

Impact of Pretransplant Diagnosis of Hepatocellular Carcinoma on Cadaveric Liver Allocation in the Era of MELD

Paul H. Hayashi,¹ James F. Trotter,¹ Lisa Forman,¹ Marcelo Kugelmas,¹
Tracy Steinberg,² Paul Russ,³ Michael Wachs,² Thomas Bak,²
Igal Kam,² and Gregory T. Everson¹

The allocation system based on the Model for End-stage Liver Disease (MELD) has led to more patients diagnosed with hepatocellular carcinoma (HCC) being transplanted. We hypothesized that more patients misdiagnosed with HCC are also being transplanted, leading to inappropriate organ allocation. Therefore, we retrospectively analyzed all liver transplants at our center from July 14, 2000, to October 22, 2002 (N = 172; 129 pre-MELD, 43 post-MELD), comparing pretransplant HCC diagnosis to explant histology. Thirty patients met the United Network for Organ Sharing (UNOS) diagnostic criteria for pretransplant HCC diagnosis. There were 25 men (median age, 52.5 yr), and 80% had hepatitis C. The proportion of patients transplanted who had an HCC diagnosis increased from 12% (15/129) pre-MELD to 35% (15/43) post-MELD implementation ($P < 0.01$). Three of 15 (20%) transplanted pre-MELD and 5 of 15 (33%) transplanted post-MELD lacked HCC in the explant ($P = 0.10$). Of the three false-positives pre-MELD, one was Status 2B already, and two received living-donor livers. Of the 5 false-positives post-MELD, three had score upgrades that led to early transplantation (13 to 29, 20 to 29, and 9 to 24) while two had MELD scores of 35 and 36 already. The percentage of organs that could have gone to patients with more advanced liver disease without HCC increased from 0% (0/129) pre-MELD to 7% (3/43) post-MELD ($P < 0.01$). Since the implementation of MELD, the proportion of patients transplanted who had an HCC diagnosis nearly tripled, and a small but significant proportion of organs are now going to patients misdiagnosed with HCC. More stringent HCC diagnostic criteria will be required to decrease the

effect that misdiagnosis has on organ allocation. (*Liver Transpl* 2004;10:42–48.)

The incidence of hepatocellular carcinoma (HCC) has increased twofold in the United States since 1980.^{1,2} While local resection can be done in selected cases, the recurrence rate in the remaining cirrhotic liver is high. Therefore, liver transplantation offers the best treatment option, if feasible.³ However, the organ shortage has led to unacceptably high waiting-list dropout due to tumor growth.⁴ Posttransplant survival on an intention-to-treat basis declined sharply through the late 1990s.⁵ In February of 2002, the scoring system based on the Model for End-stage Liver Disease (MELD) for allocation of livers was implemented. A provision prompted significant upgrades in score for patients with HCC.⁶ Preliminary results indicate that the proportion of patients diagnosed with HCC going to transplantation has increased threefold since the change in allocation.⁷

Pretransplant diagnosis of HCC in the cirrhotic patient is often based solely on imaging studies. According to the United Network for Organ Sharing (UNOS) criteria, “pre-listing biopsy is not mandatory.”⁶ Nevertheless, positive predictive value for HCC diagnosis by imaging criteria can be as low as 69%.⁸ Current policies regarding diagnosis of HCC and graft allocation raise the concern that an increasing number of livers might be allocated for misdiagnosed HCC. For these reasons, we retrospectively examined the true- and false-positive rates of HCC diagnosis in patients going to transplant before and after implementation of the current MELD-based allocation system.

Methods

Patients

This study was approved by the Colorado Multiple Institutional Review Board. All liver transplants performed at our center from July 14, 2000, to October 22, 2002, were analyzed. This time period yielded an equivalent number of transplanted patients diagnosed with HCC, pre- and post-

Abbreviations: MELD, Model for End-stage Liver Disease; HCC, hepatocellular carcinoma; UNOS, United Network for Organ Sharing; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein.

