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Comparing Neonatal Outcomes in Women with Severe Compared to Mild-Moderate Chronic Kidney Disease

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Abstract

Objectives: This study aims to stratify the outcomes of these infants born to mothers with varying stages of Chronic Kidney Disease (CKD) so as to improve obstetric counseling and prognostication. We also aim to look at other prognostic risk factors that may worsen the neonatal outcomes such as presence of hypertension, amongst others.

Setting: A single-centre retrospective cohort study was conducted in a tertiary centre.

Participants: All pregnancies of mothers with chronic renal impairment diseases were included over the period of August 2012 to December 2020. Other acute maternal renal diseases or mothers with congenital kidney abnormalities were excluded. First trimester termination of pregnancies or spontaneous miscarriages was also excluded.

Outcome Measures: Comparison was made between Severe Renal Impairment (SRI) pregnancies with CKD stage 4 to 5 or requiring RRT *vs.* those with mild to Moderate Renal Impairment (MRI) with CKD stages 1 to 3 and not requiring RRT. Analyses were done to look at prognostic values of maternal hypertension, need for anti-hypertensive medications, and RRT timing, on neonatal outcomes.

Results: Out of 74 pregnancies, 15 (20.2%) were SRI pregnancies. Pregnancy with SRI was associated with higher combined mortality or major morbidity (OR 5.889; 95% CI 1.551-22.357), prematurity (OR 15.500, 95% CI 1.913-125.582), maternal hypertension (OR 5.867, 95% CI 1.727-19.932), use of anti-hypertensive in pregnancy (OR 5.786, 95% CI 1.663-20.133) and presence of fetal distress (OR 7.125, 95% CI 1.072-47.371). Presence of hypertension and need for anti-hypertensive medications during pregnancies were associated with higher mortality, combined mortality or major morbidities, prematurity and need for caesarian section. All pregnancies requiring RRT resulted in preterm deliveries.

Conclusion: Neonates of SRI pregnancies have significantly increased risk of poorer outcomes. The presence of hypertension and need for anti-hypertensive medications were independent risk factors for worse outcomes in CKD pregnancies.

Keywords: Neonatal outcomes; Pregnancy; Chronic kidney disease; End stage renal failure; Renal replacement therapy; Prematurity

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Introduction

It is well known that mothers with Chronic Kidney Disease (CKD), particularly End Stage Renal Failure (ESRF), have high rates of pregnancy-related complications such as pre-eclampsia, miscarriages, early preterm deliveries and Small for Gestational Age (SGA) infants [1-3]. Chronic kidney disease is staged according to levels of kidney function based on Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines. This is regardless of the cause of kidney disease [3,4]. CKD is estimated to affect 3% of pregnant women in high-income countries with later stage CKD occurring in 1 in 750 pregnancies [5,6]. Few data is available on current prevalence of CKD in pregnancy in the region due to heterogenous studies and challenges in identifying kidney diseases in pregnancy.

Advances in multidisciplinary management including medical treatment and obstetric

management of mothers with CKD in the past decade have greatly improved pregnancy outcomes. This include having successful pregnancy while on dialysis and post renal transplant [7,8].

This study aims to stratify the outcomes of these infants born to mothers with varying stages of CKD, including those on dialysis and those living with functional kidney transplant, so as to improve obstetric counseling and prognostication. We also aim to look at other prognostic risk factors that may worsen the neonatal outcomes such as presence of hypertension, need for and timing of Renal Replacement Therapy (RRT), and peak levels of creatinine and urea during pregnancy.

Here, we conducted a retrospective cohort study to specifically look at pregnancy and neonatal outcomes of mothers with a range of CKD, so as to better equip these mothers on making informed decision regarding pregnancy. To our knowledge, it is the first study done in Southeast Asia that looks at the impact of CKD on pregnancy outcomes.

Materials and Methods

A retrospective cohort study was done between August 2012 to December 2020 in a tertiary care teaching institution in Singapore that provides neonatal intensive care. Data was collected from REDCap, which is a collated database of all babies born within the unit from August 2012. REDCap data is input by one doctor into an electronic database of medical records and another separate doctor counterchecks the data. All pregnancies of mothers with chronic renal impairment diseases, such as diabetes nephropathy, systemic lupus erythematous and IgA nephropathy, or ESRF, were included. Other acute maternal renal diseases such as urinary tract infection, pyelonephritis or congenital kidney abnormalities such as horseshoe kidney, were excluded. First trimester termination of pregnancies or spontaneous miscarriages was also excluded.

