Dengue Severity Risk Factors in New Caledonia -Design of Predictive Tool Usable By Doctors during the First Consultation

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Article · June 2020

DOI: 10.37421/ijphs.2020.5.182

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Volume 5:2,2020
DOI: 10.37421/ijphs.2020.5.182

International Journal of Public Health and Safety

Open Access

Dengue Severity Risk Factors in New Caledonia - Design of Predictive Tool Usable By Doctors during the First Consultation

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Abstract

Objectives: In New Caledonia (NC), Dengue circulation was detected every year since last decade. The 2017 epidemic have affected 4,379 people with 11.5% of hospital admission and 15 deaths. The aim of this work is to study the risk factors of severe dengue during the 2017 outbreak and to develop a predictive tool, based on a model, usable by doctors during the first consultation to early assess the risk for a dengue patient to progress to a severe form.

Study design: This is a non-interventional retrospective study in which a cohort of hospitalized and non-hospitalized cases, positive for dengue virus infection by qRT-PCR was documented.

Methods: Patients were classified in severe or non-severe dengue. We explored the association of dengue severity to patients' characteristics, symptoms at the first consultation, dengue serotype and previous Zika and dengue infection. A predictive model of the severity usable at first consultation was built using a multivariate analysis and a cross-validation procedure.

Results: A total of 771 dengue cases were studied, with 134 patients who developed severe dengue fever. The dengue serotype does not appear to influence the severity of the infection, whereas, an anterior dengue seems to be significantly related to a severe form. We created two predictive models based on patient characteristics and clinical signs, one for "women" and one for "men" because of the sex and age class interaction. For both models, the variables were: age, self-declared ethnicity, alert signs (mucosal bleeding, clinical liquid accumulation, abdominal pain, lethargy or anxiety) and for women model added variables were arterial hypertension, platelet aggregation inhibitor and anticoagulants treatments. The average and median AUC values for both models are > 0.80 which shows a fairly good model quality; moreover high negative predictive values (> 95%) indicate that models are quite protective.

Conclusion: This study described severity and risk factors for both hospitalized and non-hospitalized patients. The developed models can be used at the first consultation and doctors will be able to early assess the risk for dengue patient to progress to a severe form and increased surveillance with possible hospitalization.

Keywords: Dengue • Severity • Risk factors • Predictive tool

Introduction

Dengue, an infectious mosquito-borne disease, has become in recent years a major concern for international public health. Clinical manifestations of dengue fever can range from a lack of symptoms to death, from non-severe to severe symptomatic forms [1]. There are several hypotheses to explain the evolution to severe forms:

The immune hypothesis: During a first dengue infection, "facilitating antibodies" can be produced, resulting to an easiest viral entry and replication into the cells during a second infection. This could lead to an aggravate vascular hyper permeability [2]. This phenomenon has been named facilitation of antibody-dependent infection.

The viral hypothesis: Viral strain virulence could be exacerbating after specific mutation of a genome region [3].

The classification of dengue fever, according to its clinical manifestation, was often debated [4]. A classification that identifies alert signs and signs of severity has been proposed by World Health Organization, 2011. The alert signs for severe dengue are pain or tenderness in abdominal palpation, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy/anxiety, hepatomegaly, and haematocrit increase concurrent with a platelet count drop. Mortality from this disease usually affects frail individuals such as young children, or elderly people with comorbidities [6].

In New Caledonia (NC), a French island in the South Pacific (270,000 inhabitants), Dengue fever is transmitted by the mosquito Aedesaegypti, and outbreaks occur every year since last decade. This disease is part of the

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Received: 16 March, 2020; **Accepted:** 15 April, 2020; **Published:** 24 April, 2020

notifiable diseases and the NC public health services (DASS) supported by local actors lead an active fight policy against dengue: communication, prevention, mosquito control and distribution of repellent. In NC, healthcare system is composed of general practitioners, health center in each locality, the North Hospital Center (NHC), the Territorial Hospital Center (THC) and a private clinic. Dengue severe cases are all hospitalized at the THC. RT-qPCR analyses are made for patient with a time of symptoms onset less than 7 days, and IgM are researched for a time of symptoms onset over 5 days. DASS centralizes all the mandatory dengue declarations (MD): clinical cases (without biological confirmation), probable cases (with positive IGM) and confirmed cases (positive quantitative RT-qPCR). DASS' nurses contact all the cases to check physical addresses for preventive actions and complete the information on the MD (evolution of the disease with hospitalization or not).

