Operative and Short-Term Postoperative Advantages of Non-Anatomical Liver Resection for Hepatocellular Carcinoma over Anatomical Liver Resection in Patients with Liver Cirrhosis: Egyptian Experience

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Abstract

Objectives: To evaluate outcome of anatomical (AR) versus non-anatomical (NAR) liver resection procedure for patients with hepatocellular carcinoma (HCC) of ≥3cm.

Patients & Methods: The study included 134 patients who were randomly allocated into two groups (n=67), during exploration, 12 patients had inoperable or unresectable lesions and were excluded. During NAR Liver was resected along a line allowing secure surgical margin of at least 10 mm, while during AR, extent of resection was modified according to Makuuchi's criteria. Study outcomes included extent of liver resection, operative time, intra operative (IO) blood loss, frequency and amount of blood transfusion, in-hospital morbidities and mortalities, hospital stay, 30-day postoperative (PO) morbidities, re-admission and mortality rates. Also, 1year survival rates were recorded.

Results: IO complications were reported in two patients, one in each group, average surgical margin was significantly wider, mean operative time was significantly shorter and mean amount of IO blood loss was significantly less with NAR. Total in-hospital PO morbidity rate was 21.3% that was non-significantly lower, but mean in-hospital stay was significantly shorter with NAR. At the 4th month PO, one patient in NAR group developed recurrence and required re-admission to the hospital, but was unfit for surgery, the decision of the HCC committee was to receive Trans-arterial chemoembolisation(TACE). Throughout one-year follow up, the 6-m, 1- and 1-year survival rates were 96.8%, 93.7% and 90.5% for NAR and 94.9%, 89.8% and 84.7%, respectively. Both PO morbidity and mortality rates were non-significantly higher with AR versus NAR.

Conclusion: Both AR and NAR are feasible and safe for patients with HCC of ≥3 cm, but NAR has better outcome concerning operative time, IO bleeding and need for transfusion. However, follow-up morbidity and mortality rates showed non-significant difference between both procedures, despite being in favor of NAR. Only one patient who had NAR developed recurrence.

KEYWORDS: Liver resection, Anatomical, Non-anatomical, Hepatocellular carcinoma(HCC)of ≥3cm

Introduction

Liver resection & liver transplantation are the only therapeutic treatment options for several neoplastic entities of the liver either primary or secondary [(1)]. However, multiple questions needed to be answered to achieve a proper surgical decision for

approach, extent and maneuver of hepatic resection for hepatocellular carcinoma (HCC) [2].

Liver resection (LR) was formerly considered among some of the most complex operative interventions performed and is full of risk and complications [3] with non-significant difference as regards 5-year survival rate versus untreated patients [4]. Technological progress in surgical equipments for laparoscopic hepatectomy[5]and robotic liver resection and the new advents of instruments for associating liver partition and portal vein ligation for staged hepatectomymade LR more feasible and increased technical safety [6] with subsequent minimization of intraoperative (IO) and postoperative (PO) complications that was reflected as decreased morbidity and mortality rates [7]. Moreover, advantages of these progresses manifested itself as longer disease free survival (DFS) and tumor recurrence which is still the major cause of death after curative resection for HCC showed decreased rate [8].

With increased scope for application of hepatectomy as therapeutic modality for HCC more technical controversies evoked; for example the choice between the anterior or conventional approach hepatectomy concerning safety, adequacy of exposure, mortality and recurrence [9]. Also, surgical re-resection with versus without radiofrequency ablation for patients with recurrent HCC is another point of discrepancy [10]. Moreover, anatomical versus non-anatomical resection is a point of multiple quires [11, 12] and until nowadays no final conclusion was defined

Objectives

The study targets to evaluate the outcome of patients assigned for hepatectomy for hepatocellular carcinoma (HCC) on top of liver cirrhosis using anatomical (AR) versus non-anatomical (NAR) liver resection procedure in selected patients.

Design

Retrospective clinical observational study

Setting

Hepatobiliopancreatic(HBP) Surgery Department, National Hepatology and Tropical Medicine Research Institute(NHTMRI), Cairo, Egypt.

Patients & Methods

The study revised the clinical files ofpatients with a clinical diagnosis of HCC of >3cm in diameter on top of liver cirrhosis, on preoperative imaging and assigned for open hepatectomy after taking the decision by the HCC committee of the Institute, following the Guidelines for the treatment of HCC, were eligible for evaluation.

