Comparison of postoperative outcomes between DCD and DBD liver transplantation using the Comprehensive Complication Index

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SUMMARY

Liver transplantation is complex surgery and the increasing use of marginal grafts is pressurizing current postoperative outcomes. DCD grafts in particular are associated with PNF and ITBL with subsequent impaired graft survival rates. The aim of this study was to test the total burden of complications in the early postoperative period after liver transplantation between DCD and DBD grafts with the novel Comprehensive Complication Index (CCI). We performed a retrospective single-centre study of all liver transplantations performed since the start of DCD program (2001-2015). CCI (at hospital discharge and six months) was the result of ALL complications weighted by their Clavien-Dindo grade. A multiple logistic regression model was used to identify factors associated with a complex postoperative course (CCI at six months >60). In total, 441 cases were included: 115 DCD and 326 DBD grafts. Median in-hospital CCI was comparable for both groups (DCD 38.2; DBD 36.7; p=0.429). Six-months post-operative median CCI was significantly higher for DCD grafts (53.4 vs 47.2; p=0.041). Also, more DCD recipients underwent retransplantation for ITBL in this period (4% vs 1%; p=0.031). Logistic regression identified recipient BMI (p=0.046), recipient WIT (OR 1.032; 95%CI 1.008-1.056; p=0.008), and DCD graft (OR 3.913; 95%CI 1.200-12.767; p=0.024) as risk factors for a CCI >60. In conclusion, this analysis shows a comparable complication rate during the index hospital stay for DCD and DBD LT, but the CCI increases significantly for DCD recipients in six months after transplantation. Reduction of biliary complications, especially ITBL, is needed to improve the outcomes for DCD grafts.

INTRODUCTION

DCD grafts are increasingly used to overcome the organ shortage in liver transplantation (1,2). The use of these marginal grafts is associated with several complications, such as PNF, AKI and ITBL, resulting in inferior graft and recipient survival (3–6). However, recent studies show that with careful selection of DCD grafts and recipients the survival rates can reach a level comparable DBD liver transplantation (7–10). Furthermore, DCD grafts have shown to be a useful source of organs for patients waiting for a transplant with an HCC. Their time on the waitlist can be shortened before they cross Milan criteria and they are more likely to tolerate an extended criteria organ, due to their relatively low biological MELD-score (11–13).

The complexity of the surgical procedure, the severe disease of the patient and the marginal graft puts patients receiving a DCD graft more at risk for postoperative complications. However, the diversity of complications makes it difficult to compare postoperative outcomes and solid endpoints, like early postoperative mortality, have become rare due to successful retransplantation. The Comprehensive Complication Index (CCI) is a novel tool to combine all complications into one number that comprehends the entire burden of postoperative morbidity (14). It has shown its efficacy in gastro-intestinal surgery to serve as a primary outcome measure and compare treatment groups (15,16). In the early postoperative period after liver transplantation vascular complications, infections, acute rejection, EAD and kidney injury are the most common problems, while chronic rejection, recurrence of liver disease and biliary complications develop several months after transplant (17). These later (biliary) complications require often interventional therapy as well, such as endoscopic treatment, surgery or even retransplantation (18).

The aim of this study was to compare all postoperative morbidity with the novel CCI between DCD and DBD grafts up to six months after liver transplantation.

METHODS

This retrospective study was performed with approval of the Erasmus MC Institutional Review Board (MEC-2014-670). All consecutive patients who underwent deceased donor liver transplantation with age ≥18 years in our center from the start of the DCD program were included (10/2001 - 08/2015). Exclusion criteria were retransplantation, split-liver transplantation, combined liver kidney transplantation and transplant for acute hepatic failure.

