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High plasma levels of soluble ST2 but not its ligand IL-33 is associated with severe forms of pediatric dengue

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ABSTRACT

Identification of early determinants of dengue disease progression, which could potentially enable individualized patient care are needed at present times. Soluble ST2 (sST2) has been recently reported to be elevated in the serum of children older than 2 years old and adults with dengue infection and it was correlated with secondary infections as well as with severe presentations of the disease. The mechanism by which secreted ST2 is linked to severe dengue and plasma leakage remains unclear. One possibility is that IL-33 ligand may be elevated, contributing to membrane bound ST2 as part of the immune activation in dengue infection. We determined plasma levels of sST2 and the ligand IL-33 in 66 children with acute secondary dengue infections clinically classified using the guidelines of the World Health Organization, 2009. Dengue infection showed significant increases in cytokines IL-12p70, IL-10, IL-8, IL-6, IL-1β and TNFα measured by flow cytometry based assay compared to uninfected individuals. In contrast, IL-33 levels remained unchanged between infected and uninfected individuals. The levels of sST2 positively correlated with values of IL-6 and IL-8 and inversely correlated with number of median value of platelet levels. In addition to circulating cytokine positive correlations we found that sST2 and isoenzyme creatine kinase-MB (CK-MB), a marker of myocardial muscle damage present in severe dengue cases were associated. Our pediatric study concluded that in dengue infections sST2 elevation does not involve concomitant changes of IL-33 ligand. We propose a study to assess its value as a predictor factor of disease severity.

1. Introduction

Dengue is an acute febrile illness transmitted by *Aedes aegypti* mosquitoes and caused by four antigenically related strains of dengue virus (DENV 1-4). It is the fastest expanding infection in the tropics, and it is estimated that over 50 million new cases occur worldwide annually [1].

Dengue virus (DENV) can cause a broad spectrum of clinical manifestations that ranges from an acute self-limiting febrile illness to a life-threatening syndrome. Symptoms include high fever, headache, myalgias, skin rash, thrombocytopenia, coagulation alterations, hepatic inflammation and hemorrhagic manifestations. Increased vascular permeability that results in vascular leakage is the characteristic event that defines the severe presentation of dengue [2]. This wide range of clinical manifestations of the illness has required a revision of the standard disease classification. The TDR–WHO (Special Program for Research and Training in Tropical Diseases World Health Organization) proposed in 2009 that dengue cases should be categorized into three groups depending on the presence or absence of warning signs and severe symptoms which include vascular leakage, shock, bleeding and organ damage like hepatitis, encephalitis and myocarditis [1]. Few attempts to find early correlates of disease severity include studies of serum lipids (where low cholesterol levels were associated with severe dengue) [3] as well as others like pentraxin 3 [4] and correlates of severity derived from gene expression profiling [5–8] in addition to protein detection methods for specific cytokines and enzymes [9].

Multiple clinical dengue studies have reported elevated circulating levels of cytokines and chemokines, including gamma interferon (IFN-γ), tumor necrosis factor alpha (TNF-α), interleukin (IL)-1beta (IL-1β), IL-6, IL-10, IL-13, IL-8, macrophage chemo-attractant protein-1 (MCP-1), and macrophage inflammatory protein 1 beta (MIP-1β), among others. The presence of

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pro-inflammatory cytokines have been extensively studied [10–17], but their use as predictor of severity is not conclusive in determining which of any, of these cytokines or chemokines specifically discriminates mild and severe presentations of dengue.

From independent studies, a cohort of adult patients [18] and a mixed cohort of children older than 2 years old and adults [19] indicated a consistent elevation of sST2 in secondary dengue cases as well as in cases with hemorrhagic manifestations, respectively. To our knowledge, the levels of sST2 in severe dengue-induced disease of a homogeneous pediatric population of children under 2 years of age nor the relationship with IL-33 ligand not has been reported.