Data collected included maternal age, diagnosis, parity, whether RRT was initiated prior to conception or during pregnancy, peak urea and creatinine levels during pregnancy, and other comorbid conditions such as pre-eclampsia or hypertension. Renal replacement therapy included all forms of dialysis. The mothers were then grouped according to their CKD stages based on KDIGO guidelines [4], with mothers with CKD stages 1 to 3 and not on RRT in the mild to Moderate Renal Impairment (MRI) group. Mothers with CKD stage 4 to 5 or on RRT were grouped in the Serious Renal Impairment (SRI) group. Accuracy of data was maintained by separate persons collecting data in the electronic medical records compared to checking and data entry.

We hypothesized that infants born to mothers with stage 4 to 5 CKD or on RRT compared to other stages of renal diseases have increased risk of poorer neonatal outcomes. The primary outcome looked at was combined mortality and/or presence of at least one of the four major morbidities (defined as presence of Intraventricular Hemorrhage (IVH), Necrotizing Enterocolitis (NEC), Retinopathy of Prematurity (ROP) and Bronchopulmonary Dysplasia (BPD)). Secondary outcomes included prematurity, Small for Gestational Age (SGA), presence of Non-Reassuring Fetal Signs (NRFS) on Cardiotocography (CTG) monitoring, whether extensive resuscitation was required at birth, and delivery *via* Lower Segment Caesarean Section (LSCS). Prematurity is defined as any birth less than 37 weeks gestational age. SGA refers to birth weight less than 10th percentile according to the Fenton growth chart [9]. Non-reassuring fetal signs include fetal tachycardia, bradycardia, late or variable decelerations on CTG.

Statistical analysis was performed using SPSS Statistics version 17.0 for Windows (SPSS Inc, Chicago, IL, USA). Discrete variables were analyzed using the chi square. Continuous variables were analyzed using Mann-Whitney U test. $P<0.05$ was considered significant.

Apart from analyzing the pregnancy outcomes of these mothers, analyses were done to look at pregnancy outcomes in mothers with pre-existing or pregnancy-induced hypertension such as pre-eclampsia, mothers who were on anti-hypertensive medications, and whether RRT was started preconception or during pregnancy for the mothers with ESRF. A comparison of the prognostic accuracy was performed using Receiver Operating Curve (ROC) analysis and C-statistics, where the presence of mortality or any of the major morbidities above were each counted as 1.

Results

Over the 8-year period, there were a total of 74 pregnancies with CKD identified, of which 15 (20.3%) were mothers with SRI. There were 59 (79.7%) pregnancies in mothers with MRI. There was only one mother with stage 3b CKD in the SRI group who was on dialysis, rest were CKD stages 4 to 5.

Table 1 showed the comparison between antenatal and intrapartum characteristics for MRI and SRI pregnancies.

Expectedly, there were significant differences in peak urea and peak creatinine. In addition, significantly more SRI pregnancies had hypertension and need for anti-hypertensive medications, both ranging at approximately two thirds. There was a 7-fold increase in odds of fetal distress and a 16-fold increase in odds of preterm delivery. However, no significant difference was found in LSCS rates.

Table 2 showed the comparison of neonatal outcomes between MRI and SRI groups. There were statistically significant differences in the gestation at birth, with a median of 37 weeks for MRI, compared to 31 weeks for SRI, with a birth weight of 2,475 g and 1,170 g respectively. There were also significant differences in mortality and