Table 1 - donor, recipient and surgical characteristics of DCD and DBD liver transplantation

Donor	DBD (n=326)	DCD (n=115)	Total (n=441)	P-value
Age (years)	54 (44-63)	47 (38-56)	51 (43-61)	<0.001
Male gender (%)	164 (50)	64 (56)	228 (52)	0.324
Body mass index	24.5 (22.7-26.9)	22.7 (21.6-25.4)	24.2 (22.6-26.6)	0.017
Cause of death (%)				
Trauma	57 (18)	29 (25)	86 (20)	
Anoxia	12 (4)	24 (21)	36 (8)	
Cerebrovascular accident	251 (77)	57 (50)	308 (70)	
Other	6 (2)	5 (4)	11 (3)	<0.001
Location (%)				
Local	26 (8)	15 (13)	41 (9)	
National	244 (75)	97 (84)	341 (77)	
International	56 (17)	3 (3)	59 (13)	<0.001
Donor risk index				
Official	2.0 (0.4)	2.5 (0.5)	2.1 (0.5)	<0.001
Excluding DCD status	2.0 (0.4)	1.7 (0.3)	1.9 (0.4)	<0.001
Donor warm ischemia time (min)				
Asystolic (n=112)	.	16.8 (4.8)	.	.
Ischemic agonal phase (n=88)	.	13.0 (7.0)	.	.
Recipient				
Age (years)	53 (43-60)	55 (48-62)	53 (44-60)	0.016
Male gender (%)	213 (65)	79 (69)	292 (66)	0.513
Body mass index	25.2 (22.7-28.4)	25.3 (23.2-29.1)	25.2 (22.9-28.6)	0.655
Type of liver disease (%)				
Hepatitis B	30 (9)	9 (8)	39 (9)	
Hepatitis C	44 (14)	23 (20)	67 (15)	
Biliary cirrhosis	111 (34)	27 (24)	138 (31)	
Alcohol related cirrhosis	55 (17)	22 (19)	77 (18)	
Other	86 (26)	34 (30)	120 (27)	0.188
Hepatocellular carcinoma (%)	75 (23)	36 (31)	111 (25)	0.078
Child Pugh score	8 (6-10)	8 (7-10)	8 (6-10)	0.572
MELD score	14 (9-20)	15 (9-20)	14 (9-20)	0.409
Sodium (mmol/L)	138 (135-140)	138 (134-140)	138 (135-140)	0.323
Medical history(%)				
Diabetes Mellitus	70 (22)	29 (25)	99 (22)	0.408
Coronary artery disease	11 (3)	3 (3)	14 (3)	0.687
Hypertension	17 (5)	6 (5)	23 (5)	0.999
Surgical				
Operation time (hours)	7.5 (6.7-8.7)	7.6 (6.9-8.4)	7.5 (6.8-8.7)	0.551
Cold ischemia time (hours)	6.9 (5.6-8.3)	6.5 (5.8-7.4)	6.7 (5.7-8.0)	0.338
Recipient warm ischemia time (min)	28 (24-34)	28 (24-35)	28 (24-35)	0.850
Blood loss (L)	3.8 (2.4-6.5)	4.5 (3.2-6.8)	4.0 (2.5-6.5)	0.067
RBC transfusion (units)	3 (1-6)	3 (1-6)	4 (3-7)	0.734
FFP transfusion (units)	4 (0-8)	4 (0-8)	3 (1-6)	0.687
Platelet transfusion (units)	1 (0-2)	1 (0-2)	4 (0-8)	0.188
Peak postoperative serum AST (U/L)	856 (555-1699)	2657 (1311-4905)	1061 (630-244)	<0.001

AST, aspartate transaminase; DBD, donation after brain death; DCD, donation after circulatory death; FFP, fresh frozen plasma; MELD, model for end stage liver disease; RBC, red blood cells.
Continuous variables are presented in median and interquartile range.

All collected donor and recipient characteristics are displayed in **Table 1**. This data was used to calculate the donor risk index (DRI), MELD and Child-Pugh score as well (19,20). Graft allocation in the Netherlands is based on the MELD-principle. WoT of DCD donors is on the ICU and there is an obligatory 5-minute waiting time after circulatory arrest. The super-rapid retrieval technique is used to minimize the asystolic phase of DWIT (21). Exclusion criteria for DCD donors included age >60 years, body mass index (BMI) >28, aspartate transaminase (AST) >120 U/L and serum sodium > 160 mmol/L. The vascular and biliary flush is performed with University-of-Wisconsin preservation fluid. Prior to 2013 histidine-tryptophan-ketoglutarate was used as well. Standard surgical technique included piggyback cavo-caval anastomosis with only incidental use of a portocaval shunt. Operation time, cold ischemia time, and recipient WIT, intraoperative blood loss with subsequent transfusion requirements were all recorded. The peak serum AST level in the first 72 hours was used as a surrogate marker for hepatic IRI, a known marker for EAD (22). The standard immunosuppression regime changed during the study period. Until 2012 the regimen consisted of tacrolimus from day 0 and prednisolone (for 3 months). In 2012 mycophenolate mophetil (MMF) (from day 0) and basiliximab (day 0 and 4) were added and introduction of tacrolimus was postponed for kidney protection until day 5.