The experience gained during epidemics, allowed setting up a local flow chart to guide the decision of dengue hospitalization (Supplementary material 1). Since 1995, NC experienced regularly dengue epidemics of unequal importance [7]. The most significant outbreaks were in 2003 with circulation of serotype 1, in 2009 with co-circulation of dengue serotype 4 and serotype 1 and in 2013 with the serotype 1. Moreover in 2014, an outbreak of Zika virus occurred in NC with 1 392 recorded cases. In 2017, dengue outbreak was particular because of the co-circulation of serotypes 1, 2 and 3.

The 2017 epidemic have affected 4,379 cases with 2,345 confirmed cases, 180 probable cases, and 1,854 clinical cases. With 11.5% of hospital admission and 15 deaths, it appears to be a severe dengue outbreak.

In this study, we describe the characteristics of patients who had a confirmed dengue fever between January 1 and July 31, 2017 to evaluate severity. In addition, this study aims to identify severity factors in order to predict the severity of patients at the time of mandatory reporting (generally first consultation).

Materials and Methods

Studied population

The study is a retrospective study between January 1 and July 31, 2017 based on positive RT-qPCR [8] confirmed dengue cases. All patients hospitalized at the THC and patients who died because of a dengue virus infection were included and information was collected from the patient files. All patients or their relatives were contacted by phone and those who refused to participate were excluded. Based on the week of diagnosis of the hospitalized patients, we randomly selected non-hospitalized patients with a complete MD, until reaching the same number of patients as in the hospitalized subgroup.

Collected data

Data (symptoms, characteristics of patients) was collected on MD, on phone survey to complete the missing information, about hospitalization record (when appropriate) and on laboratory results related to infection for non-hospitalized patients. These data concern four main groups of variables:

• Patient information: age, sex, ethnic community, medical history and co-morbidities, existence of a previous infection of dengue and/or Zika, medical treatments, self-medication or traditional medicine (papaya leaves ...) to fight the infection, consumptions of cannabis, tobacco, alcohol or kava. Pregnancy states were also recorded.

• The symptoms at the first consultation (usually at the time of the declaration), at the hospitalization if occurred, the alert signs and signs of severity observed during the infection.

• All biological results available between the first consultation (MD), and/or at the time of hospitalization and the end of the infection, dengue serotyping by RT-PCR, IgG serology for dengue (PanBio®) and Zika (Euroimmun®) results [9].

• Patient management and his evolution of (death or not).

Patients classification

Collected data was used to classify patients in severe or non-severe dengue. According to the recommendations of WHO [5], dengue patients were classified in severe if at least one criterion was observed: severe plasma leakage leading to shock and/or fluid accumulation accompanied by respiratory distress, severe hemorrhage or, severe hepatitis with Alanine Transaminase (ALT) or Aspartate Transaminase (AST) >1000 UI/L, renal failure (Glomerular Filtration rate by MDRD equation < 60 mL/min/1.73 m^2), heart or central nervous system failure. Patients with thrombocytopenia <10 G/L with minor bleeding were also considered as severe.

Data analysis and predictive models construction

The measure of association with severity was obtained by using odds ratio and confidence intervals for the set of variables studied (median-unbiased method) using R [10]. In order to obtain a predictive model of the severity usable by doctors at the time of MD, we retained only variables known at that time. Variables for which the association with severity was significant ($p < 0.05$) as well as those for which the value of p observed was less than or equal to 0.20 in the univariate analysis were included in the multivariate analysis. A step-down procedure was used to obtain the final logistic regression model.

A cross-validation procedure using the "k-folds" method was used (with $k = 10$): we divided the dataset into k parts nearly equal, each of the k parts was used as a test game (to evaluate the performance of the model) and the other parts (k-1) were used for the training of the model. The performances of the model are evaluated with the AUC (area under curve) for the receiving operating characteristic (ROC) curve [11]. An optimal threshold was determined allowing the best sensitivity and specificity, above this threshold, the result was considered as positive and below, it was considered as negative. Sensitivity, specificity, positive predictive and negative predictive values have been determined.

