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Dengue virus infection among renal transplant recipients in Singapore: a 15-year single-centre retrospective review

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ABSTRACT

Introduction: Dengue is a mosquito-borne viral infection endemic in Singapore. Its impact in renal transplantation is limited to small case series. We aimed to characterise the clinical presentation and outcomes of dengue infection among renal transplant recipients in Singapore.

Methods: We conducted a 15-year retrospective review of dengue in renal transplant patients treated at Singapore General Hospital between January 2005 and October 2019. The diagnosis of dengue was made if there were a compatible clinical syndrome and a positive dengue diagnostic assay (Dengue NS1 antigen, IgM or RT-PCR).

Results: 31 patients were diagnosed with dengue, 18 (58.1%) were deceased donor recipients. The median age was 52 (IQR 40–61) years; 16 (51.6%) were females. The median time to diagnosis was 99 (IQR 18–169) months from transplant. The most common clinical symptoms were fever (87.1%), myalgia (41.9%), gastrointestinal symptoms (38.7%) and headache (25.8%). 19 (61.3%) patients had dengue without warning signs, 9 (29.0%) had dengue with warning signs, 3 (9.7%) had severe dengue and 30 (96.8%) were hospitalized. 17 (54.8%) patients had graft dysfunction, 16 (94.1%) of whom had recovery of graft function. 1 (3.2%) patient required dialysis and subsequently died. There were two cases of donor-derived infections (DDIs) with favourable outcomes.

Conclusion: Our experience with dengue in renal transplant recipients is concordant with published data. Although graft dysfunction is common, it is often transient with favourable outcomes. Outpatient management may be considered for mild infections. Although dengue DDIs are uncommon, more stringent donor screening may be considered in endemic regions.

Keywords: dengue, renal transplant, Singapore

INTRODUCTION

Dengue is a mosquito-borne viral infection endemic in Singapore, transmitted most commonly by the *Aedes aegypti* mosquito. Dengue virus (DENV) is a flavivirus with four distinct DENV serotypes (DENV-1–4) and infection with any of the serotypes can result in clinical manifestations ranging from dengue fever with or without warning signs, to severe infections with plasma leakage, haemorrhage and organ impairment.[1] The Aedes mosquitoes are abundant in tropical countries[2] and it is an ongoing problem for Singapore with dengue outbreaks occurring in 5-6 year cycles.[3] In 2020, Singapore saw the highest number of reported dengue cases recorded, with 35,315 notified cases.[4]

Although dengue is relatively uncommon in renal transplantation[5,6] and published reports based on small case series suggest that it has favourable outcomes, it would still be important to understand its impact and clinical outcomes in our patients, given that this is an endemic infection in Singapore, and our renal transplant programme is growing. Since the inception of the renal transplant programme in Singapore in 1970, the number of renal transplant recipients have increased over the years. In 2009, there were 359 renal transplant recipients per million population, and this has increased to 400 per million population in 2018.[7] We aim to characterise the clinical presentation and outcome of dengue infection in renal transplant recipients treated at a tertiary centre in Singapore, corroborate our findings with international data, so as to further guide and improve our clinical management.

METHODS

We conducted a 15-year retrospective review of dengue infection in renal transplant patients treated at Singapore General Hospital (SGH) between January 2005 and October 2019. The study was approved by the ethics committee of the institution (CIRB Ref: 2019/2764). All renal transplant patients who were on follow up at our centre who had dengue infection as defined

by a compatible syndrome and confirmatory laboratory tests (dengue non-structural 1 antigen (NS 1), immunoglobulin M (IgM) or reverse transcriptase-polymerase chain reaction (RT-PCR) positive) were included in the study. Renal transplant recipients with a positive dengue diagnostic tests performed during the study period were identified using the Singhealth electronic health intelligence systems (eHINTS). Their medical records were reviewed by two investigators. Patients who had isolated positive dengue IgM serology without any clinical features of dengue were excluded from the study. Patients were classified according to World Health Organization (WHO) classification 2009.[1] Patient demographics, transplant details, clinical features, laboratory findings and clinical outcomes of dengue infections were extracted.