Three forms of ST2 (also known as Interleukin-1 receptor like-1 protein IL-1RL-1) are known, called ST2L (longer membrane anchored form), ST2V (membrane bound variant form) and sST2 (shorter release soluble form) have been reported and the only known ligand of ST2 is the IL-33 cytokine [20,21]. Binding of IL-33 to membrane-expressed ST2 induce activation of NF-kB and AP-1 transcription factors and the release of pro-inflammatory cytokines [22]. Therefore we included measures of IL-33 in the current study to assess its relevance as circulating cytokine in acute disease. For the soluble form ST2 it has been found for earlier studies in patients with inflammatory disorders including autoimmune diseases [23] and sepsis [24]. In present times sST2 is currently used as a robust predictor of death and a marker of myocardial stress as the main factor associated with survival in patients with heart failure and myocardial infarction [25–31].

The present study included cases of pediatric myocarditis within the dengue severe group. Reporter elsewhere, myocarditis is present in dengue [32–35] and with moderate frequency in pediatric cases [36,37]. In view of the reported literature we included in our study measurements of isoenzyme creatine kinase MB (CK-MB) as a myocardial cell damage marker.

There are no studies where cytokines elevations are utilized to classify severe cases from the mild cases. Therefore clinical algorithms are utilized to guide the clinicians in defining the severity outcome but there are no specific cytokine measures in such algorithms [38]. The possibility to utilize sST2 as a predictor of severity outcome would require multiple clinical studies in addition to the present and past reports.

2. Methods

2.1. Patients and clinical protocol

Sixty-six dengue infected children were grouped according to revised TDR–WHO classification [1] into one of three levels of severity as follow: (i) 17 cases which presented fever higher than 38 °C, longer than 3 days and not evidence of infectious focus were classified as no warning signs dengue (DEN). (ii) For dengue with warning signs (DW) we included 21 cases had DEN with abdominal paint and/or persisting vomiting, mucosal bleeding, lethargy, hepatomegaly, decrease in the hematocrit or platelet count. (iii) 28 cases with evidence of severe bleeding, signs of vascular leakage or organ involvement were classified as severe dengue (SD). Twenty-two up to 28 patients with SD included in this study were diagnosed with dengue myocarditis.

As dengue myocarditis case was defined as follow: poor response to therapy with intravenous fluids; alteration in cardiac rhythm (bradycardia or tachycardia) and/or the need for inotropic support added at least one of the following test findings: abnormal thorax X-ray, electrocardiogram alteration (tachyarythmias and disorders of ST segment or T wave), pathological echocardiography (systolic or diastolic dysfunction) and biochemical elevation of CK-MB isoform. The criteria for dengue myocarditis cases described before have been previously utilized [36,37,39].

In all cases, the dengue diagnosis was confirmed by detection of plasma dengue-specific IgM and/or viral protein NS1 by ELISA (Panbio, AUS), according to the manufacturer's recommendations.

A written follow-up of signs and symptoms was done for hospitalized children and the information was daily collected using a format validated in previous publications [36,39].

As control, 23 healthy children were evaluated to obtain relative disease marker values.

Pediatric patients had informed consent and assent forms signed by the legal guardians. The clinical protocol utilized was approved by the ethic committee of the Facultad de Salud, Universidad Surcolombiana and the Hospital Universitario de Neiva.

2.2. Quantification of sST2 and IL-33 in plasma

Blood samples were obtained on day of admission to the Hospital, corresponding to 3–6 days after fever onset. The blood was collected in tubes containing EDTA and plasma was obtained by centrifugation and frozen at −70 °C until use. The plasma levels of sST2 and IL-33 were quantified by ELISA using commercial kits (R&D systems, MN, Catalog number: DY523 and DY3625, respectively), following the manufacture's protocols. For estimation of cytokine concentration (in pg/ml) a regression curve was utilized. The lowest concentration in the ELISA standard curves was 31 and 23 pg/ml for sST2 and IL-33, respectively.