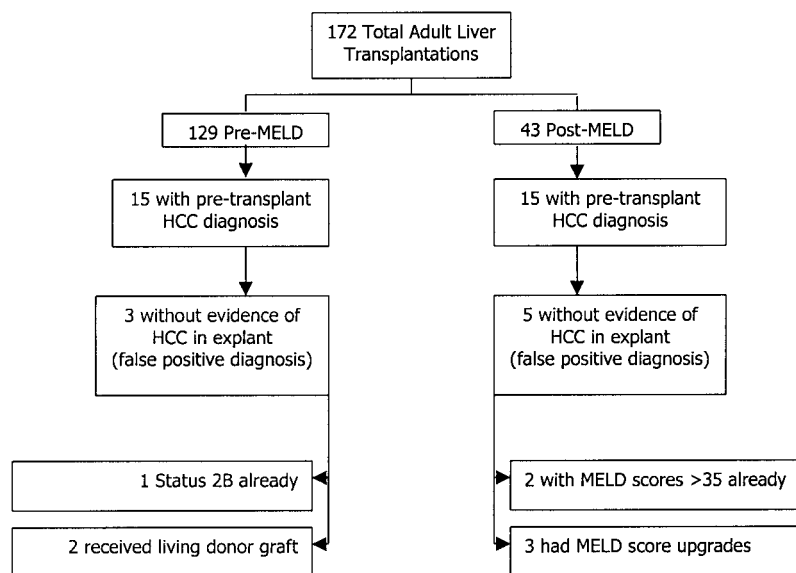
From the ¹Hepatology Section, ²Transplant Surgery Division, and ³Radiology Department of the University of Colorado Health Sciences Center, Denver, CO.

Address reprint requests to Paul H. Hayashi, Division of Gastroenterology and Hepatology, St. Louis University School of Medicine, 3635 Vista Avenue, St. Louis, MO 63110-0250. Telephone: 314-577-8764; FAX: 314-577-8125; E-mail: hayaship@slu.edu

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Published online in Wiley InterScience (www.interscience.wiley.com).
DOI DOI: 10.1002/lt.20020

Fig. 1. Hepatocellular cancer pre-transplant diagnosis and outcomes in 172 adult liver transplants. Grouped by transplantation prior to and after MELD-based allocation system. Abbreviations: MELD, Model for End-stage Liver Disease; HCC, hepatocellular carcinoma.



MELD. Those with a pretransplant diagnosis of HCC were identified by chart and computer database review. Criteria for HCC diagnosis were recorded. Demographic and other clinical information were obtained from computer databases maintained on all liver transplantations at our center.

Imaging Studies

All computed tomography (CT) scans included oral and intravenous contrast. Scans were done with dual-phase timing. Magnetic resonance imaging studies were done with axial in-phase and out-of-phase T1, axial T2, and dynamic axial gadolinium-enhanced T1 images through the liver. Imaging reports were used to retrospectively identify those patients with lesions suspicious for HCC. Confirmation of pretransplant clinical diagnosis of HCC was obtained by record and transplant database review.

Histology

Clinical diagnosis was correlated with histologic reports of explanted livers that were nominally sectioned at 0.5 to 1.0 cm. Whenever possible, explants were reexamined when HCC-diagnosed pretransplant was not found.

Definitions

A false-positive diagnosis was defined as pretransplant clinical diagnosis and no evidence of HCC on explant histology. If patients had received any ablative therapies prior to transplantation, such as radiofrequency ablation or chemoembolization, they were not counted as having a false-positive diagnosis when histology showed no residual cancer. We defined a "misallocated graft case" as any patient with a false-positive HCC diagnosis and upgraded on the waiting list because of the presumed presence of HCC. Patients transplanted prior to February 27, 2002 (date of MELD-based allocation system

implementation), were labeled the "Pre-MELD" group, and those after were labeled the "Post-MELD" group.

Statistical Analysis

We used binomial analysis to determine whether there were any significant changes in the proportions of transplants for HCC diagnosis and misdiagnosis pre- and post-MELD implementation. We compared methods of diagnosis between false-positive and true-positive diagnosis groups using chi-square. We compared alpha-fetoprotein (AFP) levels and tumor size (tumor burden) between these same groups by *t* test, and number of tumors by rank sum testing (SPSS for Windows software, version 11.5.0, SPSS Inc., Chicago, IL; and Stata Statistical Software, Release 7.0, StataCorp, College Station, TX).