Categorical variables are presented as absolute numbers with percentages, and continuous variables as median values with interquartile ranges (IQR).

RESULTS

Thirty-one renal transplant patients were diagnosed with dengue during the study period. Patient demographics are presented in Table 1. The median age at time of diagnosis was 52 (IQR 40 - 61) years and 16 (51.6%) were females. The most common clinical symptoms were fever (87.1%), myalgia (41.9%), gastrointestinal symptoms (38.7%) and headache (25.8%); mucosal bleeding (9.7%), arthralgia (9.7%), rash (6.5%) were uncommon. Based on the WHO 2009 dengue classification (1), 19 (61.3%) had dengue without warning signs, 9 (29.0%) had dengue with warning signs, and 3 (9.7%) had severe dengue. Of the 9 patients who had dengue with warning signs, 2 had pleural effusion, 3 had mucosal bleeding with epistaxis and haematuria, the remaining patients had lethargy with laboratory features of increase in haematocrit with concurrent rapid decrease in platelet counts. Of the 3 patients with severe dengue, 2 had plasma leakage leading to shock or respiratory distress and 1 had multi-organ failure. See Table 2 and 3. The median duration of clinical illness was 7 (IQR 6-7) days.

Majority (96.8%) of our patients were presumed to have primary infection as dengue IgG serology was not routinely done. Only 1 patient was tested for and had a negative dengue IgG serology in our series and confirmed to have primary dengue infection.

All patients were on immunosuppressive therapy at time of dengue diagnosis, with combination of prednisolone, mycophenolate mofetil (MMF)/ mycophenolic acid (MYF) and tacrolimus (FK) being the most common immunosuppressive regimen. Of the 25 patients who were on an anti-metabolite immunosuppressant (MMF/ MYF/ Azathioprine), 11 (44.0%) had their immunosuppressant discontinued and 5 (20.0%) had their doses reduced during the episode of dengue due to leukopenia, thrombocytopenia or deranged liver function tests. Of these 16 patients who had their doses discontinued or reduced, 11 (68.8%) were restarted back on full dose of anti-metabolite immunosuppressant within 2 weeks of discharge upon recovery of their cell counts. There were 26 patients who were on calcineurin inhibitors, of which 9 (34.6%) had their doses adjusted based on drug levels while the rest of the patients were kept on their existing doses. Eight (25.8%) had no change in their immunosuppression throughout the course of dengue infection. There was 1 case of biopsy proven rejection that occurred 5 months post dengue episode. This patient had just undergone an ABO incompatible living donor renal transplant 1 month prior to the dengue episode. She was followed up closely and had recovery of platelets at 3 days post discharge. However, her MYF was not resumed back to her old dose then due to concerns of persistent viremia as her repeat serum dengue RT-PCR was still positive. Her dose of MYF was increased back to her old dose 19 days after discharge when her serum dengue RT-PCR turned negative. She was subsequently noted to have rising creatinine, worsening proteinuria and microscopic haematuria at 5 months post dengue episode and her renal biopsy showed evidence of antibody mediated rejection.

Most of the dengue infections were community acquired; the median time to diagnosis of dengue was 99 (IQR 18 - 169) months from transplant. Interestingly, 2 patients had donor-

derived dengue, and developed the infection on day 10 and day 9 post-transplant.[8] Patient 30 and patient 31 (see Table 2) received the kidneys from the same donor. Patient 31 had undergone an uncomplicated transplant surgery, and was recovering well until he developed fever on the 5th postoperative day. He subsequently developed thrombocytopenia and he was tested positive for dengue serotype 2 (DEN-2). Patient 30 was asymptomatic, but his laboratory tests revealed thrombocytopenia and leukopenia. Given that he received the kidney from the same donor, he was screened and tested positive for DEN-2 as well, raising the possibility that the dengue infections were donor derived. Investigations later revelated that both recipients had received the pair of kidneys from an aviremic, but dengue viuric donor.

