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Dengue fever in the immunocompromised: a retrospective cohort study on Reunion Island

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Abstract

Introduction Dengue fever (DF) is the most worldwide prevalent arbovirus associated diseases. Our study aimed to describe DF in immunocompromised patients on Reunion island and to compare it with data from non-immunocompromised patients. Methods In a retrospective cohort study that enrolled as confirmed DF all patients with positive reverse transcriptase chain reaction (rt-PCR) admitted to the University Hospital of Reunion in 2019, we identified immunocompromised patients to compare their socio-demographic, clinical and biological characteristics to non-immunocompromised. Results From the 847 patients with confirmed DF, 41 were immunocompromised. They were significantly older (p=0,001), presented significantly higher Charlson score (p<0,001), and more frequent severe dengue (p=0,001 and p=0,003 respectively). From immunocompromised patients, those with neoplasm were distinguished by higher Charlson score and risk of severe dengue. Conclusion This cohort warns clinicians about a particularly high risk of severe dengue in patients with solid neoplasm, a population significantly older and more comorbid.

Introduction

The World Health Organization declared dengue one of the top ten threats to global health in 2019 [1], with around 57 million cases reported and more than 36,000 related deaths worldwide [2]. Transmitted through *Aedes aegypti* and *Ae. albopictus* mosquito bites, dengue virus can induce a wide range of clinical presentation, from asymptomatic to severe dengue (including haemorrhagic forms)[1, 2].

While comorbidities or prior dengue virus infection have been described as risk factors for poor outcome in DF [3–5], data on DF in the immunocompromised patients remain scarce and heterogeneous. Given the worldwide spread of *Aedes*, we might face epidemics in developed countries where the use of immunosuppressants and chemotherapy is common, thus affecting different kinds of population (and further potentially unaware of DF)[6]. To date, no guidelines dedicated to the management of DF in immunocompromised patient have been published and we need to better identify the issues and predictors of severity for this population.

Reunion island recently experienced dengue epidemics. Between 2018 and 2024, several major epidemic waves confirmed in more than 70,000 patients, leading to over 2,500 hospitalizations, occurred due to DENV-2 and DENV-1 [7, 8].

Our study aims to describe demographic, clinical, and biological features, outcome, and care evaluation of DF in immunocompromised patients in Reunion island and to compare it with data from non-immunocompromised patients.

Methods

From the previously described EPIDENGUE database [9], we set up a retrospective cohort study that enrolled as confirmed dengue all patients with positive reverse transcriptase chain reaction (RT-PCR)

admitted to the University Hospital of Reunion between January 1 and June 30, 2019. Criteria for probable DF, severe DF and warning signs were based on the World Health Organization (WHO) 2009 definitions [10]. Co-infections were concomitant infection by another pathogen than dengue virus. Complications were any medical event occurring during hospitalization for DF.

Population

Medical records of all patients admitted to the University Hospital of Reunion island for a clinical suspicion of dengue infection were systematically reviewed. We retrieved socio-demographic, clinical and biological data for each patient. We selected patients with positive RT-PCR. Immunocompromised patients were identified by the following comorbidities : hemopathy, solid neoplasm, solid organ transplant, stem cell allograft, cirrhosis, HIV (human immunodeficiency virus) and auto-immune diseases with undergoing immunosuppressant treatment [11, 12]. Medical records were secondly rescreened to exclude the patients that were not considered as immunocompromised at the time of DF diagnosis from the immunocompromised group: HIV seropositive with lymphocytes CD4 over 200 per mm3, corticosteroid therapy under 10mg per day, neoplastic diseases in remission, localised skin neoplasm, auto-immune diseases not requiring immunosuppressive treatment or treated with immunomodulators alone such as hydroxychloroquine or colchicine. We also excluded patients with diabetes and chronic kidney disease (including patients treated with dialysis, data not shown) that were studied separately [9]. We compared data from the previously identified immunocompromised patients (ID group) with data from other patients (non-ID group). Within the ID group we furthered conducted post-hoc analysis by separating patients with neoplasm from non-neoplasm immunocompromised patients to compare them.

Statistical analysis

For bivariate analysis, quantitative variables were expressed as mean and standard deviation or median and interquartile ranges (1st – 3rd quartiles). Qualitative variables were expressed as numbers and percentages. A univariate analysis was conducted between immunocompromised patients and non-immunocompromised. Percentages were compared using Chi-square and Fisher exact tests, as appropriate. Means were compared using the student t test or the non-parametric Mann-Whitney test, as appropriate. Normality was checked by the Shapiro-Wilk test and homogeneity of variance by the Levene test. Analyses were performed using IBM SPSS Statistics (Version 23). For all these, observations with missing data were ruled out and a two-tailed p value < 0.05 was considered significant.