Preoperative Management

All patients underwent clinical, radiological and laboratory evaluation for assessment of general condition, fitness for surgery, liver condition, extent of lesion, and of assigned level of hepatectomy. Laboratory investigations included liver function tests, α-fetoprotein assay and kidney function tests. Liver function was assessed according to Child-Pugh (CP) grading score. Radiological assessment included abdominal ultrasonography and Triphasic CT study, +/- Dynamic Magnetic resonance imaging(Dynamic MRI) to evaluate the local lesion extension, presence of ruptured HCC or abdominal spread and to evaluate the presence and severity of ascites if present. Hepatic angiography was performed whenever indicated but chest X-ray and CT chest with contrast were mandatory for all patients.

Operability included cirrhosis of CP score A or very early B(score7) with peripheral and/or exophitic lesions not necessitating major resection and lesions in non-cirrhotic patients who require major hepatectomy and the remaining liver will be not less than 30% in case of normal liver & and not less than 50% in case of cirrhotic liver after assessment with CT scan volumetry. Patients with advanced lesions on preoperative

imaging, ruptured HCC, recurrent lesions, cirrhosis of CP Score late B and more, bad general condition and patients who were unfit for general anesthesia were excluded from the study. Patients found to have unresectable lesion for any cause or lost during follow-up were also excluded from the study.

Surgical Techniques

a) Non-anatomical liver resection (NAR)
   - Liver will be resected along a line allowing secure surgical margin of at least 10 mm. However, if 10-mm safety surgical margin was impossible, trans-parenchymal resection was performed without exposing the tumor surface. Liver parenchyma was transected using either the Harmonic Ultrasonic dissector or the thermo ablative instrument (as Habib Needle).

b) Anatomical liver resection (AR)
   - Hepatectomy surgical decision making was modified according to Makuuchi's criteria [13] including presence or absence of ascites, serum total bilirubin (TB) level, and plasma ICG-15 retention rate (ICG-15 RR). Surgical decision will be
     A. Patients with controllable or no ascites with normal TB level will have bi- or trisegmentectomy if ICG-15 RR is normal, left lobectomy or right monosegmentectomy if ICG-15 RR was 10-19% and subsegmentectomy if ICG-15 RR was 20-29%
     B. Patients with controllable or no ascites with serum TB of 1.1-1.5 mg/dl or had normal serum TB with ICG-15 30-39% will have limited resection and those had serum TB of 1.6-1.9 mg/dl, or had normal serum TB with ICG-15 RR ≥40% will have enculeation.
     C. Patients with incontrollable ascites, controllable or no ascites with serum TB ≥2 mg/dl will not undergo resection and will be excluded from the study [14].
   - During anatomic resection accurate decision of the resection area, accurate approach to the portal triad to be resected and full exposure of the landmark vessels on the cutting surface, such as the right and middle hepatic veins, in the cases of anatomic resection of the whole segment were fulfilled.
   - Liver resection was conducted along the demarcation line appearing after occlusion of the portal vein and hepatic artery in hemihepatectomy and sectoriectomy, or after injection of dye into the portal vein confining the tumor-bearing area under intraoperative ultrasound guidance in the case of anatomic segmentectomy and subsegmentectomy

Study outcomes

- Operative data including extent of liver resection, operative time, intraoperative (IO) blood loss, frequency and amount of blood transfusion, in-hospital morbidities and mortalities, hospital stay, 30-day PO morbidities, re-admission and mortality rates were recorded.
- The 1-year survival rate after hepatectomy and differentiated according to surgical procedure was also recorded.

Results

The study included 134 patients who were allocated into two equal groups (n=67). During exploration, 12 patients had inoperable or unresectable lesions and were excluded; 8 from AR and 4 from NAR groups (Fig. 1). Patients' data showed non-significant ($p>0.05$) difference between studied groups (Table 1).