Laboratory findings are presented in Table 3. Seventeen (54.8%) patients had graft dysfunction, of whom 10 (58.8%) had > 20% but ≤ 50% rise in serum creatinine from baseline, and 7 (41.2%) had > 50% rise in serum creatine from baseline; 16/17 (94.1%) patients had full recovery of graft function. Only 1 (3.2%) required dialysis; this same patient later demised from hospital acquired pneumonia. Dengue mortality rate was 3.2%.

Most physicians chose to manage the patients in hospital; 30 (96.8%) patients were admitted. The median length of stay was 8 (IQR 6 -13) days.

DISCUSSION

This study identified 31 renal transplant patients who were diagnosed with dengue infection from January 2005 to October 2019. To our knowledge, this is one of the larger case series reported in Southeast Asia[5] and the largest from Singapore, a country endemic for dengue infection. Figure 1 shows the trend of dengue cases in Singapore and among renal transplant recipients in our institution from 2005 to 2019.[9] In 2019, we saw the highest number of dengue cases among renal transplant patients in our cohort, 6 (19.4%) of cases. In general, dengue trends in the renal transplant population parallel community peaks. This highlights the

importance of nationwide prevention and control efforts to curb the spread of dengue in the community in order to minimize risk of transmission to renal transplant patients. At the same time, it is equally important to educate renal transplant patients living in, or travelling to regions endemic for dengue on safe living practices. They should be mindful of outbreaks and dengue clusters in their community, take precautionary measures to prevent mosquito bites, and to adopt practices to prevent mosquito breeding in their residences.

Dengue in renal transplant is largely a community acquired infection and our study found that clinical course parallels that of the immunocompetent host,[5,10] with fever, myalgia, gastrointestinal symptoms and headache being the most common symptoms. Graft dysfunction is common (~54.8% of cases), but this is transient, with recovery of graft function in most of our patients (94.1%). Only 1 patient in our series required dialysis. This is concordant with other studies on renal transplant patients with dengue. Similar rates of graft dysfunction ranging between 55% and 77% were reported[5,11,12] with majority of patients having full recovery of kidney function within 2 weeks post acute dengue. This however appears higher compared to the general population, where the incidence of acute kidney injury typically ranges from 1.2% to 29.6%.[13-17] Having said this, we acknowledge there were slight differences in the definitions used for graft dysfunction among the various studies. Although graft dysfunction may be transient, it is still important that close monitoring and titration of fluid balances in the renal transplant patient with acute dengue infection is practiced to ensure favourable outcomes and full recovery of kidney function. Additionally, graft dysfunction can be considered as a criteria for patient triage and admission.

The mortality rate of acute dengue infection in our renal transplant population is comparable to published data in the same population group; reported mortality rates range from 0-7%.[12,18-20] We reported only 1 death (3.2%), which was contributed by hospital acquired pneumonia and not directly related to dengue infection. However, it is important to note that

the overall mortality from dengue in the renal transplant population is still higher than the general population, where mortality rates among hospitalized patients ranges from 0.17-0.77%.[21]

CMV coinfection has been described in other studies with prevalence of 5-66%.[12,22] A recent study by Fernandes-Charpiot et al[11] showed that subgroup of patients with dengue infection and CMV coinfection had worse thrombocytopenia, higher rate of acute graft dysfunction and longer hospitalisation time, however there was no difference in graft loss and mortality rate. In our series, there was only 1 patient (3.1%) with CMV coinfection (see Table 2). This patient had CMV viremia with no end organ disease and was treated successfully with intravenous ganciclovir. She was on prednisolone, cyclosporin and azathioprine with no recent change in her immunosuppressant doses prior to admission. Although our patient had graft dysfunction, her renal function recovered back to baseline upon discharge.

The management of immunosuppression in the setting of acute dengue infection remains an art as there are currently no established guidelines to guide its use. In our study, we found that majority of physicians chose to suspend or reduce dose of anti-metabolite agents due to leukopenia, thrombocytopenia or deranged liver function test during the course of dengue. Of the 16 patients who had their anti-metabolite immunosuppressants stopped or reduced, 1 patient subsequently developed biopsy-proven rejection 5 months after dengue episode. She had acquired acute dengue infection within 1 month of transplantation, and her MYF was dose reduced in view of persistent viremia. This highlights the challenges of titrating immunosuppression in renal transplant recipients with dengue infection, especially within the first 6 months of transplantation; dose reduction of immunosuppression for viral control may potentially place the patient at a higher risk of acute rejection. A large case series by Nasim et al[12] showed that the anti-metabolite immunosuppressants had no effect on the severity and duration of thrombocytopenia or leukopenia. Thus, it may be safe and prudent for physicians

to restart patients on their regular immunosuppressants soon after recovery from dengue to reduce the risk of graft rejection.