Results

Study population

From the 2365 patients included in the EPIDENGUE database, 1518 patients without RT-PCR performed or with DENV negative RT-PCR were excluded (Fig. 1), leaving 847 patients with a DENV positive RT-PCR eligible to the analysis. Of the remaining, 806 were not immunocompromised (non-ID group) and 41 were immunocompromised (ID group). Six groups were further identified by immunosuppression causes

(Fig. 1). Among the six patients with auto-immune diseases, three were treated by anti-TNF, two by methotrexate and one by azathioprine. All transplanted patients were renal transplant recipients. Among the 13 patients with neoplasm, six had prostate cancer, three breast cancer, three lung cancer and one digestive tract neoplasm; the 13 patients were treated as follows: five were under hormonotherapy, three under chemotherapy, two under tyrosine kinase inhibitors and three received no treatment. From the ten diagnosed hemopathies, four were multiple myeloma (treated either by proteasome inhibitors, alkylating agents, anti CD38 monoclonal antibody or immunomodulators), one was primary amyloidosis (treated by anti CD38 monoclonal antibody), one was acute myeloid leukemia (untreated), one was high grade B cell lymphoma (treated by CAR T cell therapy), one was B-cell acute lymphocytic leukemia (treated by antimetabolites), one was chronic lymphoid leukemia (untreated) and the last one was follicular lymphoma (untreated). Of the four cirrhosis, three were primarily alcoholic cirrhosis and one non-alcoholic steatohepatitis (patients are detailed in Appendix 3).

Comparison of immunocompromised (ID group) and non-immunocompromised (non-ID group) (Table 1**).**

Table 1
Comparison of dengue fever characteristics between immunocompromised (n = 806) and non-immunocompromised (n = 41) populations, La Réunion island, 2019.

	Non-immunocompromised n = 806	**Immunocompromised n = 41**	**p**
Demographic data			
Age (years) (Mean +/- SD)	47.7 +/- 23.3	59.9 +/- 18.3	**0.001**
Age (Median (IQR))	47 (28;68)	65 (51;76)	
Sex (female) (n(%))	463 (57)	19 (46)	0.164
Hypertension	214 (27)	20 (49)	**0.003**
Chronic kidney disease	47 (6)	12 (29)	**< 0.001**
Diabetes mellitus	140 (17)	11 (27)	0.143
Hypercholesterolemia	67 (8)	5 (12)	0.222
Chronic bronchitis	9 (1)	2 (5)	0.095
Anticoagulation	38 (5)	6 (15)	**0.016**
Antiaggregants	95 (12)	6 (15)	0.619
Charlson score (Median (IQR))	1 (0;3)	4 (2;9)	**< 0.001**
Clinical data			
Fever	667 (83)	39 (95)	**0.018**
Persistant vomiting	35 (4)	6 (15)	**0.011**
Diarrhea	143 (18)	14 (34)	**0.015**
Asthenia	531 (66)	32 (78)	0.096
Anorexia	353 (44)	19 (46)	0.749
Arthralgia	319 (40)	15 (37)	0.701
Myalgia	429 (53)	17 (42)	0.141
Headache	401 (50)	15 (37)	0.098
Retroorbital pain	154 (19)	9 (22)	0.657
Back pain	141 (18)	10 (24)	0.279

DIC: disseminated intravascular coagulation, IQR: interquartile range, SD: standard deviation