Table (1): Data of patients of studied groups

		Group AR	Group NAR	P value
Age (years)		48.3±10.2	52±8.4	0.726
Sex; Males: Females		41:18	50:13	0.694
Weight (kg)		79.6±5.6	79±4.2	0.629
Height (cm)		169.8±3.3	170.2±5.2	0.819
Body mass index (kg/m^2)		27.6±1.9	27.1±2.4	0.793
Total bilirubin (mg/dl)	<1	38 (64.4%)	37 (58.7%)	0.481
	1.1-1.5	13 (22%)	16 (25.4%)	
	1.6-1.9	8 (13.6%)	10 (15.9%)	
	Average	1.09±0.34	1.1±0.4	0.846
Serum albumin (gm/dl)		3.97±0.5	3.98±0.6	0.684
Serum ALT (mg/dl)		29.1±3.1	28.7±3.4	0.794
Serum AST (mg/dl)		31.8±5.2	31.9±5	0.839
INR		1.16±0.26	1.14±0.24	0.619
ICG-15 RR	Normal (<10%)	6 (10.2%)	8 (12.7%)	0.584
	10-19%	14 (23.7%)	16 (25.4%)	
	20-29%	24 (40.7%)	27 (42.9%)	
	30-39%	12 (20.3%)	12 (19%)	
	≥40%	3 (5.1%)	0	

Data are shown as mean±SD& numbers

All patients had HCC lesions of ≥3cm in its greatest diameter with non-significant difference between both groups. During AR one patient had injury of common bile duct that required choledecojejunostomy, while another in group NAR developed intraoperative injury of an aberrant vascular tree that required temporary clamping using Prengel's maneuver till clamping of the bleeders and control of bleeding and after completion of surgery peritoneal toilet and surgicele was applied to the hepatic surface; for a total IO complication rate of 1.6%. All other patients, irrespective of the procedure, completed their IO course uneventfully without intraoperative complications. Average surgical margin was significantly wider with NAR than with AR. Moreover, mean operative time was significantly shorter and mean amount of IO blood loss was significantly less with NAR. Only 4 patients; 3 had AR and one had NAR required IO blood transfusion for a rate of 3.3% with non-significant difference between both groups (Table 2).

Table (2): Intraoperative data of patients of studied groups

			Group AR	Group NAR	P value
Lesion-related data	Average of greatest diameter (cm)		5.8±0.8	5.9±1.2	0.702
	Surgical margin (mm)		0.75±0.37	1.04±0.32	0.001**
Operative data	Operative time (min)		340±73.5	303±86.1	0.012*
	Operative blood loss (ml)		440±113	397±88.3	0.022*
	IO blood transfusion	Yes	3 (5.1%)	1 (1.6%)	0.278
		No	56 (94.9%)	62 (98.4%)	

Data are shown as mean±SD& numbers; *: significant difference at <0.05 level; **: significant difference at <0.01 level

During hospital stay 26 patients developed PO morbidities for a total PO morbidity rate of 21.3% that was non-significantly higher with AR versus NAR. Seven patients developed wound-related complication three patients had wound-site superficial inflammations and two patients developed stitch sinus and all responded to conservative treatment, while the remaining two patients developed deep wound-layers infection that required stitch removal for evacuation and cleansing and the wound was drained and allowed to heal by secondary intention.

Seven patients developed paralytic ileus with delayed return of intestinal motility with subsequent delayed onset of oral intake and prolonged the duration of intravenous fluid intake, however, all responded to conservative treatment. One patient developed peritonism secondary to biliary leak and on CT examination there was no definite collection site and patient was managed conservatively. Another patient developed manifestations of acute abdomen and CT scan abdomino-pelvic showed small subphrenic collection in one and was drained using CT-guided aspiration, the second had a hematoma which showed heterogeneous pattern on CT scan study indicating starting liquefaction, conservative management failed and patient required 2nd look surgery for drainage and abdominal toilet.

Three patients developed reactionary right basal pleural effusion that was mild just obliterating the costophrenic angle in two, but in the 3rd the effusion was moderate and induced lower lung opacification, so required insertion of drainage chest tube. Another two patients developed chest infections that responded to conservative treatment in one, while the other required admission to ICU for respiratory support, but unfortunately progressed to acute respiratory failure and died three days after ICU admission. Four patients developed diabetic coma that was controlled in three using intensive insulin in three, while the 4th had progressed to hyperosmolarity and failed to respond to fluid and intensive insulin therapy and died. One patient developed deep venous thrombosis that was resolved completely on conservative medical treatment and resolution was assured by Doppler examination.