At our centre, most renal physicians chose to admit renal transplant patients infected with dengue, 30 (96.8%) patients were admitted. The median length of stay was 8 (IQR 6 -13) days. This is in contrast to the practice in non-transplant patients where dengue is increasingly managed in the community. As illustrated by Ang et al, the proportion of dengue cases hospitalized during three epidemic periods declined from 93.2% in 2004–2005 to 58.1% in 2007 and subsequently 28.9% in 2013–2014 with no concomitant increase in adverse outcomes based on the case fatality rate.[21] This practice of managing dengue in the community was in response to the Singapore Ministry of Health (MOH) providing periodic guidelines on the management of dengue during epidemics and refining criteria for hospital referral and admission. This practice however was not adopted in our renal transplant unit, where 96.8% of the patients were admitted, and majority (61.3%) did not have warning signs or severe dengue. This could be attributed to the more cautious approach managing dengue in transplant recipients. Based on WHO's recommendations[23] and our findings, renal transplant recipients with acute dengue may be considered for outpatient management with close follow-up. They include patients who have (a) no warning signs, (b) are able to maintain adequate oral hydration with satisfactory urine output, (c) no signs of plasma leakage and (d) absence of graft dysfunction. Close follow-up to monitor their blood counts and renal function is recommended. They should also be advised to have sufficient bed rest, hydration and to monitor for warning signs as defined by WHO. On the contrary, it would be prudent to admit patients with renal impairment or dengue with warning signs for hydration, and to monitor them for signs of plasma leakage.

Donor derived infections (DDIs) with dengue are uncommon, with only a few cases reported in literature. Although dengue is a vector-borne viral infection, acquisition of dengue

through needle stick injury, as well as receipt of blood products, hematopoietic stem cell transplant, and solid organ transplants has been described.[24-26] Interestingly, we found 2 cases of proven dengue DDIs in our series; both recipients had received their organs from the same donor. In Singapore, a dengue endemic country, all solid organ donors and recipients are routinely screened for dengue in the blood by RT-PCR at time of transplant. This practice has been instituted since 2016 (per communication with national organ transplant unit (NOTU)). In this case, both donor and recipients were tested negative for dengue at the time of organ procurement. When both recipients later tested positive for dengue (based on clinical symptoms and laboratory findings), follow up with NOTU revealed that the donor had developed acute dengue infection 2-3 weeks prior to organ harvest with serological conversion. Although the donor was aviremic at time of organ donation, dengue PCR was detected in her leftover urine sample suggesting that she had prolonged shedding of dengue virus in the kidneys, resulting in the DDIs.[27] Currently, there are no international recommendation for universal screening of urine dengue PCR in organ donors living in endemic regions. However, because of this incident case, the NOTU has since augmented the donor workup, and revised their policy as of 8th of April 2021 to routinely screen organ donors for dengue by testing both blood and urine for dengue RT-PCR. To date, there is no consensus on whether organs from dengue infected donors can be used. Although donor derived dengue was recognized early in patients 30 and 31 and outcomes were favourable (no bleeding complications, nor impact on graft dysfunction), complications of donor derived dengue are not uncommon. Clinical symptoms for early dengue may be non-specific and diagnoses may be delayed if dengue were not suspected. In addition, severe cases of donor derived dengue infections have also been reported; recipients may suffer severe bleeding complications (e.g. persistent haemorrhage from operative site, haemorrhagic shock), develop major organ complications (including allograft dysfunction and loss) and potentially demise from the infection.[28,29]

In this study, a spectrum of dengue cases in the renal transplant population hospitalised with dengue was described. This would inform the renal transplant community of the clinical manifestations of dengue in this unique population to aid clinical assessment, triaging and management. We also acknowledge the limitations of this study due to its retrospective nature, and potential recall bias. We acknowledge that patients who had only mild symptoms or asymptomatic may not have sought medical attention at our hospital and would not be captured in our database. Furthermore, information on dengue serotypes was not available for all patients, thus its impact on clinical outcomes cannot be described.