Results

Studying cohort

Hospitalized patients: Between January 01 to July 31, 416 patients were hospitalized at the THC with a positive dengue PCR result. After checking the inclusion criteria (21 unreachable people, 2 refusals), 383 cases were included. Among these patients, 8 deaths were attributable directly to dengue, 2 were associated with highly advanced cancers and 3 were due to a very significant deterioration of the general state with loss of autonomy and deaths.

Non-hospitalized patients: Among non-hospitalized patients with a positive dengue PCR result, 388 patients were included.

Signs of severity

For the 383 hospitalized patients, 130 (34%) were severely ill. The most observed signs of severity were AST= 1000 IU/L (14%) and Thrombocytopenia <10 G/L with minor bleeding (12.3%). For the 388 non-hospitalized patients, one presented severe bleeding (platelet <10 G/L and bleeding), one with ALT≥ 1000 IU/L and two died without being hospitalized (Table 1). Thus, we were able to study 771 dengue cases (with a positive

PCR result) between January 1st and July 31st, 2017 with 134 patients who developed severe dengue fever.

Table 1. Severity signs observed in hospitalized, non-hospitalized and severe patients.

Characteristics	Hospitalized (N=383)	Non hospitalized (N=388)	Severe cases (N=134)
AST < 1000 UI/L or NR	329 (85.9%)	388	80 (59.7%)
AST ≥ 1000 UI/L	54 (14.1%)	0	54 (40.3%)
ALT <1000 UI/L or NR	359 (93.7%)	387 (99.7%)	109 (81.3%)
ALT ≥ 1000 UI/L	24 (6.3%)	1 (0.3%)	25 (18.7%)
No thrombocytopenia <10G/L	336 (87.7%)	387 (99.7%)	86 (64.2%)
Thrombocytopenia <10 G/L +bleeding	47 (12.3%)	1 (0.3%)	48 (35.8%)
No severe haemorrhage	361 (94.3%)	387 (99.7%)	111 (82.8%)
Severe haemorrhage	22 (5.7%)	1 (0.3%)	23 (17.2%)
No shock	357 (93.2%)	388	108 (80.6%)
Shock	26 (6.8%)	0	26 (19.4%)
Alive	370 (96.6%)	386 (99.5%)	119 (88.8%)
Death	13 (3.4%)	2 (0.5%)	15 (11.2%)

Description of severe and non-severe patients and risk factors

General characteristics of the patients: We highlighted a significant link between severity and age (age groups of the 20-30 years and the more than 60 years more at risk than the 30-40 years) and between severity and self-declared ethnicity (Melanesian and Polynesian seem to be more at risk than the European) (Table 2). It should be noted that pregnancy has not emerged as a risk factor for women. Comorbidities associated with severity are obesity, arterial hypertension (AHT), diabetes, renal failure, dyslipidaemia and hepatitis B. Regarding the treatments taken by patients at the time of dengue fever, the use of PAI (Platelet Aggregation Inhibitor) as well as anticoagulants seems to be significantly associated with severity. Tobacco seems to be significantly related to severity of dengue fever (Table 3).

Table 2. General characteristics of severe and non-severe patients, odds ratio, confidence interval 95% and p-value.

Characteristics		Severe (%) N=134	Non severe (%) N=637	OR [IC 95%] p
Age class (year)	≤10	10 (7.5%)	99 (15.5%)	0.9 [0.4-2.3] p=0.9
	[10-20]	19 (14.2%)	143 (22.4%)	1.2 [0.6-2.7] p=0.6
	[20-30]	31 (23.1%)	89 (14.0%)	3.2 [1.6-6.9] p<0.01
	[30-40]	12 (9.0%)	112 (17.6%)	Reference
	[40-50]	17 (12.7%)	77 (12.1%)	2.0 [0.9-4.7] p=0.1
	[50-60]	15 (11.2%)	56 (8.8%)	2.5 [1.1-5.8] p=0.03
	[60-70]	12 (9.0%)	32 (5.0%)	3.5 [1.4-8.6] p<0.01
	>70	18 (13.4%)	29 (4.6%)	5.7 [2.5-13.6] p<0.01
Sex	Men	67 (50.0%)	303 (47.6%)	Reference
	Women	67 (50.0%)	334 (52.4%)	0.91 [0.6-1.3] p=0.6
Self-declared ethnicity	Melanesian	50 (36.8%)	167 (19.6%)	2.4 [1.4-4.1] p<0.01