Mean duration of in-hospital stay was significantly shorter with NAR versus AR procedure. Throughout 30-day PO, 5 patients (4.2%) developed additional morbidities, one patient developed mild ascites and was managed conservatively, another developed diabetic coma and was re-admitted for intensive insulin therapy and was discharged after being controlled. One patient developed severe chest pain and was admitted to ICU but unfortunately died immediately because of having acute pulmonary embolism. Two patients developed post-hepatectomy syndrome, both were re-admitted and one of them died 3 days after re-admission.

At the 4th month PO, one patient in NAR group developed HCC recurrence and required re-admission to the hospital, but unfortunately he was unfit for surgery and was transferred to receive Trans-arterial chemo-embolisation(TACE). During 6-m follow-up three patients developed deterioration of liver function with concomitant ascites that was moderate in two, but was severe in the third patient who progressed to liver cell failure and died.

Table (3): Short-term PO data of patients of studied groups

			Group AR	Group NAR	P value
In-hospital	Types complications	Wound-related	4 (6.8%)	3 (4.8%)	0.684
		Chest	3 (5.1%)	2 (3.2%)	
		Abdominal	4 (6.8%)	5 (7.9%)	
		Diabetic	2 (3.4%)	2 (3.2%)	
		Vascular	1 (1.7%)	0	
	Total morbidity rate		14 (23.8%)	12 (19.1%)	
	Mortality		1 (1.7%)	1 (1.6%)	0.823
	Stay		13±3.4	11.7±3.1	0.031*
30-day	Morbidity		3/58	2/62	0.768
	Mortality		1/58	1/62	0.276
6-m	Recurrence		0	1/62	
	Morbidity		3/57	0/62	0.768
	Mortality		1/57	0/62	0.276

Data are shown as numbers, mean±SD& ratios; *: significant difference at <0.05 level

At the end of 1-year PO, another 3 patients died; 2 in AR and one in NAR group for a total 1-year mortality rate of 10.2% and 6.3%, respectively with non-significantly higher mortality rate among patients had AR versus NAR procedure.