Results

Patients and Pretransplant Diagnosis of HCC

Of the 172 adult patients transplanted between July 14, 2000, and October 22, 2002, 129 were transplanted

Table 1. Age, Gender and Diagnosis of 30 Patients with Pretransplant Diagnosis of Hepatocellular Carcinoma

Median age	52.5 years
Gender	26 men & 4 women
Hepatitis C	14 (47%)
Hepatitis C/ALD	11 (37%)
Hepatitis B	2 (6.7%)
Autoimmune hepatitis	2 (6.7%)
ALD	1 (3.3%)
Abbreviations: ALD, alcoholic liver disease.	

Table 2. Comparison of Method of HCC Diagnosis Between Pre-MELD Versus Post-MELD and False-Positive versus True-Positive Groups

	Overall n = 30 (%)	Pre-MELD n = 15 (%)	Post-MELD n = 15 (%)	<i>P</i> Value†	False-Positive HCC n = 8 (%)	True-Positive HCC n = 22 (%)	<i>P</i> Value†
CT*	25 (83)	15 (100)	10 (67)	NS	6 (75)	19 (86)	NS
MRI	16 (53)	8 (53)	8 (53)	NS	5 (63)	11 (50)	NS
Ultrasound	12 (40)	5 (33)	7 (47)	NS	1 (13)	11 (50)	NS
Histology	1 (3.3)	1 (6.7)	0 (0)	NS	0 (0)	1 (5)	NS
Diagnosis made on one test only	11 (37)	4 (27)	7 (47)	NS	5 (63)	6 (27)	NS

Abbreviations: HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; CT, computed tomography; NS, not statistically significant ($p > 0.05$); MRI, magnetic resonance imaging.
 * Computer tomography with oral and intravenous contrasts, dual phase.
 † χ^2 calculations comparing proportions of CT, MRI, ultrasound and histologic HCC diagnosis: pre-MELD versus post-MELD and false-positive versus true-positive HCC diagnostic groups.

prior to the MELD-based allocation system and 43 after. Of the 30 patients with a pretransplantation diagnosis of HCC, 15 were in the pre-MELD group and 15 in the post-MELD group. Therefore the proportion of recipients with a diagnosis of HCC increased nearly threefold (15/129, or 12%, vs. 15/43, or 35%, $P < 0.001$; Fig. 1).

Table 1 shows the demographics of the 30 patients diagnosed with HCC pretransplant. All 30 met UNOS diagnostic criteria for HCC. Only one had histologic confirmation of HCC prior to transplantation. Nineteen (63%) were diagnosed by more than one imaging modality. Diagnostic methods are shown in Table 2. The overall method of diagnosis did not change before and after implementation of the MELD-based allocation system, nor did the proportion of diagnosis made on a single imaging study differ before and after MELD.

Maximum TNM stage, size, and number of tumors based on imaging studies for all 30 patients (pre-MELD vs. post-MELD) are shown in Table 3. Many of those over T2 stage were transplanted by living donation. Median and mean waiting times with an HCC diagnosis did not differ pre- and post-MELD (median, 42 days [2–311] vs. 37 days [7–382], $P = 0.47$; mean, 86.13 days [± 95.96] vs. 62.73 days [± 94.17], $P = 0.51$). AFP values were available for 26 of the 30 patients (13 pre-MELD and 13 post-MELD). The mean AFP was 568.3 ng/mL (range, 2.1 to 8,918.2). There was no significant difference in mean AFP comparing the pre-MELD group with the post-MELD group (217.9 vs. 918.7, $P = 0.32$).

False-Positive HCC Diagnosis

Eight patients diagnosed with HCC prior to transplant had no evidence of cancer in their explanted liver. TNM stage, tumor size, and number of tumors based on imaging studies for these eight patients and the remaining 22 with HCC confirmed in the explant are shown in Table 4. Only three of the total cohort had imaging at stage T1. The proportion of T1 stage tumors falsely diagnosed with HCC was similar to the proportion of T2 stage tumors falsely diagnosed (33% vs. 37.5%, $P =$ not significant). Diagnostic criteria and proportion of diagnoses made with a single imaging study did not differ between the true-positives and false-positives (Table 2). Mean AFP levels were not significantly different between the false-positive diagnosis group and the true-positive diagnosis group (213.9 ng/mL vs. 725.9 ng/mL, $P = 0.34$). None of the eight falsely diagnosed patients had received ablative therapies such as chemoembolization. Three were transplanted prior to the change to MELD and five after (Fig. 1). Therefore, the false-positive rate of HCC diagnosis increased but did not reach statistical significance (3 of 15, or 20%, vs. 5 of 15, or 33%, $P = 0.10$). The mean sum of tumor diameters on pretransplant imaging was smaller in the false-positive cohort than in the true positive cohort (3.00 cm vs. 5.15 cm, $P = 0.05$; Table 5). The median number of lesions identified on pretransplant imaging was not significantly different between the false-positive and the true-positive groups (1.5 vs. 2.0, $P = 0.46$).