In conclusion, we found that our data on dengue infection in renal transplant population supports published international data and further adds confidence to the management of these patients in a dengue endemic country. Additionally, we provide recommendations on donor screening and considerations for patient triage to safely manage more patients in an outpatient setting. Management of immunosuppressants is important in this group of patients and further studies are required to provide better guidance for renal transplant physicians.

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Table I. Patient demographics

Characteristics	
Age, in years; median (IQR)	52 (40-61)
Gender, n (%)	
Female	16 (51.6%)
Male	15 (48.4%)
Ethnicity, n (%)	
Chinese	21 (67.7%)
Malay	8 (25.8%)
Indian	2 (6.5%)
Others	0 (0%)
Type of kidney transplant, n (%)	
Deceased donor transplant	18 (58.1%)
Living donor transplant	13 (41.9%)
Immunosuppression therapy at time of dengue diagnosis, n (%)	
Pred + MMF/ MYF + FK	12 (38.7%)
Pred + MMF/ MYF + CsA	4 (12.9%)
Pred + Aza + CsA	4 (12.9%)
Pred + CsA	4 (12.9%)
Pred + MMF/ MYF + SIR	2 (6.5%)
Pred + FK	2 (6.5%)
Pred + Aza	1 (3.2%)
Pred + ERL	1 (3.2%)
Pred + Aza + SIR	1 (3.2%)

Aza, Azathioprine; CsA, Cyclosporin; ERL, Everolimus; FK, Tacrolimus; IQR, Interquartile range; MMF, Mycophenolate mofetil; MYF, Mycophenolic acid; Pred, Prednisolone; SIR, Sirolimus

Table II. Clinical characteristics of all 31 kidney transplant patients with dengue infection.

	Age / Gender	Confirmatory lab method			Year of diagnosis	Time from transplant	Duration of clinical illness	Clinical manifestations	Co-infection	WHO classification	Graft dysfunction	Outcome
		NS1	**IgM**	**RT-PCR**								
1	34 M	ND	Pos	ND	2005	89 months	5 days	Fever, headache, myalgia	Nil	DF	No	Recovered
2	58 F	ND	Pos	ND	2005	108 months	9 days	Fever, headache	UTI	DF	Yes	Recovered
3	50 F	ND	Pos	Neg	2005	12 months	8 days	Fever	Nil	DF with WS	No	Recovered
4	55 F	ND	Pos	Neg	2005	2 months	8 days	Lethargy, haematuria	Nil	DF with WS	Yes	Recovered
5	65 F	ND	Equivocal	Pos	2006	186 months	7 days	Fever, vomiting, giddiness, dyspnoea	HAP	SD	Yes	Demised (HAP)
6	52 F	ND	Equivocal	Pos	2008	269 months	7 days	Fever, myalgia, lethargy, vomiting, diarrhoea, rash, poor appetite	Nil	DF with WS	Yes	Recovered
7	61 M	ND	Neg	Pos	2008	101 months	7 days	Fever, dyspnoea, oliguria, abdominal pain	CAP	SD	Yes	Recovered
8	61 F	ND	Pos	ND	2009	22 months	6 days	Fever, myalgia	UTI	DF	Yes	Recovered
9	58 M	ND	Pos	ND	2009	169 months	5 days	Fever, diarrhoea	Nil	DF with WS	Yes	Recovered
10	34 F	ND	ND	Pos	2011	31 months	6 days	Fever, diarrhoea, headache, lethargy	Nil	DF with WS	No	Recovered
11	50 F	ND	Neg	Pos	2011	92 months	8 days	Fever, myalgia, productive sputum	Nil	DF	Yes	Recovered
12	36 M	ND	Pos	ND	2011	215 months	8 days	Fever, diarrhoea	GE	DF	Yes	Recovered
13	57 F	ND	Neg	Pos	2012	64 months	6 days	Fever, dysuria, vomiting	UTI, CMV reactivation	DF	Yes	Recovered
14	52 F	ND	Pos	ND	2013	50 months	8 days	Fever, myalgia, headache	Nil	DF	Yes	Recovered
15	39 M	Pos	Neg	Pos	2013	61 months	7 days	Fever, back pain, arthralgia, headache, poor appetite	Nil	DF	No	Recovered
16	37 M	Pos	Neg	Pos	2013	139 months	7 days	Fever, rash	Nil	DF	No	Recovered
17	52 F	Pos	ND	Pos	2014	99 months	6 days	Fever, myalgia, headache	UTI	DF	Yes	Recovered
18	53 M	Pos	ND	ND	2014	99 months	7 days	Fever, diarrhoea, cough, epistaxis	CAP	DF with WS	Yes	Recovered
19	60 F	Pos	Pos	ND	2015	262 months	7 days	Fever, sore throat, blocked nose	Nil	DF	No	Recovered