Duration of hospital and ICU admission, recipient and graft survival were all documented. The CCI was calculated using the original algorithm with all complications that occurred during hospital admission and up to six months after transplantation using the Clavien-Dindo classification (14,23). The range of the CCI is 0-100, with 100 equaling death. In case of retransplantation, a grade 4A complication was scored and thereafter follow up was terminated to prevent progression of CCI points for the first graft that were actually a complication from the re-transplant graft. ITBL was defined as postoperative symptomatic strictures and associated dilatation of the intrahepatic or hilar bile duct(s). These symptoms were (1) confirmed by endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography or percutaneous transhepatic cholangiography, (2) in the presence of a patent hepatic artery confirmed by ultrasound and (3) required biliary endoscopic or percutaneous intervention or retransplantation.

Statistical analysis

Data were analyzed with IBM SPSS Statistics V24 (IBM Corporation, Armonk, NY, USA). The student's t-test was used to compare normally distributed continuous variables. Nonparametric continuous variables were compared using the Mann-Whitney-U test. To compare categorical variables the Chi-square test or Fisher's exact test were used.

P-values <0.05 were considered statistically significant. A multiple logistic regression model with all relevant donor, recipient and surgical characteristics was used to identify factors associated with a complicated course after liver transplantation (CCI >60 at six months after transplant). Long-term survival rates were estimated using Kaplan-Meier methods. The median follow up period was 6.9 years.

RESULTS

During the study period 634 liver transplants were performed at our center: 120 DCD and 504 DBD grafts. The following transplants were excluded: 85 retransplantations, 10 split-livers, 16 combined liver-kidney transplants and 77 transplants for acute hepatic failure. Two cases were excluded because of missing data and 3 recipients who died within 24 hours after transplant (all DBD grafts). This lead to an inclusion of 441 liver transplants: 115 DCD and 363 DBD liver transplants.

Baseline characteristics

Baseline characteristics are displayed in **Table 1**. Median donor age was 51 years and DCD donors were significantly younger (47 vs. 54 years; p<0.001). Median BMI was lower in the DCD donors as well (22.7 vs. 24.5; p=0.017). After correction for DCD transplantation the DRI was significantly lower in the DCD group (1.7 vs. 2.0; p<0.001). Median age of the recipients was 53 years and significantly higher in those who received a DCD graft (55 vs. 53 years; p=0.016). Both Child-Pugh and MELD-score prior to transplant were comparable in both groups. The cold ischemia time was 6.9h in the DBD group, compared to 6.5h in the DCD group (p=0.338). Recipient WIT was 28 minutes in both groups. The transfusion requirement was comparable for both groups as well. Postoperative peak serum AST was significantly higher in DCD recipients (2657 vs. 856 U/L; p<0.001).

Postoperative outcomes and the Comprehensive Complication Index

Postoperative outcome parameters in the first six months after liver transplantation are shown in **Table 2**. All in-hospital outcome parameters were comparable for DCD and DBD grafts. After six months the mortality rate was 11% in the DCD group, compared to 7% in the DBD group (p=0.152). The retransplantation rate was higher in DCD recipients (15% vs. 5%; p=0.001). A tendency towards more biliary complications was observed in the DCD group (34% vs. 26%; p=0.081). Furthermore, the incidence of ITBL in this period was significantly higher in this group (11% vs. 3%; p<0.001). More DCD recipients received a retransplant for ITBL as well (4% vs. 1%: p=0.031).