Of the three false-positives pre-MELD, one was Status 2B already, and two received living-donor livers. Of

Table 3. TNM Stage, Tumor Sizes, and AFP Levels for 30 Patients With Pretransplant Diagnosis of Hepatocellular Carcinoma, Grouped by Transplantation Prior to and After February 27, 2002 (Pre-MELD and Post-MELD)

Transplanted	TNM	Tumor Burden*	Tumor 1	Tumor 2	Tumor 3	Tumor 4	Tumor 5	AFP (ng/mL)
Pre-MELD	T1	1.1	1.1					5.3
"	T2	2	2					31.3
"	T2	2.5	2.5					345.9
"	T2	3	3					NA
"	T2	3.8	3.8					402.5
"	T2	2.6	1.7	0.9				4.1
"	T2	3.7	2.9	0.8				8.7
"	T2	4.1	2.9	1.2				55.8
"	T3	6.5	6.5					11.3
"	T3	6	4	2				NA
"	T3	8.7	4.9	3.8				64.8
"	T4a [†]	6	3	1	1	1		47.3
"	T4a	7.3	2.1	2.1	2.1	1		12.3
"	T4a	8.1	4	1.5	1.3	1.3		97.7
"	T4a	11.1	5	3	1.5	0.8	0.8	1,746
Post-MELD	T1	0.8	0.8					6.4
"	T1	1.3	1.3					17.3
"	T2	2.2	2.2					471
"	T2	2.8	2.8					1,071
"	T2	3	3					2.7
"	T2	4.5	4.5					NA
"	T2	1.9	1	0.9				1,294
"	T2	3	2	1				5.7
"	T2	3	1.6	1.4				2.1
"	T2	4	2	2				5.6
"	T2	8	2.9	2.6	2.5			10.5
"	T3	7	7					8,918
"	T3	7.9	3.9	2	2			NA
"	T4a [†]	4.8	1.4	1.3	1.3	0.8		126.8
"	T4a	6.5	2.8	1.3	1.2	1.2		12.7

Abbreviations: AFP, Alpha-fetoprotein; MELD, Model for End-stage Liver Disease; NA, not available.

* Sum of all tumor maximum diameters on imaging studies. When more than one imaging studies were done, the study yielding the largest sum was taken.

[†]Four or more tumors, any size.

the five false-positives post-MELD, two had MELD scores over 30 and would not have benefited from the HCC score. The remaining three patients did have score upgrades from 13 to 29, 20 to 29 and 9 to 24 (Fig. 1). Therefore, the percentage of organs going to falsely diagnosed HCC patients increased after the MELD system implementation (from 0 of 129, or 0%, to 3 of 43, or 7%, $P < 0.001$).

Discussion

Patients with HCC are often removed from the waiting list due to death and/or tumor growth. Intention-to-treat analysis revealed decreased survival for such patients as waiting times increased.^{4,5} On February 27,

2002, the MELD-based allocation system was implemented.^{6,9,10} The system provided additional MELD points for HCC diagnosis and resulted in a tripling of HCC patients undergoing transplant.^{6,7} With this increase, we were concerned that more patients falsely diagnosed with HCC were allocated livers.

Our center also experienced a threefold increase in the proportion of transplants for patients diagnosed with HCC and an increase in organs going to patients falsely diagnosed with HCC (from 0% to 7%). We found no differences in diagnostic criteria before and after MELD and between true- and false-positives. None of the false positives had received ablative therapies that could eliminate detectable cancer in the explants.