	European	26 (22.5%)	210 (38.7%)	Reference
	Polynesian	26 (17.8%)	87 (11.6%)	2.4 [1.3-4.4] p<0.01
	Metis/Other	16 (16.4%)	160 (29.9%)	1.0 [0.5-1.8] p=0.9
	Not specified	13 (6.5%)	13 (0.3)	8.0 [3.3-19.4] p<0.01
Women	Not pregnant	64 (95.5%)	302 (90.4%)	Reference
	Pregnant	3 (4.5%)	32 (9.6%)	0.5 [0.1-1.4] p=0.2

Table 3. Comorbidities, treatment and risk behaviour of severe and non-severe patients and results of the univariate analysis.

	Characteristics	Severe (%) N=134	Non severe (%) N=637	OR [CI 95%] p
Comorbidities	Obesity	44 (32.8%)	116 (18.2%)	2.2 [1.4-3.3] p<0.01
	Arterial hypertension (AHT)	35 (26.1%)	61 (9.6%)	3.3 [2.1-5.3] p<0.01
	Diabetes	14 (10.4%)	33 (5.2%)	2.1 [1.1-4.1] p=0.03
	Renal failure	5 (3.7%)	4 (0.6%)	6.1 [1.5-25.9] p=0.01
	Heart diseases	10 (7.5%)	21 (3.3%)	2.4 [1.0-5.1] p=0.04
	Dyslipidemia	10 (7.5%)	25 (3.9%)	2.9 [1.4-5.6] p<0.01
	Hepatitis B	3 (2.2%)	2 (0.3%)	7.1 [1.1-61.4] p=0.04
	Lung diseases	8 (6.0%)	56 (8.8%)	0.7 [0.3-1.4] p=0.3
	Cancer	6 (4.5%)	14 (2.2%)	2.1 [0.7-5.4] p=0.2
Treatment	Non-Steroidal Anti-Inflammatory (NSAI)	2 (1.5%)	15 (2.4%)	0.7 [0.1-2.4] p=0.6
	Platelet aggregation inhibitor (PAI)	19 (14.2%)	21 (3.3%)	4.8 [2.5-9.3] p<0.001
	Anticoagulants	6 (4.5%)	4 (0.6%)	7.3 [2.0-30.1] p<0.01
	Traditional medicine	26 (19.4%)	119 (18.7%)	1.1 [0.6-1.7] p=0.8
Risk behaviour	Cannabis	7 (5.2%)	22 (3.5%)	1.6 [0.6-3.6] p=0.3
	Tobacco	43 (32.1%)	152 (23.9%)	1.5 [1.0-2.3] p=0.05
	Alcohol (>3units/day)	5 (3.7%)	11 (1.7%)	2.2 [0.7-6.4] p=0.2
	Kava	6 (4.5%)	30 (4.7%)	1.0 [0.4-2.2] p=0.9

Alert signs: 93.3% of patients who developed a severe form have at least one alert sign (Table 4) which is significantly more than the non-severe (45.7%). Each sign of severity is significantly associated with a severe form in univariate analysis. In addition, having at least 2 alert signs seems more associated with severity than having only one. 30% of patients with at least one alert sign evolved into a severe form whereas 2.5% of patients with no alert sign progressed to a severe form.

Table 4. Alert signs in severe and non-severe patients.

Characteristics	Severe (%) N=134	Non severe (%) N=637	OR [CI 95%] p
Alert signs	125 (93.3%)	291 (45.7%)	16.2 [8.5-35.0] p<0.001
Mucosal bleeding	89 (66.4%)	146 (22.9%)	6.6 [4.4-10.0] p<0.001