Table 2 - postoperative outcome parameters after liver transplantation with DCD and DBD grafts

In-hospital	DCD (n=115)	DBD (n=326)	Total (n=441)	P-value
≥1 severe complication (CD grade 3B) (%)	39 (34)	113 (35)	152 (35)	0.884
Postoperative ventilation days	0 (0-1)	0 (0-1)	0 (0-1)	0.117
Length of stay ICU (days)	3 (2-4)	3 (2-4)	3 (2-4)	0.557
Length of stay entire admission (days)	20 (15-28)	19 (15-29)	19 (15-29)	0.825
Retransplantation (%)	7 (6)	11 (3)	18 (4)	0.206
Death (%)	11 (10)	20 (6)	31 (7)	0.216
Within six months				
Readmission (%)	54 (47)	142 (44)	196 (44)	0.528
Death (%)	13 (11)	23 (7)	36 (8)	0.152
Biliary complications				
All biliary complications* (%)	39 (34)	83 (26)	122 (28)	0.081
Anastomotic biliary complications** (%)	21 (18)	59 (18)	80 (18)	0.969
Ischemic type biliary lesions (%)	13 (11)	9 (3)	22 (5)	<0.001
Retransplantation (%)				
Total	17 (15)	17 (5)	34 (8)	0.001
Hepatic artery thrombosis	5 (4)	9 (3)	14 (3)	0.372
Portal vein thrombosis	3 (3)	1 (1)	4 (1)	0.056
Primary non function	4 (3)	1 (1)	5 (1)	0.018
Ischemic type biliary lesions	5 (4)	3 (1)	8 (2)	0.031
Other	0	3 (1)	3 (1)	0.403

CD, Clavien Dindo; DBD, donation after brain death; DCD, donation after circulatory death; ICU, intensive care unit.
Continuous variables are presented in median and interquartile range.
* Include all biliary complications: ischemic type biliary lesions, anastomotic complications and treatment for incidental cholangitis without diagnosed underlying disease.
** Requiring at least endoscopic or percutaneous treatment.

The CCI at hospital discharge and six months after transplant is displayed in **Figure 1**. The median CCI at hospital discharge was 37.1 and comparable for DCD and DBD grafts (38.2 vs. 36.7; p=0.434). On the contrary, six months after transplant recipients in the DCD group had a significantly higher CCI (53.4 vs 47.2; p=0.041). To assess the origin of the overall difference at six months, all complications were divided into four categories: surgical (including hepatic artery thrombosis (HAT), rebleed, perforation), medical (PNF, kidney injury, rejection, diabetes mellitus (DM), myocardial infarction, stroke, etc.), biliary complications (including ITBL and anastomotic strictures) and infections. There were no significant differences in these subgroups for DCD and DBD grafts after six months, but a trend was observed for a higher CCI in the DCD groups for biliary (p=0.071) and medical (p=0.051) complications.

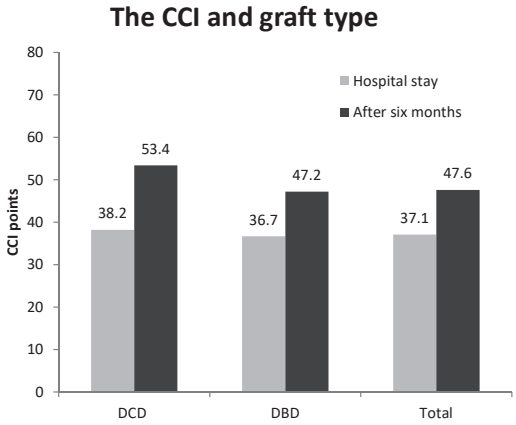

Figure 1 – CCI for recipients of DCD and DBD grafts at hospital discharge and six months after liver transplantation

Factors associated with a high Comprehensive Complication Index after six months

A multiple logistic regression model (**Table 3**) was used to identify donor, recipient and surgical factors associated with a complicated postoperative course (CCI >60 after six months). For example, one re-operation for bleeding (grade 3B) and re-admittance at ICU for respiratory sepsis (grade 4B) during hospital admittance and one endoscopic treatment for ITBL (grade 3A) and one course of antibiotics for a pneumonia after discharge (grade 2) lead to a CCI of 63.7 at six months. Three factors were associated with a CCI >60: Recipient BMI (OR 1.052; p=0.046), duration of recipient WIT (OR 1.032; p=0.008) and use of a DCD graft (OR 3.913; p=0.024).

Long term survival

The five-year estimated graft (71%) and patient (81%) survival are displayed in **Figure 2**. Recipients who received a DCD graft had a significantly lower five-year estimated graft survival (60% vs.75%; p=0.002). However, there was no significant difference observed in the estimated patient survival (DCD 75%; DBD 82%; p=0.090).