	Non-immunocompromised n = 806	Immunocompromised n = 41	p
Demographic data			
Alert signs	285 (35)	14 (34)	0.886
0	522 (65)	27 (66)	0.365
1	223 (28)	8 (20)	
2	54 (7)	5 (12)	
3	7 (1)	1 (2)	
Biological data (in blood)			
CRP at consultation (mg/l)	18.6 +/- 30.6	17.4 +/- 26.7	0.251
Creatinine at consultation (µmol/l)	104.0 +/- 108.0	134.0 +/- 108.0	**0.001**
Maximal creatinine	110.0 +/- 124.0	188.0 +/- 218.0	**< 0.001**
Sodium at consultation (mmol/l)	136.5 +/- 3.3	136.4 +/- 3.2	0.668
Maximal sodium	138.7 +/- 3.5	138.6 +/- 3.1	0.935
Hemoglobin at consultation (g/dl)	13.4 +/- 2.0	12.8 +/- 2.1	**0.028**
Platelets at consultation (G/L)	166.0 +/- 79.0	154.0 +/- 74.0	0.429
Minimal thrombopenia (G/L)	142.0 +/- 81.0	101.0 +/- 72.0	**0.002**
Monocytes at consultation (G/L)	0.6 +/- 0.3	0.6 +/- 0.3	0.387
Lymphocytes at consultation (G/L)	0.8 +/- 0.7	1.7 +/-5.5	0.344
Hematocrit at consultation (%)	39.4 +/- 5.1	37.4 +/- 6.6	**0.028**
Maximal hematocrit (%)	40.3 +/- 5.1	40.0 +/- 7.1	0.391
Medical care and evolution			
Consultation delay (days) (Mean +/- SD)	2.5 +/- 2.7	2.0 +/- 2.7	0.068
Hospitalisation	357 (44)	29 (71)	**0.001**
Length of hospitalization	5.3 +/- 4.9	4.9 +/- 2.7	0.805

DIC: disseminated intravascular coagulation, IQR: interquartile range, SD: standard deviation

	Non-immunocompromised n = 806	Immunocompromised n = 41	p
Demographic data			
(days) (Mean +/- SD)			
Coinfections	69 (9)	8 (20)	**0.026**
Complications	43 (5)	8 (20)	**0.002**
Severe dengue criteria			
Severe dengue	149 (19)	16 (39)	**0.003**
Organ failure	80 (10)	11 (27)	**0.002**
State of shock	20 (3)	2 (5)	0.289
Respiratory distress	17 (2)	0	1
Severe haemorrhage	38 (5)	4 (10)	0.140
Hepatic failure	12 (2)	1 (2)	0.478
Renal failure	22 (3)	7 (17)	**< 0.001**
Heart failure	21 (3)	1 (2)	1
Neurological failure	31 (4)	3 (7)	0.224
DIC	34 (4)	3 (7)	0.417
Death	13 (2)	2 (5)	0.161
DIC: disseminated intravascular coagulation, IQR: interquartile range, SD: standard deviation			

The general characteristics of the patients are summarized in Table 1. Sex ratio was similar in both groups. ID patients were significantly older (p = 0.001), presented with more comorbidities such as chronic kidney disease resulting in a higher Charlson score (p < 0.001). Clinical presentation was marked by more frequent fever (p = 0.018), diarrhea (p = 0.011) and persistent vomiting (p = 0.015) in ID group. At hospital presentation, ID patients presented with a lower hemoglobin level (p = 0.028); other biological parameters were similar in both groups. During follow-up, ID patients presented lower minimal thrombopenia (p = 0.002). Even if they did not initially present with more warning signs for severe dengue, ID group patients were more likely hospitalized (p = 0.001), presented with more complications (p = 0.002) and met criteria for severe dengue more frequently (p = 0.003). However, the duration of hospital stay was not longer, and mortality was not higher than in the non-ID group. The most frequent criteria for severe dengue in ID group was acute renal failure. Additionally, severe haemorrhages tended to be more frequent in ID group, but the difference was not significant.

Analysis of immunodepression subgroups (Table 2**).**

Table 2
Comparison of immunodepression subgroups.

	Hemopathy n = 10	**Solid neoplasm n = 13**	**Allograft n = 2**	**Graft n = 6**	**Cirrhosis n = 4**	**Autoimmune diseases n = 6**
Demographic data						
Median age (min-max)	62 (8–82)	75 (45–80)	55 (51–59)	58 (30–74)	73 (50–77)	40 (23–68)
Sex (female) (n(%))	4 (40)	5 (39)	1 (50)	3 (50)	2 (50)	4 (67)
Comorbidities						
Diabetes mellitus	2 (20)	4 (30)	1 (50)	3 (50)	1 (25)	0
Chronic kidney disease	2 (20)	4 (30)	0	5 (83)	1 (25)	0
Charlson score (Median (IQR))	2.5 (2;4.75)	10 (6–12)	3.5 (3;-)	4.5 (2;8)	5.5 (2.25–11.75)	1 (0;3)
Severe dengue						
Severe dengue	4 (40)	7 (54)	0	1 (17)	1 (25)	3 (50)
IQR: interquartile range, SD: standard deviation						

The incidence of patients meeting severe dengue criteria varied in the different subgroups of immunosuppression as follows: solid neoplasm (n = 7/13), autoimmune diseases under immunosuppressive therapies (n = 3/6) and hemopathies (n = 4/10), cirrhotics (n = 1/4), graft recipients (n = 1/6) and allograft recipients (0/2) (Table 2). Patients with neoplasm were older and and more comorbid than other subgroups.