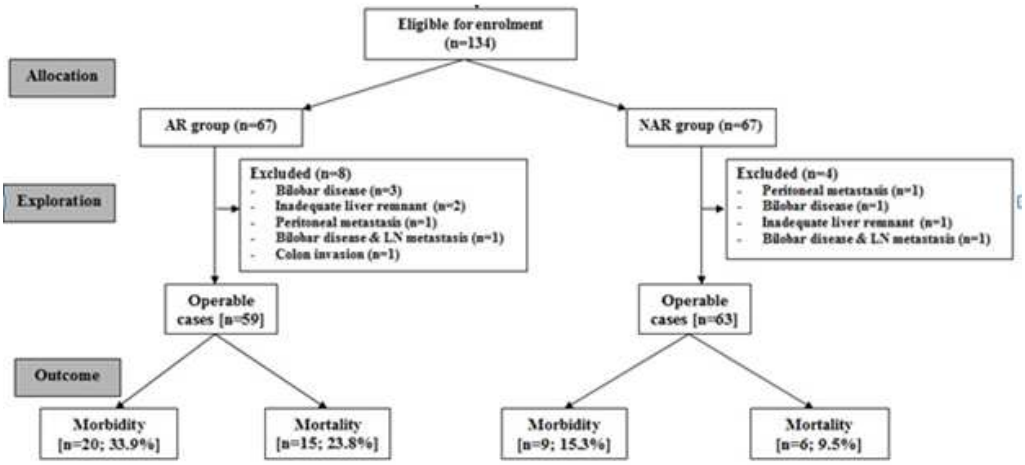


Figure 1: Consort Flow sheet

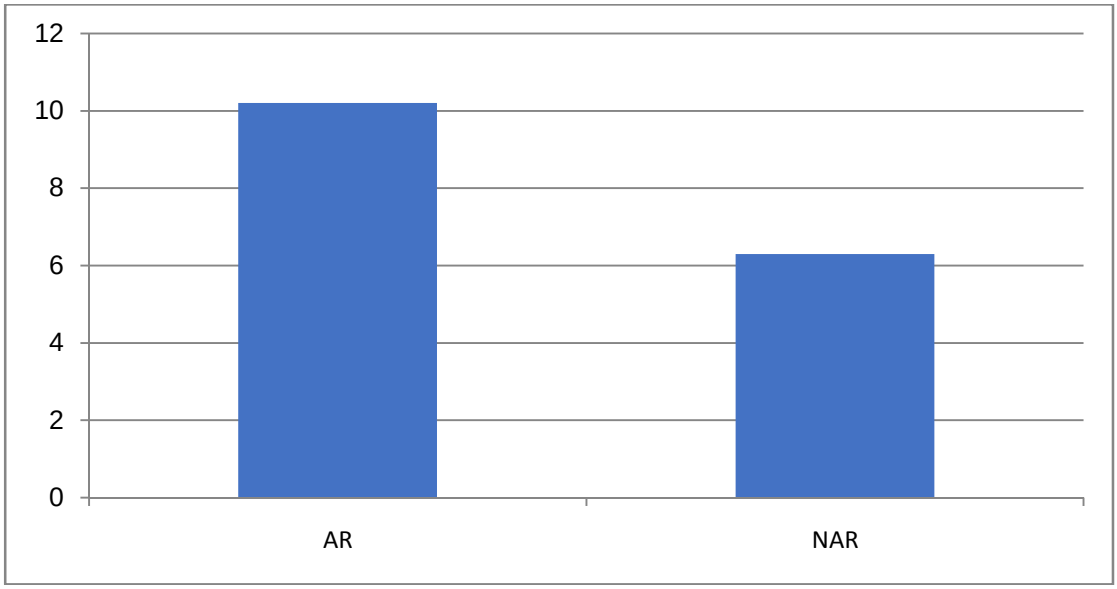


Fig:2. Mortality rates after one year of studied patients

Discussion

The outcome of hepatectomy and the choice of the approach and extent of resection; all are still a matter of debate. The current study compared the outcome of HCC patients with liver cirrhosis assigned for open hepatectomy using either anatomical (AR) or non-anatomical resection (NAR). For patients underwent AR, the surgical decision concerning the extent of resection was modified according to Makuuchi criteria [13] with a trial to get a surgical margin of about 10-mm, while during NAR there was no limitation for the extent of resection other than getting an acceptable surgical margin that was significantly wider than margin available on AR and this could be considered as an advantage for NAR- Figure 1.

Moreover, operative time was significantly shorter and amount of IO blood loss was significantly less with NAR than AR and only one patient required IO blood transfusion versus three patients had AR. These data points to the feasibility and safety of NAR and could be attributed to the facts that NAR procedure being dependent on tumor localization and clamping method minimized dissection with subsequent reduction of operative blood loss and need for transfusion. Also, minimizing dissection reduced surgical trauma that resulted in shortened PO catabolic stage and allowed shortened PO recovery period and hospital stayespecially in cirrhotic liver patients with preservation of more liver parenchyma.

In line with findings, **Lalmahomed et al.** [15] reported that after NAR, patients received significantly less blood transfusions and hospital stay was significantly shorter and concluded that NAR can be used as a save procedure to preserve liver parenchyma. Also, **Sui et al.** [16]found NAR reduced the operation time and blood transfusion requirement than AR and **Tang et al.** [17]reported that anatomic liver resection for HCC does not provide significant benefit in blood loss during operation compared with NAR. Thereafter, **Qureshi et al.** [18] documented that NAR whenever feasible can be performed safely and **Chen et al.** [19]found patients who underwent AR had longer operation time. Figures I & II showe intra-operative field and specimen for both anatomical and Non anatomical Hepatectomy.

During 6-m PO follow-up, 20 patients of AR group (33.9%), while 14 patients of NAR group (22.2%) developed PO morbidities. Throughout one year follow up, the

6-m, 1-year survival rates were 96.8%, and 93.7% for NAR and 94.9%, and 89.8%, respectively-figure 2. Both PO morbidity and mortality rates were non-significantly higher with AR versus NAR. These figures go in hand with **Lalmahomed et al.** [15]and **Sui et al.** [16]who reported no significant difference in morbidity, mortality or survival according to resection type. Also, **Tang et al.** [17]reported that anatomic liver resection for HCC does not provide significant benefit in 1-, 3- and 5-year survival rate or PO morbidity and **Chen et al.** [19]found PO morbidity, hospital and 30-day mortality rates and disease-free and overall survival rates showed no significant differences between anatomic and nonanatomic resection.