DISCUSSION

Our results show with use of the CCI that outcome of DCD and DBD liver transplantation is comparable during the index hospital stay, but that DCD recipients experience more complications in the long run. This study thus confirms the outcomes of other publications, reporting both similar and detrimental outcome in DCD liver transplantation and shows the dynamic increase of total burden of complications, depending

Table 3 - multiple logistic regression model to identify factors associated with a CCI >60 six months after liver transplantation

Recipient	Odds ratio	95% CI	P-value
Age	1.007	0.998-1.027	0.481
Gender	1.255	0.792-1.990	0.334
Body mass index	1.052	1.001-1.105	0.046
MELD score	1.018	0.992-1.045	0.168
Indication for transplant			
Biliary cirrhosis	1.000	.	0.231
Viral hepatitis	0.744	0.401-1.380	0.348
Alcohol related cirrhosis	0.944	0.488-1.825	0.863
Other	1.379	0.800-2.376	0.247
Donor			
Age	1.003	0.988-1.018	0.692
Gender	1.123	0.735-1.718	0.591
Body mass index	1.005	0.948-1.065	0.869
DCD graft	3.913	1.200-12.767	0.024
Surgical			
Cold ischemia time	1.091	0.983-1.211	0.102
Recipient warm ischemia time	1.032	1.008-1.056	0.008
>5 units RBC transfusion	1.440	0.896-2.313	0.132

CI, confidence interval; DCD, donation after circulatory death; MELD, model for end stage liver disease; RBC, red blood cells.

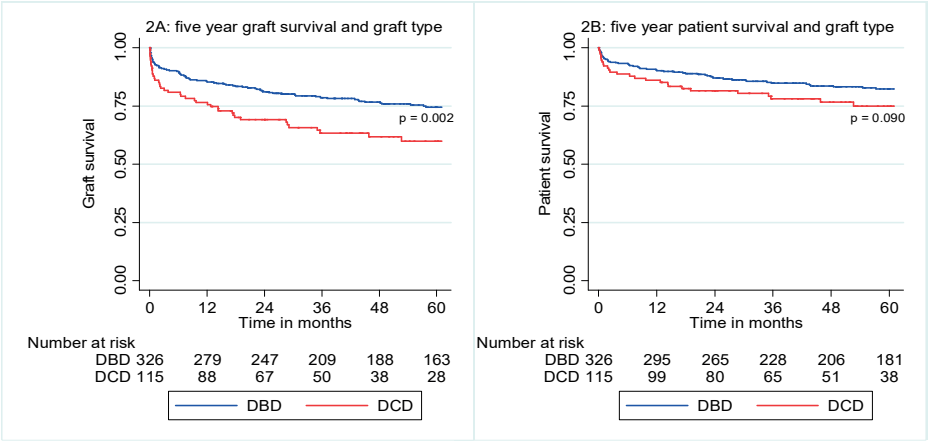

Figure 2 - Five year graft (A) and patient (B) survival after DCD and DBD liver transplantation

on the time frame that is analyzed (3,5,7,24,25). The novelty of our study lies in the method of comparing outcomes between DCD and DBD grafts. With the new CCI as a continuous variable, we can actually show the extent of difference in morbidity between the grafts and how the burden of complications increases over time.

The potential complications after DCD liver transplantation require a delicate selection of grafts and matching recipients. Known factors that impair outcomes of DCD grafts are both recipient and donor age and BMI, MELD-score, and prolonged cold and warm ischemic times (26,27). Our DCD and DBD cohorts show similar recipient characteristics with comparable MELD and Child-Pugh scores, previous medical history and even a higher recipient age in DCD recipients. The donor age limit of 60 years in DCD transplantation led to a lower donor age. Also, according to a protocol cut-off level of 28 for BMI in DCD donors to minimalize severely steatotic liver grafts, BMI was significantly lower in the DCD group. Importantly, cold and recipient warm ischemia times were comparable for DCD and DBD grafts.