Clinical liquid accumulation	18 (13.4%)	35 (5.5%)	2.7 [1.4-4.8] p<0.001
Abdominal pain	61 (45.5%)	124 (19.5%)	3.5 [2.3-5.1] p<0.001
Persistent vomiting	14 (10.4%)	34 (5.3%)	2.1 [1.0-3.9] p=0.03
Hepatomegaly	8 (6.0%)	9 (1.4%)	4.4 [1.6-12.0] p=0.004
Increase in hematocrit + drop in platelets count	31 (23.1%)	42 (6.6%)	4.3 [2.5-7.1] p<0.001
Lethargy/ anxiety	26 (19.4%)	51 (8.0%)	2.8 [1.6-4.6] p<0.001
One alert sign	50 (37.3%)	175 (27.5%)	10.8 [5.4-24.1] p<0.001
2 or + alert signs	75 (56.0%)	23 (18.2%)	24.3 [12.4-53.9] p<0.01

Viral infection: Dengue serotype does not appear to influence the severity of the infection. Having a previous dengue fever, confirmed by biological results seems to be related to a severe form in a significant way (Table 5). However, unique statement of previous dengue fever is not related to severity. As the statement of a previous Zika infection, having an anterior Zika infection does not appear to be related to severity.

Table 5. Serotypes, previous dengue and Zika infections of severe and non-severe patients and results of the univariate analysis.

Characteristics		Severe (%) N=134	Non severe (%) N=637	OR [CI 95%] p
Serotype	1	104 (77.6%)	461 (72.4%)	1.3 [0.8-2.3] p=0.3
	2	19 (14.2%)	113 (17.7%)	Reference
	3	7 (5.2%)	24 (3.8%)	1.7 [0.6-4.5] p=0.3
	NR	4 (3.0%)	39 (6.1%)	1.6 [0.4-5.1] p=0.5
Anti-dengue IgG antibodies	Negative	49 (36.6%)	474 (74.4%)	Reference
	Doubtful	2 (1.5%)	14 (2.2%)	1.5 [0.2-5.5] p=0.6
	Positive	65 (48.5%)	106 (16.6%)	5.9 [3.9-9.1] p<0.001
	NR	18 (13.4%)	43 (6.8%)	4.0 [2.1-7.5] p<0.001
Self-declared previous dengue		8 (6.0%)	60 (9.4%)	0.6 [0.3-1.3] p=0.2
Anti-ZikaIg G antibodies	Negative	95 (70.9%)	479 (75.2%)	Reference
	Doubtful	1 (0.7%)	20 (3.1%)	0.3 [0.01-1.4] p=0.1
	Positive	17 (12.7%)	82 (12.9%)	1.1 [0.6-1.8] p=0.9
	NR	21 (15.7%)	56 (8.8%)	1.9 [1.1-3.2] p=0.03
Self-declared previous Zika		0 (0%)	24 (3.8%)	-

Construction of a predictive model of severity at first consultation

An interaction between sex and age class was found. So, we created a model for "women" and a model for "men". For both models, a step-down procedure and a cross-validation by the k-fold method were applied. The average and median AUC values are > 0.80 which shows a fairly good model quality, moreover high negative predictive values (> 95%) indicate that models are quite protective (Supplementary material 2). For both final models, the variables were: age, self-declared ethnicity, alert signs (mucosal bleeding, clinical liquid accumulation, abdominal pain, lethargy/anxiety) and for women model added variables were AHT, PAI and anticoagulants treatments.

An optimal threshold of 0.2 is obtained for the "women" model and 0.12 for the "men" model. Based on both models, a calculation tool, using a spread sheet, has been developed to calculate a severity score based on the characteristics of the dengue patient at the MD (first consultation). If the score exceeds the threshold, the patient may be considered at risk of developing severe dengue (Supplementary material 3).

Discussion

The 2017 epidemic of dengue was remarkable in its severity as 33.9% of hospitalized people developed signs of severity with an important level of liver injuries (14.1%). In French Guyana, the percentage of severity was 29%, 24% and 12% respectively for the 2009, 2010 and 2013 epidemics [12]. The majority of severe dengue cases were hospitalized and the flow chart used for the hospitalization of dengue cases seems quite efficient. However, 2 people have died without having been hospitalized and two others (in our non-hospitalized studied population) developed severe signs.

This study has highlighted the importance of alert signs in the severity prediction and the necessity to make them appear on the MD. Ethnicity, based on self-declaration, must be added as it seems to be a major risk factor [13,14]. In univariate, tobacco can be considered as a risk factor for severity, which is in line with work done in Brazil on dengue-related mortality [15]. Moreover, as shown in other studies, it appears that the severity is related to comorbidities such as obesity [16], arterial hypertension [14], diabetes [14,17], renal failure [15], heart diseases [18] and dyslipidemia are also significantly associated with dengue severity.