In support of the efficacy and safety of NAR, **Pandanaboyana et al.** [20] through analysis of data of patients with colorectal liver metastasis (CRLM) who underwent either AR or NAR found the need for PO transfusion, overall complications and 90-day mortality were significantly higher with AR.

Unfortunately, at the 4th month PO, one patient in NAR group developed early recurrence and required re-admission to the hospital for redo surgery, but unfortunately he was unfit for surgery and was transferred to receive Trans-arterial chemo-therapy(TACE)and this was the only case developed recurrence throughout the observation period. However, this case could not be a limitation for NAR especially with the more efficient safety margin and indicated the possibility of microscopic spread that may escape during resection and anatomical resection could not be the grantee for prevention of a similar event.

In line with this assumption, review of literature concerning the impact of type and extent of resection on disease free survival (DFS) rate showed discrepant results where **Qureshi et al.** [18] documented that NAR does not compromise the oncological outcomes. **Feng et al.** [21]and **Hokuto et al.** [22]reported that despite the higher incidence of local recurrence after NAR and the shorter time to first local recurrence it has no impact on overall DFS that showed no difference between two groups. Recently, **Pandanaboyana et al.** [20] documented that NAR is associated with better overall survival and DFS than AR without compromising margin status, but NAR increases the need for repeat liver resections.

On contrary, **Kaibori et al.**[23]and**Tan et al.** [24] reported that AR decreases the risk of tumor recurrence and improves OS in patients with a primary, solitary HCC of <5.0 cm in diameter. However, these studies got that conclusion on studying HCC cases with lesion <5 cm in diameter, while the current study evaluated the outcome of patients had lesion ≥3 cm.

In support of the discrepancy concerning recurrence after AR and NAR, **Huang & Lu** [25] and **Moris et al.** [26] compared outcomes from the published comparative studies within the literatures and reported that considering the 5-year OS and DFS rates, AR for HCC is superior to NAR, but heterogeneity detection within the analysis suggests these results should be interpreted with caution and further well designed studies are required to address this issue.

Conclusion

Both anatomical and non-anatomical liver resectionsare feasible and safe for patients had HCC of ≥3 cm. NAR did better concerning operative time, IO bleeding and need for transfusion especially in cirrhotic liver patients(the majority of patients in our country). However, follow-up morbidity and mortality rates showed non-significant difference between both procedures, despite being in favor of NAR. Only one patient had NAR developed early recurrence. These results need wider scale multi-center comparative studies to establish the ideal procedure to be applied especially with the

increasing incidence of HCC in Egyptian community and the increasing practice of hepatectomy in multiple centers.

Figure I
Anatomical hepatectomy

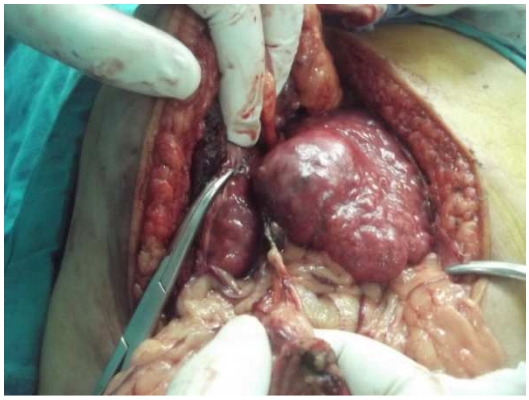
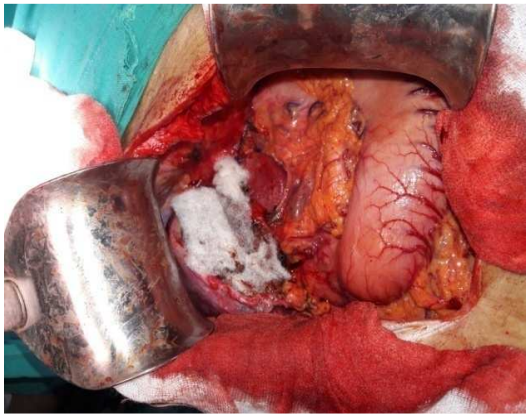



Figure II
Non Anatomical hepatectomy

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