The recently developed CCI is based on a formula used in the economic world, which incorporates multiple factors influencing the globalization of a corporation decision. With this formula all complications, weighted by severity, are integrated in a linear scale from 0 to 100. It facilitates reporting not only of the in-hospital morbidity, but also at various postoperative follow up moments, e.g. the six-months morbidity. In this study, the CCI proves again its easy applicability to longitudinal assessment of complications over time, as illustrated in the analysis of the six-months follow up. Also, the CCI correlates well with more traditional complication parameters, such as length of stay, grade 3 and higher complications and graft survival, which adds clinical relevance to this new global marker of morbidity. The major benefit of the CCI is that although the incidence of particular complications may be low, the accumulation of all complications and their severity is accounted for in the value of the CCI.

Our regression model identified DCD grafts as the main factor associated with a CCI of >60 after six months. We chose this cut-off because of the clinical example given in the results. Furthermore, Schlegel *et al* recently showed in a risk assessment of high MELD recipients that the median CCI for recipients with MELD >30 was 56 after one year (28). The CCI in this study correlated well with several preoperative risk scores for graft survival after liver transplantation as well. Other significant factors in our model included recipient BMI and prolonged recipient WIT. Obesity is a known factor in surgery for infectious complications and long-term outcomes, but results in liver transplantation are not conclusive and malnutrition is here an important factor

as well (29–31). Recipient WIT aggravates hepatic IRI, but recent studies focus more on the impact of the obligatory DWIT in DCD liver transplantation (32,33). DWIT is per definition not present in DBD donors, but this period is indirectly represented through the DCD graft factor in our multivariable model.

Parallel to the classical outcomes, the CCI showed no differences between DBD and DCD recipients during the index in-hospital stay, probably reflecting effective donor-recipient matching to balance the risks intrinsic to the use of a DCD graft. However, after six months more recipients in the DCD group developed biliary complications and required a retransplant. The progression of the CCI showed a similar picture: during the initial hospital admittance values were equal, but after six months the CCI was significantly higher for DCD graft recipients. The calculation of the CCI for the subgroups showed that mainly biliary and medical complications were more common and required more treatment in the DCD group within the first six months. Because only 22 recipients developed ITBL in this period, we did not create subgroup to evaluate the CCI for ITBL alone. The higher retransplantation rate at six months after DCD liver transplantation was predictive for a worse long-term outcome in our cohort and DCD recipients had a lower 5-year estimated graft survival. Earlier studies on this subject are not conclusive and several studies have reported impaired long-term graft survival for DCD grafts as well, while others showed results comparable with DBD grafts (8,34–36). The discrepancies between these studies is likely the result of variation in the selection of DCD donors and recipients between countries and transplant centers. The five-year patient survival was not inferior for DCD grafts in this study, probably due to our liberal retransplantation policy for patients with a failing graft due to ITBL. If ITBL as a late effect of the use of DCD liver grafts can be prevented, the outcome of DCD liver grafts can become truly comparable to that of DBD liver grafts. Hypothermic oxygenated and normothermic machine perfusion are currently under study to improve graft quality and show promising results in expanding the viable organ donor pool and decrease ITBL requiring retransplantation (37,38).

This study has several limitations. Data was collected retrospectively, but performed by only one individual, leading to a consistent interpretation and registration of complications. Our DCD and DBD cohorts are comparable for most of the pretransplant characteristics, but inherent to the use of high-risk grafts, some donor and recipient characteristics were significantly different, as described above. This reflects however the actual clinical situation in many institutions using DCD grafts, because of stricter donor and recipient selection criteria when DCD grafts are used. Therefore, we de-

cided not to balance the groups using propensity matching in this cohort. Recipients requiring retransplantation form a unique group: a 4A complication was scored for retransplantation and we terminated follow up after retransplantation, because we encountered a case with a retransplant for PNF and the recipient developed ITBL after retransplantation. Also, the CCI is originally developed for surgical complications, while in liver transplantation postoperative infections and medical complications are common as well.

In conclusion, with the use of the CCI this study provides a new view on postoperative complications and graft usage in liver transplantation. Patients receiving a DCD graft have a similar course during the postoperative hospital stay, but more complications occur thereafter in the first six months. Biliary complications such as ITBL, are major contributors to the morbidity of DCD liver transplantation. The following graft survival is impaired for DCD grafts as well. The novel graft persevering techniques, such as machine perfusion, are essential to improve the overall outcomes of DCD grafts.

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