As shown in recent studies [19,20], the dengue serotype does not appear to influence the severity of the infection. On the other hand, having previous dengue (serology IgG positive) seems to be significantly related to a severe form, which is in accordance with the hypothesis of facilitation of antibody-dependent infection [2]. This is in line with what was highlighted in many studies and a meta-analysis [21]. On the other hand, the simple declaration of previous dengue fever is not linked to severity. So just asking to people if they have previous dengue is not efficient. Having previous Zika infection does not seem to be related to a severe form of dengue, which is not consistent with work done on mice [22].

In this study, we decided to develop a predictive tool of severity, based on a model that can be used during the first consultation at the time of mandatory reporting, before having biological results. Some models have been developed yet to predict dengue severity but using the biological results [23–25] Another model for predicting severity for hospitalized cases during the 2017 epidemic in NC, bases on biological results have been developed [26]. Our tool can be used at the first consultation by the doctor when he strongly suspects a dengue fever, to determine the risk for his patient to develop a severe form. However, it is important to emphasize that this is only a help and it will not replace the doctor's opinion. This model can now be used by DASS' nurses when they are calling the patients to evaluate the risk of severity and advise the patient to see his doctor again.

Conclusion

This study described dengue patients in terms of severity and alert signs for hospitalized and non-hospitalized patients. It found that among the people who had a diagnosis of dengue, the severe form cases were hospitalized in a vast majority. The predictive tool can be used at first consultation and doctors will be able to early assess the risk for dengue patient to progress to a severe form and increase surveillance with possible hospitalization.

Ethics Statement

Informed consent was obtained for all participating patients or their relatives. This non interventional study was approved by New Caledonia's Advisory Committee on Ethics for Life and Health.

Acknowledgments

We first want to thank patients and their relatives for their participation. We also thank StéphaneChabaud and ViktoriaTaofifenua, from DASS-NC, for their work on mandatory dengue declarations. We finally thank private laboratories for their help in recording biological results of non-hospitalized patients in the context of the MD. In memory of our co-worker and friend, Dr DesclouxElodie, who is recently disappeared.

References

1. Grange, Laura, Etienne Simon-Loriere, AnavajSakuntabhai, and Lionel Gresh, et al. "Epidemiological risk factors associated with high global frequency of inapparent dengue virus infections." *Front Immunol* 5 (2014): 280.
2. Halstead, SB. "Dengue Antibody-Dependent enhancement: knowns and unknowns. *Microbiol Spectr* 2 (2014).
3. Fragnoud, Romain, GlauciaParanhos-Baccalà, and FrédéricBedin. "Dengue sévère: des hypothèses de la pathogénicité aux outils de pronostic." *Virologie* 18(2014): 59-74.
4. Hadinegoro, Sri Rezeki S. "The revised WHO dengue case classification: does the system need to be modified?." *PaediatrInt Child Health* 32(2012): 33-38.
5. World Health Organization. "Comprehensive guideline for prevention and control of dengue and dengue haemorrhagic fever." (2011).
6. Pang, Junxiong, Yee-Sin Leo, and David C Lye. "Critical care for dengue in adult patients: an overview of current knowledge and future challenges." *Curr Opin Crit Care* 22(2016): 485-490.
7. https: //dass.gouv.nc/votre-sante/documents-rapports-etudes.
8. Trioplex Real-time RT-PCR Assay: Centers for Disease Control and Prevention. Available from: https: //www.cdc.gov/zika/pdfs/trioplex-real-time-rt-pcr-assay-instructions-for-use.pdf
9. Johnson, Barbara W, Brandy J Russell, and Robert S Lanciotti. "Serotype-specific detection of dengue viruses in a fourplex real-time reverse transcriptase PCR assay." *J Clin Microbiol* 43 (2005): 4977-4983.
10. RC Team. "R Core Team R: a language and environment for statistical computing." (2015).
11. Robin, Xavier, NatachaTurck, AlexandreHainard, and Natalia Tiberti, et al. "pROC: an open-source package for R and S+ to analyze and compare ROC curves." *BMC bioinformatics* 12 (2011): 77.
12. Flamand, Claude, Camille Fritzell, Christelle Prince, and Philippe Abboud, et al. "Epidemiological assessment of the severity of dengue epidemics in French Guiana." *PLoS One* 12 (2017).
13. Guzman, Maria G, GP Kouri, Jr Bravo, and Maritza Soler, et al. "Dengue haemorrhagic fever in Cuba. II. Clinical investigations." *T Roy Soc Trop Med H* 78(1984): 239-241.
14. Pang, Junxiong, AgusSalim, Vernon J Lee, and Martin L Hibberd, et al. "Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study." *Plos Neglect Trop D* 6 (2012).
15. Amâncio, FredericoFigueiredo, Tiago PiresHeringer, LilianeBoaventuraFassy, and FredericoBruzzi de Carvalho, et al. "Clinical profiles and factors associated with death in adults with dengue admitted to intensive care units, Minas Gerais, Brazil." *PloS one* 10 (2015): e0129046.
16. Zulkipli, MohdSyis, MaznahDahlui, Devi Peramalah, and Hoe Victor CheeWai, et al. "The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis." *Plos Neglect Trop D* 12 (2018): e0006263.
17. Lee, Min-Sheng, Kao-Pin Hwang, Tun-Chieh Chen, and Po-Lian Lu, et al. "Clinical characteristics of dengue and dengue hemorrhagic fever in a medical center of southern Taiwan during the 2002 epidemic." *J Microbiol Immunol Infect* 39 (2006): 121-129.
18. Pang, Junxiong, Jung Pu Hsu, Tsin Wen Yeo, and Yee Sin Leo, et al. "Diabetes, cardiac disorders and asthma as risk factors for severe organ