As the additional risk of severe dengue observed in ID group was mainly related to patients with neoplasm (n = 23, including solid neoplasm and hemopathy), we further compared them (Appendix 1). Patients with neoplasm were significantly older (64.3 years +/- 17.4 vs 54.4 years +/- 18.3, p = 0.046) and presented more comorbidities (median Charlson score: 7 (IQR: 2–11) vs 3 (IQR: 2–7), p = 0.026). Clinical presentation was similar. At hospital presentation, biological parameters were similar in both groups, except for C-Reactive Protein (median CRP: 11 (IQR: 4–48) vs 6 (IQR: 2–11), p = 0.038). Proportion of Severe DF was higher in patients with neoplasms than other IDs (48% vs 28%), without reaching

significativity (p = 0.188). Severe DF cases were mainly due to acute renal failure (22%) and severe bleeding (13%) in the ID group, twice as many as in the non-ID group.

Discussion

This study that focused on DF in different types of immunosuppression, showed an increased risk of severe dengue in this population. Despite the small size and the heterogeneity of our sample, patients with solid neoplasm explained increased risk of severe dengue in ID group. This subgroup was distinct from other immunocompromised groups by being significantly older and presenting more comorbidities which is concordant with the previously described association between comorbidities and the risk of severe DF [3–5].

The presence of more severe dengue in our population was difficult to predict as patients did not present more frequent warning signs, highlighting the need for refining warning signs in immunocompromised patients as in general population [13, 14]. Fortunately, if renal failure was the main criteria to classify DF as severe (n = 9/16) in this cohort, all patients completely recovered from it, and only two patients presented non-severe haemorrhagic signs. Thus, mortality rates remained low.

In literature, the best described subgroup of immunodepression are kidney transplant recipients with severe dengue frequency ranging between 10 and 30% of cases which is in agreement with our findings [15–21]. The better prognosis of transplant recipients could be at least partly explained by the role played by the immune response in severe dengue development; some authors hypothesized that severe immunosuppression should protect from the risk of antibody-dependent enhancement (ADE) and thus reduce the risk of secondary severe dengue [22, 23].

Similarly, as previously described in another cohort in Reunion island, our patients with autoimmune diseases did not present higher risk of severe dengue [24]. Some postulated that cross reactivity of autoantibodies could explain less severe dengue in autoimmune population [25]. No other DF cohort included patients with neoplasm.

An important question when taking care of immunocompromised patients with infection is the interruption of immunosuppressors. In our cohort, the treatment was discontinued or reduced in half (3/6) of the patients with auto-immune diseases but only one (1/8) patient from the transplanted group. As it has been stated that immunosuppressive drugs discontinuation was associated with more graft rejection [15, 22] and our findings on transplant recipient are reassuring, this attitude seems justified.

Our study has some limits. The choice to restrict inclusion to patients with positive PCR led more specificity in DF diagnosis but also limited the size of our population and thus our statistical power. Due to this low number of ID patients and the heterogeneity of immunodepression subtypes, we could not evaluate specific risk for each subgroup. As Reunion Island faces dengue epidemics since 2018, we might hypothesize that a lack of experience of clinicians lead to over hospitalization of fragile populations like immunocompromised inducing interpretation biais.

Conclusion

To conclude, this cohort warns clinicians about a particularly high risk of severe dengue in patients with solid neoplasm, a population significantly older and more comorbid than other immunocompromised patients.

Interestingly, our data are reassuring for DF occurring in other immuncompromised population and encourage continuation of immunosuppressive therapy at acute stage of dengue fever especially in transplantation. Further studies on those specific populations are warranted for more power prompt to guide accurate care.

Declarations

Ethical approval

This monocentric retrospective observational study was conducted in accordance with the MR-004 reference methodology (registration number 2206739) of the French Data Protection Authority (CNIL), in compliance with the General Data Protection Regulation (GDPR). According to French regulations, retrospective studies based on routinely collected data do not require approval from an ethics committee (article R1121-1, decree n°2017 – 884 of 9 May 2018, art. 2). Nevertheless, the ethical aspects of the study were reviewed and approved by the Institutional Review Board of the University Hospital of Réunion. The EPIDENGUE database was registered with the French Health Data Hub (n° F20201021104344). The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed about the study, and non-opposition to participation was collected in accordance with French regulations and approved by the IRB. All data were anonymized before analysis and extracted from patients' medical records.