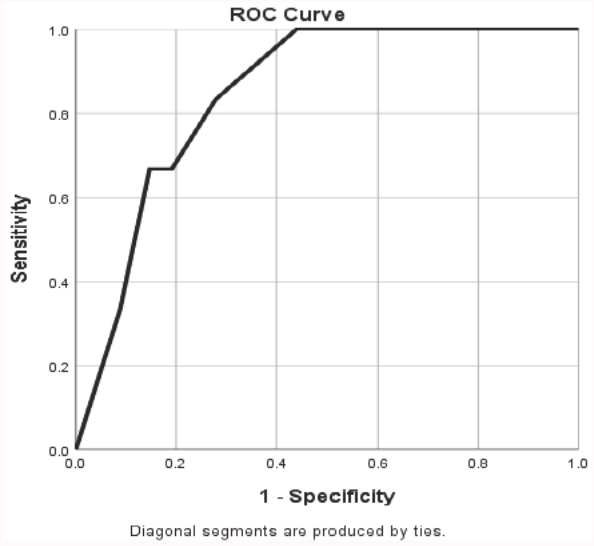

Figure 1: ROC (C-statistics) of CKD staging with respect to mortality or major morbidities.

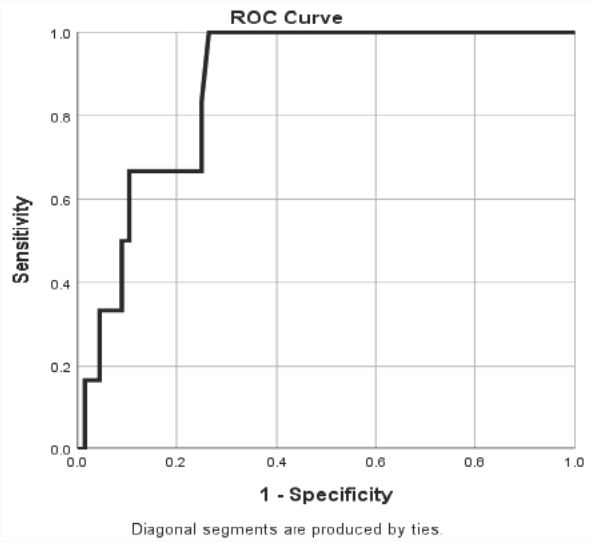

Figure 2: ROC (C-statistics) of peak creatinine with respect to mortality or major morbidities.

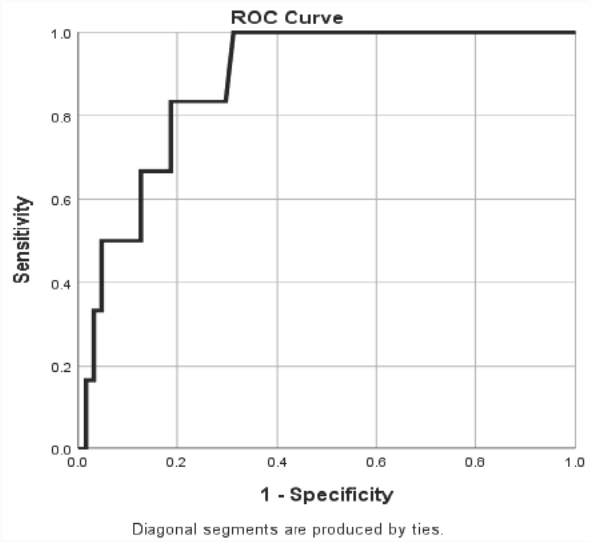

Figure 3: ROC (C-statistics) of peak urea with respect to mortality or major morbidities.

combined mortality with major morbidities. 13.3% of SRI pregnancies resulted neonatal deaths, compared to none in the MRI pregnancies. Similarly, the OR for mortality or major morbidities is almost 6-fold increase. There were no significant differences in gender, incidence of SGA or need for extensive resuscitation between the two groups.

In Table 3, we analyzed the association between hypertension and need for anti-hypertensive medications, which likely denoted those with higher blood pressure and complications, and outcomes. Presence of hypertension and need for anti-hypertensive medications during pregnancies were associated with higher mortality, combined mortality with major morbidities, prematurity and need for caesarian section.

Table 4 shows the association between timing of RRT and outcomes among renal patients. There were a total of 11 out of the 15 mothers in the SRI group that were on RRT. The 6 mothers had RRT initiated preconception while 5 mothers had RRT initiated post-conception. All post-conception RRTs were started after the first trimester. Compared to no RRT neonates, pre-conception RRT had higher risk of prematurity and extensive resuscitation while post-conception RRT had higher risk of mortality, combined mortality or morbidity and prematurity. Comparing pre- with post-conception RRT outcomes, no significant differences were found.