2.3. Quantification of cytokines in plasma

The quantification of IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNFα in the same samples which sST2 and IL-33 were measured, was performed by using a cytometric bead array (CBA, Human Inflammatory Kit, catalog number 551811, Becton Dickinson, San Jose, CA) following the manufacturer's recommendations. A FACSCalibur and FACSCanto II cytometers were used. The sensitivity limit for each cytokine (in pg/ml) was 7.2 for IL-1β, 2.5 for IL-6, 3.6 for IL-8, 3.3 for IL-10, 1.9 for IL-12p70 and 3.1 for TNFα.

2.4. Clinical laboratory tests

Routine clinical laboratory tests of the Hospital Universitario de Neiva were done. To perform hematological and biochemical profile on each patient during hospitalization, a Beckman Coulter LH 500 (impedance based) and Synchron LX20 pro (chromatographic based) equipment were used, respectively.

2.5. Statistical analysis

GraphpadPrism software (Prism 6) was used for statistical analysis. To determine the difference between two or more independent groups, Mann–Whitney and Kruskal–Wallis tests were used, respectively. If the P value for the Kruskal–Wallis test of statistical significance was smaller or equal than $P < 0.05$, Bonferroni–Dunn tests were performed by computing a Student's t-statistic for each group of dengue severity to obtain the P values. The degree of correlation between variables was evaluated using the Spearman rank test. For statistical proposes, values below than the sensitivity limit, half of the respective values were assigned.

3. Results

3.1. Demographic, clinical and other findings

In Table 1 the summary of demographic and laboratory findings for each group is shown. Age, gender, weight and days of illness were no different in all evaluated groups. In agreement with the

Table 1
Patient cohort description.

		Healthy	DEN	DW	SD
Demographic characteristics					
N		23	17	21	28
Age-months, median (range)		72 (48–120)	72 (24–132)	72 (7–132)	60 (6–144)
Gender% (n)	Female	53% (12)	42% (7)	52% (11)	42% (12)
	Male	47%(11)	58% (10)	48% (10)	58% (16)
Days of fever		NF[a]	3 (2–5)	4 (3–5)	4 (3–8)
Laboratory findings: median (range)					
Number of platelets (10^3/mm^3)		156 (120–203)	96[b] (39–202)	44[c] (13–111)	37[c] (12–99)
Hematocrit (%)		37 (33–42)	37 (34–40)	36.2 (21–46)	36 (22–49)
Hemoglobin (mg/dL)		12 (11–14)	12 (11–13)	12 (7–15)	12.5 (7–15)
Total CK (UI/L)		ND[d]	132 (53–1,631)	120 (47–3,118)	167 (39–2,528)
CK-MB (UI/L)		ND[d]	23 (7–55)	15 (7–49)	19 (7–145)
Aspartate transaminase (U/L)		ND[d]	105 (27–368)	184 (58–840)	99 (46–270)
Alanine transaminase (U/L)		ND[d]	31 (17–662)	62 (20–564)	41 (21–205)

[a] NF: no Fever.
[b] Significant difference when compared with healthy, DW and SD groups ($P < 0.0001$, Bonferroni–Dunn's pos-test).
[c] Significant difference when compared with healthy, and DEN groups ($P < 0.0001$, Bonferroni–Dunn's pos-test).
[d] Not determined.

severity of clinical, number of platelets circulating in SD and DW groups was significantly lower than DEN and healthy children (Table 1). However, biochemical markers as total CK, CK-MB or transaminases were not significantly different in dengue infected groups although a tendency of high levels of total CK ($P = 0.07$, Kruskal–Wallis test) and Alanine transaminase ($P = 0.08$, Kruskal–Wallis test) were found in SD and DW, respectively (Table 1).