Author Contribution

ML compiled, analyzed and interpreted the patient data. RH performed the statistical analysis of the data. ML, RH and AB were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

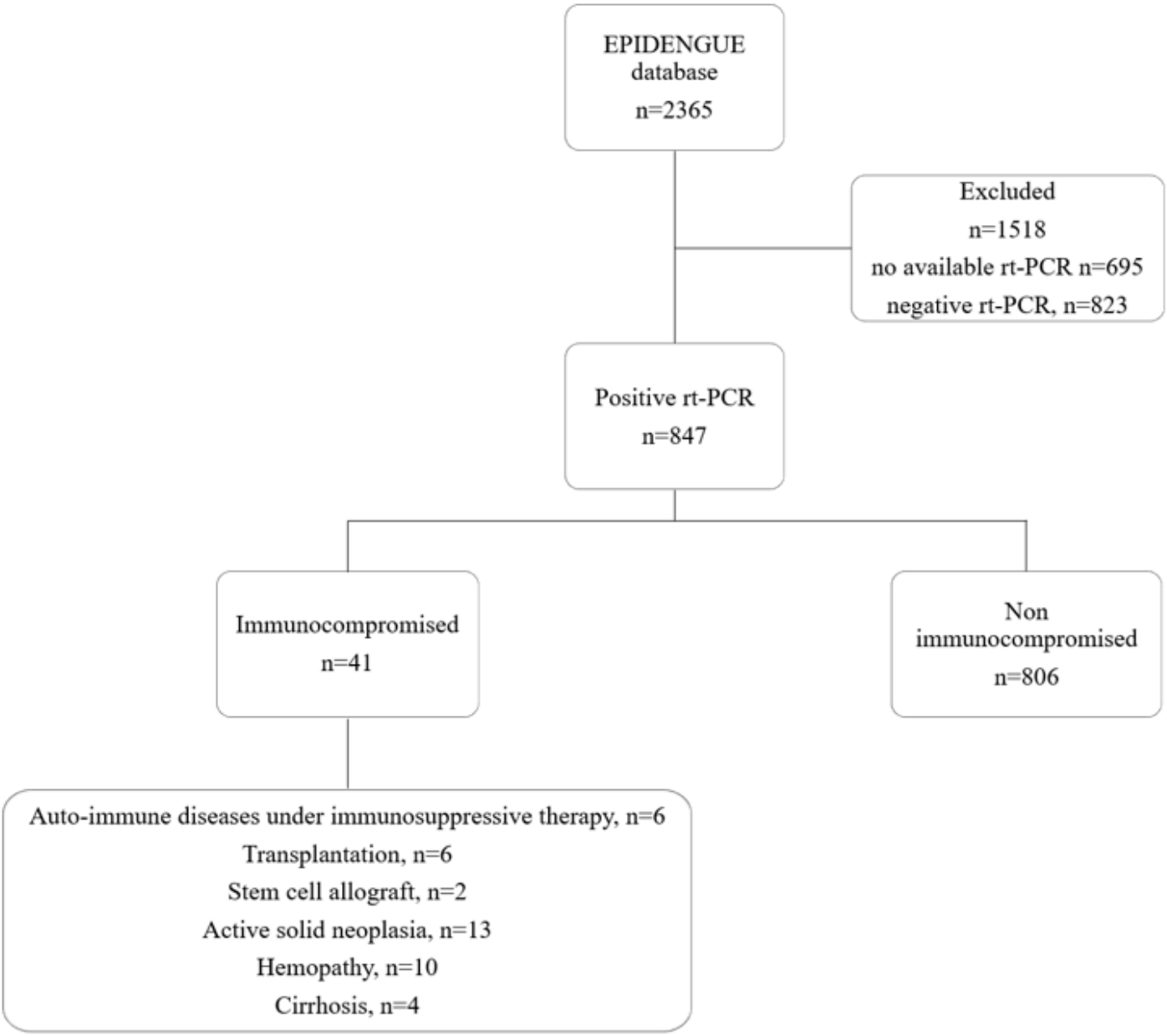


Figure 1

Flow-chart.

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