Table 4. TNM Stage, Tumor Sizes, and AFP Levels for 30 Patients With Pretransplant Diagnosis of Hepatocellular Carcinoma, Grouped By False-Positive and True-Positive Diagnosis

HCC Dx	TNM	Tumor Burden*	Tumor 1	Tumor 2	Tumor 3	Tumor 4	Tumor 5	AFP (ng/mL)
False-positive	T1	1.3	1.3					17.3
"	T2	2	2					31.3
"	T2	2.5	2.5					345.9
"	T2	3	3					2.7
"	T2	1.9	1	0.9				1,294
"	T2	3	1.6	1.4				2.1
"	T2	3	2	1				5.7
"	T4a [†]	7.3	2.1	2.1	2.1	1		12.3
True-positive	T1	0.8	0.8					6.4
"	T1	1.1	1.1					5.3
"	T2	2.2	2.2					471
"	T2	2.8	2.8					1,071
"	T2	3	3					NA
"	T2	3.8	3.8					402.5
"	T2	4.5	4.5					NA
"	T2	2.6	1.7	0.9				4.1
"	T2	3.7	2.9	0.8				8.7
"	T2	4	2	2				5.6
"	T2	4.1	2.9	1.2				55.8
"	T2	8	2.9	2.6	2.5			10.5
"	T3	6.5	6.5					11.3
"	T3	7	7					8,918
"	T3	6	4	2				NA
"	T3	8.7	4.9	3.8				64.8
"	T3	7.9	3.9	2	2			NA
"	T4a [†]	4.8	1.4	1.3	1.3	0.8		126.8
"	T4a	6	3	1	1	1		47.3
"	T4a	6.5	2.8	1.3	1.2	1.2		12.7
"	T4a	8.1	4	1.5	1.3	1.3		97.7
"	T4a	11.1	5	3	1.5	0.8	0.8	1,746

Abbreviations: AFP, Alpha-fetoprotein; HCC Dx, hepatocellular carcinoma diagnosis; NA, not available.

* Sum of all tumor maximum diameters on imaging studies. When more than one imaging studies were done, the study yielding the largest sum was taken.

[†]Four or more tumors, any size.

Our positive predictive values for HCC diagnosis are similar to those reported in the literature when diagnosis is based on imaging studies without angiography. Using ultrasound, contrast-enhanced CT and/or MRI within 6 months of transplantation, Libbrecht et al. diagnosed HCC with 79–82% specificity, but the positive predictive value was 69%, similar to that of our study.⁸ Brancatelli et al. had a positive predictive value of 63% using helical CT.¹¹ MRI's positive predictive value can be as low as 37%.¹² Nationally, 21% of transplanted HCC cases under the MELD system had no HCC on explant results reported to UNOS.⁷ This rate may increase, since only 86% of the pathology reports have been submitted. There may be a reporting bias,

with those not yet reported harboring a higher false-positive rate.

The present system has shifted allocation significantly toward patients with early HCC diagnosis. Unless histologic diagnosis is required, there will always be some patients inappropriately receiving upgrades due to false diagnosis of HCC. The transplant community must decide on an acceptable misdiagnosis rate. At one extreme, there is the analogy of acute appendicitis, where a high false-positive diagnosis rate is acceptable and desirable. Of course, appendectomy is a relatively minor surgery without the potential harm to another patient awaiting treatment. At the other extreme, oncologists often require tissue diagnosis of cancer prior

Table 5. Maximum Tumor Burden and Number of Tumors on Pretransplant Imaging: Pre-MELD versus Post-MELD and False-Positive versus True-Positive HCC-Diagnosed Cases

	Overall (n = 30)†	Pre-MELD (n = 15)	Post-MELD (n = 15)	<i>P</i> Value	False-Positive HCC (n = 8)	True-Positive HCC (n = 22)	<i>P</i> Value
Tumor burden* (mean)	4.57 cm	5.10 cm	4.05 cm	0.28‡	3.00 cm	5.15 cm	0.05‡
Number of tumors§ (median)	2.0	2.0	2.0	0.64	1.5	2.0	0.46

Abbreviations: MELD, Model for End-Stage Liver Disease; HCC, hepatocellular carcinoma.

† One of the 30 patients diagnosed with HCC by biopsy, but prior MRI sizing of tumor used for calculations.