20	73 M	ND	Pos	Pos	2015	328 months	7 days	Cough, myalgia, diarrhoea, lethargy, poor appetite	Nil	DF with WS	Yes	Recovered
21	66 M	Pos	ND	Pos	2015	108 months	6 days	Fever	Nil	DF	No	Recovered
22	36 M	Pos	ND	Pos	2015	2 months	5 days	Lethargy	URTI	DF	No	Recovered
23	63 M	Pos	ND	ND	2017	193 months	7 days	Fever, myalgia, arthralgia, cough, headache, back pain	Nil	SD	Yes	Recovered
24	62 M	Pos	Neg	Pos	2018	3 months	7 days	Fever, nausea, vomiting, lethargy, poor urine output	Nil	DF	Yes	Recovered
25	40 M	Pos	ND	Pos	2018	21 months	3 days	Fever, arthralgia, headache, myalgia	Nil	DF	Yes	Recovered
26	60 F	ND	ND	Pos	2019	18 months	5 days	Fever, sore throat, cough, myalgia	URTI	DF	No	Recovered
27	49 F	Pos	Pos	Pos	2019	199 months	7 days	Fever, vomiting, lower back pain	Nil	DF with WS	Yes	Recovered
28	50 F	Pos	Pos	Pos	2019	72 months	2 days	Fever, myalgia, poor appetite	Nil	DF	Yes	Recovered
29	53 F	Pos	ND	Pos	2019	1 month	10 days	Fever, poor appetite	Nil	DF with WS	No	Recovered
30	39 M	ND	ND	Pos	2019	10 days	0 days	Asymptomatic, leucopenia	Nil	DF	No	Recovered
31	63 M	ND	ND	Pos	2019	9 days	5 days	Fever, thrombocytopenia, transaminitis	Nil	DF	No	Recovered

CAP, community acquired pneumonia; CMV, cytomegalovirus; DF, Dengue fever; DF with WS, Dengue fever with warning signs; F, female; GE, gastroenteritis; HAP, hospital acquired pneumonia; M, male; ND, not done; Neg, negative; Pos, positive; SD, severe dengue; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Table III. Clinical characteristics and laboratory parameters