involvement among adult dengue patients: A matched case-control study." *Sci Rep* 7 (2017): 1-10.

19. Rocha, Benigno AM, Adriana O Guilarde, Angela FLT Argolo, and Marianna Peres Tassara, et al. "Dengue-specific serotype related to clinical severity during the 2012/2013 epidemic in centre of Brazil." *Infect Dis Poverty* 6 (2017): 116.
20. Yung, Chee-Fu, Kim-Sung Lee, Tun-Linn Thein, and Li-Kiang Tan, et al. "Dengue serotype-specific differences in clinical manifestation, laboratory parameters and risk of severe disease in adults, Singapore." *Am J Trop Med Hyg* 92 (2015): 999-1005.
21. Soo, Kuan-Meng, Bahariah Khalid, Siew-MooiChing, and Hui-Yee Chee. "Meta-analysis of dengue severity during infection by different dengue virus serotypes in primary and secondary infections." *PloS one* 11 (2016).
22. Fowler, Angela M, William W Tang, Matthew P Young, and AnilaMamidi, et al. "Maternally acquired Zika antibodies enhance dengue disease severity in mice." *Cell HostMicrobe* 24 (2018): 743-750.
23. Nguyen, Minh Tuan, ThiNhanHo, Van VinhChau Nguyen, and Thanh Hung Nguyen, et al. "An evidence-based algorithm for early prognosis of severe dengue in the outpatient setting." *Clin Infect Dis* 64 (2017): 656-663.
24. Pang, Junxiong, Tun-Linn Thein, Yee-Sin Leo, and David C. Lye. "Early clinical and laboratory risk factors of intensive care unit requirement during 2004–2008 dengue epidemics in Singapore: a matched case–control study." *BMC Infect Dis* 14 (2014): 649.
25. Sigera, PonsugeChathurani, RanmaleeAmarasekara, Chaturaka Rodrigo, and SenakaRajapakse, et al. "Risk prediction for severe disease and better diagnostic accuracy in early dengue infection; the Colombo dengue study." *BMC Infect Dis* 19 (2019): 680.
26. Marois, Ingrid. "Study of patients hospitalized during the 2017 dengue epidemic in New Caledonia and development of a predictive model of severe dengue." (2018).

How to cite this article: Carole Forfait, Marois I, Aubert D, Valiame A,Gourinat AC, Descloux E, Hartmann E and Laumond S. "Dengue Severity Risk Factors in New Caledonia - Design of Predictive Tool Usable By Doctors during the First Consultation". Int J Pub Health Safe 5 (2020) doi: 10.37421/ijphs.2020.5.182