Peak urea, peak creatinine and CKD staging respectively were found to have the highest AUROC in terms of predicting mortality or major morbidities. All 3 markers had low standard errors, are significant and have asymptotic 95% confidence intervals not crossing 0.5 (Table 5, 6).

Discussion

Our study confirmed that CKD in pregnancy, particularly SRI, was an important risk factor. In the SRI group, the median gestation and birth weight was only 31 weeks and 1,170 grams, compared to the term gestation and 2,470 grams in MRI. These were not only statistically significant, but large clinical significant differences. In the SRI group, the mortality was 13% and 40% of these babies suffered either mortality or at least 1 of 4 major morbidities, namely IVH, ROP, NEC and BPD. It is well known that these 4 major morbidities often translate to poorer long term neurodevelopmental outcomes, requiring more outpatient visits and multidisciplinary interventions, with the presence of an increasing number of these morbidities associated with worse outcomes [10,11].Some of our study results are similar to previous meta-analysis done by Zhang et al. [12] in 2015, which analyzed pregnancy outcomes of women with CKD *vs.* women without CKD. In that study, CKD pregnancies showed statistically significant higher odds of preeclampsia (OR 10.36, 95% CI 6.28-17.09), higher rate of pregnancy failure (OR 1.80, 95% CI 1.03-3.13), premature birth (OR 5.72, 95% CI 1.03-10.03), cesarean section (OR

Table 1: Comparison of antenatal and intrapartum characteristics between MRI and SRI groups.

	MRI pregnancies (n=59)	SRI pregnancies (n=15)	SRI *vs.* MRI	P value
	Median ± IQR	Median ± IQR	Odds ratio (95% CI)	
Peak urea during pregnancy (mmol/L)	5.9 ± 4.9	18 ± 7.8	N/A	<0.001
Peak creatinine during pregnancy (mmol/L)	70 ± 58	514 ± 334	N/A	<0.001
	N (%)	N (%)		
Hypertension in pregnancy (n=23)	15 (25.4)	10 (66.7)	5.867 (1.727-19 932)	0.003
Need for an i-hypertensive during pregnancy (n=22)	14 (23.7)	9 (64 3)	5.786 (1.663-20.133)	0.003
NRFS (n=5)	2 (3.4)	3 (20 0)	7.125 (1.072-47.371)	0.022
LSCS (n=54)	42 (71.2)	13 (86.7)	2.631 (0.536-12.924)	0.22
Preterm delivery (n=42)	28 (47.5)	14 (93.3)	15.500 (1.913-125.582)	0.009

*IQR: Interquartile Range

Table 2: Comparison of Neonatal outcomes between MRI and SRI groups.

	MRI pregnancies (n=59)	SRI pregnancies (n=15)	SRI *vs.* MRI	P value
	Median ± IQR	Median ± IQR	Odds ratio (95% CI)	
Birth weight (g)	2475 ± 1095	1170 ± 1185	N/A	<0.001
Gestational age (weeks)	37 ± 4	31 ± 7	N/A	<0.001
	N (%)	N (%)		
Gender (male)%	57.60%	33.30%	2.720 (0.826-8.952)	0.092
Mortality (n=2)	0	2 (13.3)	N/A	0.004
Combined mortality or major morbidity (n=12)	6 (10.2)	6 (40.0)	5.889 (1.551-22.357)	0.005
SGA (n=21)	18 (30.5)	3 (20.0)	0.569 (0.143-2.266)	0.42
Intubation or ECM (n=5)	3 (5.1)	3 (20.0)	4.667 (0.838-25.995)	0.059

*IQ: Interquartile Range

Table 3: Association between hypertension and anti-hypertensive medications and outcomes among all renal patients.