Clinical characteristics (N = 31)	
Clinical manifestations, n (%)	
Fever	27 (87.1%)
Myalgia	13 (41.9%)
Gastrointestinal symptoms	12 (38.7%)
Headache	8 (25.8%)
Mucosal bleeding	3 (9.7%)
Arthralgia	3 (9.7%)
Rash	2 (6.5%)
Pleural effusion	4 (12.9%)
Ascites	1 (3.2%)
WHO 2009 Dengue Classification, n (%)	
Dengue infection without warning sign	19 (61.3%)
Dengue infection with warning sign	9 (29.0%)
Severe dengue	3 (9.7%)
Laboratory findings	
Dengue confirmatory test, n (%)	
NS1 antigen	13 (41.9%)
IgM	12 (38.7%)
RT-PCR	19 (61.3%)
Complete blood count, median (IQR)	
Platelet count at diagnosis (x 10^9/L) [Ref range: 140-440]	126 (72-173)
Nadir platelet count (x 10^9/L)	31 (17-90)
White cell count at diagnosis (x 10^9/L) [Ref range: 4.0-10.0]	5.2 (4.0-7.1)
Nadir white cell count (x 10^9/L)	2.8 (1.8-4.0)
Lymphocyte count at diagnosis (x 10^9/L) [Ref range: 1.0-3.0]	0.8 (0.4-0.9)
Nadir lymphocyte count (x 10^9/L)	0.5 (0.3-0.6)
Hematocrit at diagnosis (%) [Ref range: 36-46]	41 (34-44)
Peak hematocrit (%)	41 (34-44)
Blood chemistry, median (IQR)	
ALT at diagnosis (U/L) [Ref range: 6-66]	32 (21-55)
ALT peak (U/L)	76 (24-118)
AST at diagnosis (U/L) [Ref range: 12-42]	39 (29-101)
AST peak (U/L)	108 (42-172)
Cr at time of dengue diagnosis (μmol/L) [Ref range: 37-75]	140 (102-212)
Cr at time of dengue resolution (μmol/L)	112 (82-152)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; IgM, Immunoglobulin M; NS1, Non-structural 1; RT-PCR, reverse transcriptase-polymerase chain reaction

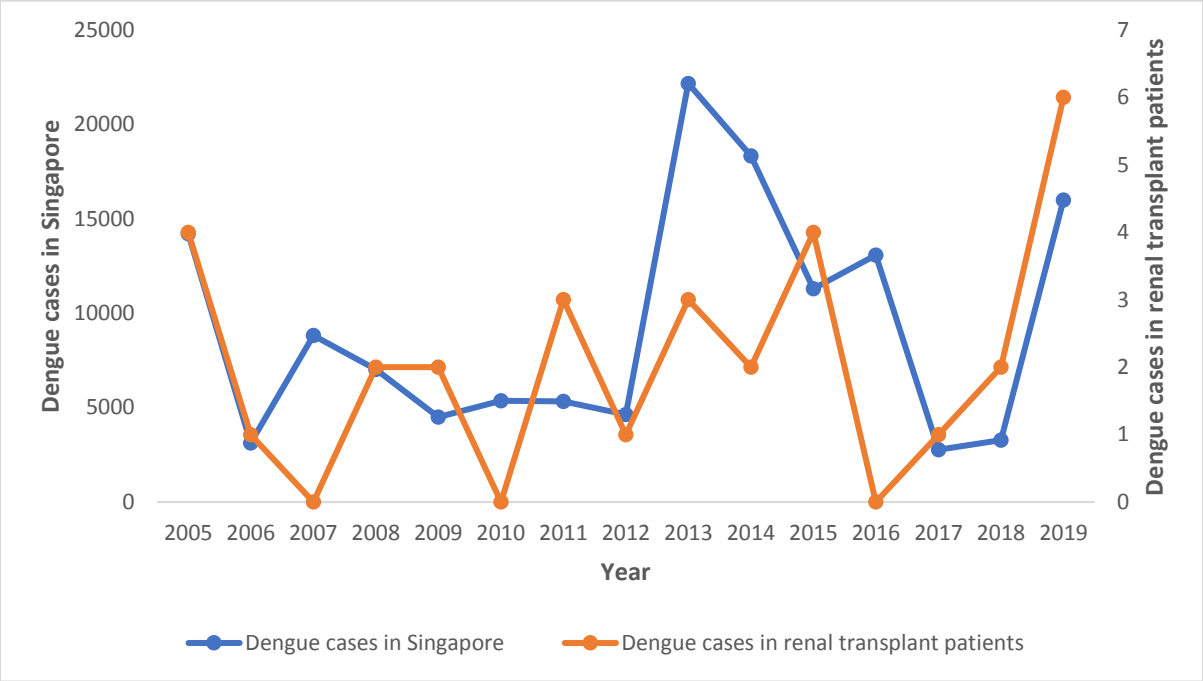

Fig. 1 Dengue trend in Singapore[9] and among renal transplant patients over the years