCSF criteria has AFP 2 times higher than UCSF patients.

	UCSF Criteria (+)	UCSF Criteria (-)
Sex W	22 (81.48)	5 (18.52)
Sex M	30 (73.17)	11 (26.83)

In our group, patients included in UCSF criteria are predominant women.

DISCUSSION

The adoption of the Milan criteria offered a promising 5-year post-OLT survival around 75%. Although Milan criteria is well validated (*Table 1*), the cutoff size and number are rather arbitrary[13]. Thus, many find Milan criteria to be overly stringent, limiting a few potentially acceptable candidates from transplant. Imaging technique, protocols, and expert interpretation are also variable among transplant centers. This further leads to questioning of the cutoff tumor number and size dictated by the MC[10]. For these reasons, a number of experts are looking into expanding or modifying the criteria for OLT listing[27, 29-31].

An attempt to expand beyond Milan criteria was done in 2001 by University California at San Francisco (UCSF). They developed the UCSF criteria: *single nodule <6.5 cm; or multiple nodules with the largest <4.5 cm in diameter and the sum of total diameters <8 cm.* Comparing UCSF to Milan criteria, the survival rate after transplant appeared to be similar[14, 6].

Alpha-fetoprotein (AFP) is the main biomarker available for the management of hepatocellular carcinoma (HCC). The most frequent cut-off value reported in the literature is 400 ng/mL[9]. Moreover, many other cut-off values have been suggested, such as 100 ng/Ml and 200 ng/mL. The level of evidence to define an optimal value is very weak and thus calls for further studies[7].

The selection of HCC patients for liver transplant is not a trivial task. It requires a balance between maximizing benefit in HCC patients and minimizing harm to non-HCC patients due to the scarce resource[3].

Liver transplantation not only treats the tumor burden, but also removes the liver disease and theoretically prevent potentially liver failure associated with liver resection[22].

The major limitation of liver transplantation is shortage of organs that leads to increased waiting time on the list[32].

CONCLUSION

In our group,we obtain mortality rate 1/5 approximate (21.37%). DFS is influenced by Millan criteria and our patients out of UCSF classification has a low DFS compared with patients which fulfill these criteria. DFS is better for women than men with more than 15 months. A high grade of Edmonson-Steiner classification is unfavourable prognostic factor for these patients. Patients with VHB infection has the lowest DFS.

Liver transplantation is an effective treatment for hepatocellular carcinoma in patients with cirrhosis, especially those meeting the Milan criteria. Thus, the Milan criteria became the standard for determining eligibility for transplant. Meanwhile,

the extension San Francisco criteria determined a good DFS compared with the patients out of UCSF.

In our study, we use the last pre-transplant value of AFP to perform our analyses with a cut-off value 100 ng/Ml. It is showed that only the last pre-transplant value of AFP independently predicted survival.

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