	Presence of hypertension in pregnancy compared to none		Anti-hypertensive medications in pregnancy compared to none	
	Odds ratio	P value	Odds ratio	P value
Mortality	N/A	0.045	N/A	0.033
Combined mortality or morbidity	15.667 (3.083-79.613)	<0.001	45.833(5.382-390.289)	<0.001
SGA	1.303 (0.455-3.734)	0.627	1.559(0.538-4.519)	0.419
Prematurity	41.333(5.148-331.842)	<0.001	34.1(4.254-273.324)	<0.001
Intubation or ECM	4.476 (0.76-26.375)	0.078	5.158(0.871-30.528)	0.05
NRFS	3.205(0.499-20.574)	0.205	1.524 (0.237-9.801)	0.661
LSCS	6.109(1.284-29.075)	0.013	12(1.492-96.504)	0.004

Table 4: Association between timing of RRT and outcomes among renal patients.

	RRT initiated preconception compared to no RRT		RRT initiated post conception compared to no RRT		RRT initiated post *vs.* preconception	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Mortality	0.912 (0.847-0.982)	0.756	15.5 (0.811-296.280)	0.019	N/A	0.251
Combined mortality OR morbidity	4.000 (0.616-25.964)	0.122	12.0 (1.700-84.693)	0.003	3.000 (0.255-35.334)	0.376
SGA	0.878 (0.790-0.974)	0.101	0.538 (0.056-5.123)	0.584	N/A	0.297
Prematurity	1.194 (1.036-1.375)	0.017	1.161 (1.019-1.324)	0.029	N/A	N/A
Intubation or ECM	10.000 (1.28-78.117)	0.01	5.0 (0.419-59.657)	0.163	0.500 (0.031-7 994)	0.621
NRFS	4.000 (0.349-45.898)	0.233	5.0 (0.419-59.657)	0.163	1.250 (0.058-26.869)	0.887
LSCS	1.848 (0.201-16.978)	0.582	1.478 (0.154-14.178)	0.733	0.800 (0.037-17.196)	0.887

Table 5: Receiver Operating Curve analysis of various predictive factors for mortality or major morbidities. (Please refer to figure 1 to 3 for actual ROC curves).

Area Under the Curve					
Test variable	Area Under the Curve (C statistics)	Std Error	Asymptotic Significance	Asymptotic 95% CI	
				Lower Bound	Upper Bound
Gestation age	0.114	0.042	0.002	0.032	0.196
CKD staging	0.847	0.058	0.005	0.734	0.96
RRT timing	0.316	0.137	0.137	0.066	0.566
Peak Creatinine during pregnancy	0.874	0.05	0.003	0.777	0.971
Peak Urea during pregnancy	0.882	0.051	0.002	0.781	0.982

4.85, 95% CI 3.03-7.76) and SGA (OR 2.67, 95% CI 2.01-3.54). The difference in our study would be that instead of comparing with no CKD, we had the opportunity to compare MRI *vs.* SRI in terms of CKD severity.

In another study done by He et al. [13] in 2018 that compared pregnancy outcomes in patients with stage 3 to 4 CKD *vs.* stage 1 to 2, there was significantly lower live birth rate, gestational age and birth weight in the group of pregnant patients with stage 3 to 4 CKD than in the group of pregnant patients with stage 1 CKD. The study also looked at the effect of pregnancy on the renal function of women with CKD and found that there was no acceleration of kidney disease progression in these women. In our study, we had the ability to look at pregnancy outcomes of the most severe stage 5 CKD too, instead of stopping at CKD stage 4.

Table 6: Suggested Cut-off values from ROC curve for risk markers, based on balancing sensitivity against specificity (Please refer to figure 1 to 3 for actual ROC curves).

Parameter	Sensitivity	Specificity
CKD staging =< 3.5 CKD stage >3.5	0.667	0.809
Cr =< 387 umol/l Cr >387 umol/l	0.667	0.897
Urea =< 12.35 mmol/l Urea >12.35 mmol/l	0.833	0.812

We believed that CKD stages 4 to 5, particularly the inclusion of stage 5 CKD may be associated with the highest risk of adverse outcomes. By including women with CKD stage 5 and women on RRT, we are better able to counsel these high-risk women on possible outcomes as well as advice on how best to prepare for the pregnancy, for example, optimizing blood pressure control and having increased dialysis to improve outcomes [14-16].

Our study found significant differences in the birth weight and gestational age between MRI compared to SRI pregnancy neonates. There were also higher odds of prematurity (OR 10.500, 95% CI 1.278-86.276) but not SGA. For those with SRI, the risk of prematurity is as high as 93.3% (OR 15.500 [95% CI 1.913-125.582], p<0.01). In addition, we found that compared to MRI pregnancies, SRI pregnancies had high risks of mortality, mortality or major morbidities, fetal distress.