* Sum of all tumor maximum diameters on imaging studies. When more than one imaging studies were done, the study yielding the largest sum was taken.

‡ Two tailed *t* test.

§ Number of tumors seen on pre-transplant imaging studies.

|| Rank sum test.

to chemotherapy. While tissue diagnosis is ideal, it can be impractical in advanced cirrhosis. Coagulopathy, tumor vascularity, and ascites increase the risk of biopsy, and there is still a remarkable false-negative rate.¹³

An acceptable false-diagnosis rate and a system to obtain this rate must be found between these extremes. In April 2003, the MELD score upgrades for HCC diagnosis were decreased.¹⁴ Those patients receiving an upgraded score must have imaging every 90 days showing persistence of tumor. Our three false-positive cases transplanted due to MELD upgrades would have been transplanted quickly with the new score upgrades as well. Based on MELD scores of subsequent transplants done in their respective blood groups, these three transplants would have been delayed by only 16, 42, and 45 days.

More stringent criteria for receiving more MELD points will likely be required. Hepatic angiogram could increase accuracy. Torzilli et al. obtained positive and negative predictive values of 99.3% and 100%, respectively, using ultrasound, CT followed by angiography, and Lipiodol-CT in 107 HCC patients undergoing tumor resection.¹⁵ However, angiography is invasive and most appropriate when immediate chemoembolization is planned.

For T1 lesions, we presently document tumor growth before applying for upgrade. However, regenerative nodules can grow as well. Excluding T1 cases from score upgrade would have decreased the proportion of organs going to falsely diagnosed HCC patients from 3 out of 43 (7%) to 2 out of 43 (4.7%). With this small sample size, we are unable to comment on the clinical impact of such an exclusion policy.

We had a trend of lower positive predictive value after MELD implementation ($P = 0.10$). Our diagnostic criteria did not change pre- and post-MELD. Every decision to upgrade is made at a weekly conference attended by the hepatologists, radiologist, histopathologist, transplant coordinators, and surgeons. Imaging studies, medical records, and labs are reviewed. Decisions are made by consensus. A single liver histopathologist reads all explant slides. While we cannot rule out diagnostic bias post-MELD, it is more likely that the trend was due to increased screening for HCC. Aggressive screening finds smaller lesions, which are more likely to be falsely diagnosed as HCC (Table 5).

Our study was retrospective, relying primarily on histologic and radiologic reports. The numbers of patients diagnosed with HCC was small. One could argue that the two pre-MELD false-positive HCC patients receiving living-donor transplants may have been upgraded to Status 2B at other centers. However, even with such an assumption, the rate of inappropriate liver allocation before and after MELD would still be significantly increased (from 1.5% to 7%, $P = 0.02$). Also, the increase in the proportion of HCC cases being transplanted in the first 6 months after MELD implementation may be due to the many HCC patients with lengthy accrued waiting times (i.e., a “catch-up” effect). However mean and median waiting times did not differ between the pre-MELD and post-MELD groups in this small cohort of patients.

The histologic examination of the explants was not always done with the foreknowledge of an HCC diagnosis, potentially increasing the miss rate for small tumors. While the protocol of explant examination calls for 0.5 to 1.0 cm slicing, meticulous adherence to such

protocol likely did not occur in 100% of cases. Every effort was made to reexamine the explanted liver when no HCC was found, but such efforts were not uniformly documented. Nevertheless, two studies in which meticulous sectioning and correlation with imaging studies were done still yielded positive predictive values of only 37–63%, similar to our rate.^{11,12}

Despite these shortcomings, our study reflects clinical practice and similar data emerging from UNOS⁷ and other centers.¹¹ It provides a cautionary note as the transplant community continues to grapple with the issue of liver allocation to HCC patients. Seven-percent allocation of organs to patients misdiagnosed with HCC represents approximately 315 organs per year nationwide. The recent decrease in HCC upgrades given diminishes the advantage to HCC patients, but it will not change the misdiagnosis rate. For now, our center limits upgrades for HCC to those with biopsy or angiographic confirmation and a minimum 2-cm-diameter size. For lesions smaller than 2 cm, we document growth on serial imaging. Further data from other centers are required to fully delineate the proportion of patients upgraded for HCC based on a false diagnosis.

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