Looking at risk factors within CKD pregnancies, hypertension during pregnancy as well as need for anti-hypertensive had higher odds of mortality, combined mortality or morbidity, prematurity and need for caesarian section. Although we are unable to gather the actual blood pressure readings of these CKD pregnancies due to practical constraints, we surmised that need for anti-hypertensive medications was a good marker denoting those pregnant mothers with worse blood pressure control or with higher risk of complications. These findings were rather similar to the study done by He et al. [13] that showed that having higher blood pressure, proteinuria and therapy in early pregnancy (including antihypertensive drugs and immunosuppressive agents), were significant risk factors for adverse pregnancy outcomes (severe preeclampsia, intrauterine death, neonatal death, early preterm birth [<34 weeks], very low birth weight infants [<1500 g]). The knowledge of having better blood pressure control may reduce the risk of combined mortality or morbidity in our cohort could serve as a reminder on the importance of better blood pressure control during pregnancies.

We did not find the timing of RRT initiated post-conception *vs.* preconception, to have any significant difference in outcomes. On the other hand, in our study, all infants born to mothers on RRT were premature. We found this to be a clinically significant result which would greatly aid in the counseling of such pregnancies. This finding was similar to systematic reviews which also showed a high incidence of prematurity for those on RRT compared to none [17] but, did not show significant differences in gestational age or birth weight between preconceptions *vs.* post conception RRT groups [14].

We conducted ROC analysis of the predictive values of various factors and found that peak urea and peak creatinine during pregnancy, as well as the CKD staging had excellent prognostic values for predicting mortality or major morbidities. Suggested cut off values based on the ROC curve best fit balancing sensitivity with specificity were derived, with CKD stage 3, peak creatinine levels of above 387 umol/l and peak urea of above 12.35 mmol/l denoting higher risk groups.

Some limitations of our retrospective cohort study included it being a small sample size over a long period of time, given the constraints of relative lower prevalence of renal impairment in pregnancies. We were not able to look at some of the other potential confounders that may affect the pregnancy outcomes, such as, presence of proteinuria, underlying disease etiology, presence of other systemic diseases, medications that the mothers were on due to practical constraints.

Further studies that look at comparing the mild to moderate stages of CKD with mothers without CKD will aid in counseling of mothers with the milder stages of CKD, although these would require significantly larger numbers. Long term outcomes on these high-risk pregnancies for both mothers and infants would also be needed. As the range of CKD is wide and diagnosis is variable across countries, future studies with well-defined disease characteristics as well as more specific outcomes could be designed.

Strengths and Limitations

- The study specifically looks at high grade CKD in pregnancies, including mothers on RRT. Previous studies looking at different stages only included up to stage 4, but not stage 5.
- C-statistics for prognostic ability of peak urea and peak creatinine during pregnancy and CKD staging were excellent, with suggested cut-off values derived from the ROC analysis.
- All pregnancies requiring RRT, whether preconception *vs.* post conception, resulted in preterm deliveries. This would assist in the counseling of such pregnancies.
- Small sample size over a long period of time, given the constraints of relative lower prevalence of renal impairment in pregnancies.
- We were not able to look at some of the other potential confounders that may affect the pregnancy outcomes, such as, presence of proteinuria, underlying disease etiology, presence of other systemic diseases, medications that the mothers were on due to practical constraints.

Conclusion

Pregnancy in CKD patients are high risk and multi-disciplinary team approach is necessary to improve the pregnancy outcomes. Neonates of SRI pregnancies have significantly increased risk of mortality, combined mortality and morbidity, preterm birth, and need for extensive resuscitation. The presence of hypertension and anti-hypertensive medications were independent risk factors for poorer outcomes in CKD pregnancies. C-statistics for prognostic ability of peak urea and peak creatinine during pregnancy and CKD staging were excellent, with suggested cut-off values derived from the ROC analysis. The results of this study will aid in counseling and managing women with CKD who are considering pregnancy, such as optimizing blood pressure control and having increased dialysis to improve neonatal outcomes.

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