3.2. Levels of sST2 but not IL-33 are associated with the severity of illness

To determine if sST2 and IL-33 are related with clinical severity in pediatric population, levels of both factors were measured in plasma from children with DEN, DW and SD and compared to the healthy control group (Fig. 1A and B). The median (and value ranges) for sST2 was 35 pg/ml (range of values 15–517 pg/ml), 489 pg/ml (range values of 15–6603 pg/ml), 1739 pg/ml (range of 15–12,824 pg/ml) and 4151 pg/ml (range of 384–113,621 pg/ml) for healthy, DEN, DW and SD groups, respectively (Fig. 1A). The levels of sST2 in the four groups were statistically different ($P < 0.0001$, Kruskal–Wallis test). The highest and significant sST2 level was found in the clinically severe dengue group (Fig. 1A) showing an increment in sST2 proportional to the severity of the disease.

We evaluated the plasma levels of IL-33, known as the unique ligand of ST2. In general, values obtained were below the sensitivity level and no significant differences were found, regardless of patient group analyzed ($P = 0.79$, Kruskal–Wallis test) (Fig. 1B). No associated with severe form of dengue infection in children were observed.

3.3. Plasma levels of cytokines

The cytokines were detected by cytometry-based assay. IL-12p70 (A), TNFα (B), IL-10 (C), IL-6 (D), IL-1β (E) and IL-8 (F) for the three groups of children with different clinically manifestation of dengue severity, and for the healthy group, were performed. A significant difference ($P < 0.01$, Kruskal–Wallis test) was found for all the six tested cytokines when comparing patients with dengue to healthy individuals. Plasma levels of IL-6 and IL-8 were significantly higher ($P < 0.001$ and $P = 0.001$, using Bonferroni–Dunn's multiple comparison test) in children with severe clinically infection (DW or SD) compared to children with mild dengue (DEN) (Fig. 2D and F). However, there were no significant differences between the two severity groups of dengue (DW and SD) for any of the tested cytokines (Fig. 2A–F).

3.4. Associations of secreted factors in patients with DENV infection

We compared levels of sST2 with other inflammatory cytokines in all dengue-infected children. IL-12p70, TNFα, IL-10 and IL-1β did not correlate with sST2 levels ($P > 0.2$, Spearman test, data not shown). A statistically significant positive correlation was found between sST2, IL-6 and IL-8 (Fig. 3A and B). In addition, the value

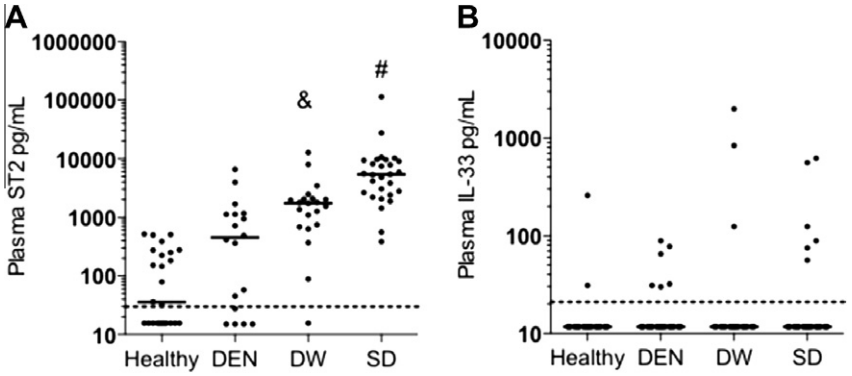

Fig. 1. Plasma sST2 (A) and IL-33 levels (B) were determined by commercially available ELISAs in healthy volunteers ($n = 23$), DEN ($n = 17$), DW ($n = 21$) and SD ($n = 28$). The dotted lines represent the sensitivity level of the test. Horizontal lines represent the median. Statistical significant differences were found between all analyzed groups for sST2 but not for IL-33 ($P < 0.0001$ and $P = 0.78$ respectively, Kruskal–Wallis test). $^{\&}P = 0.001$ compare to healthy individuals, and $^{\#}P < 0.001$ when compare to healthy and DEN groups. Bonferroni–Dunńs multiple comparison test (post hoc test) was utilized to allow sample comparisons with different n values.

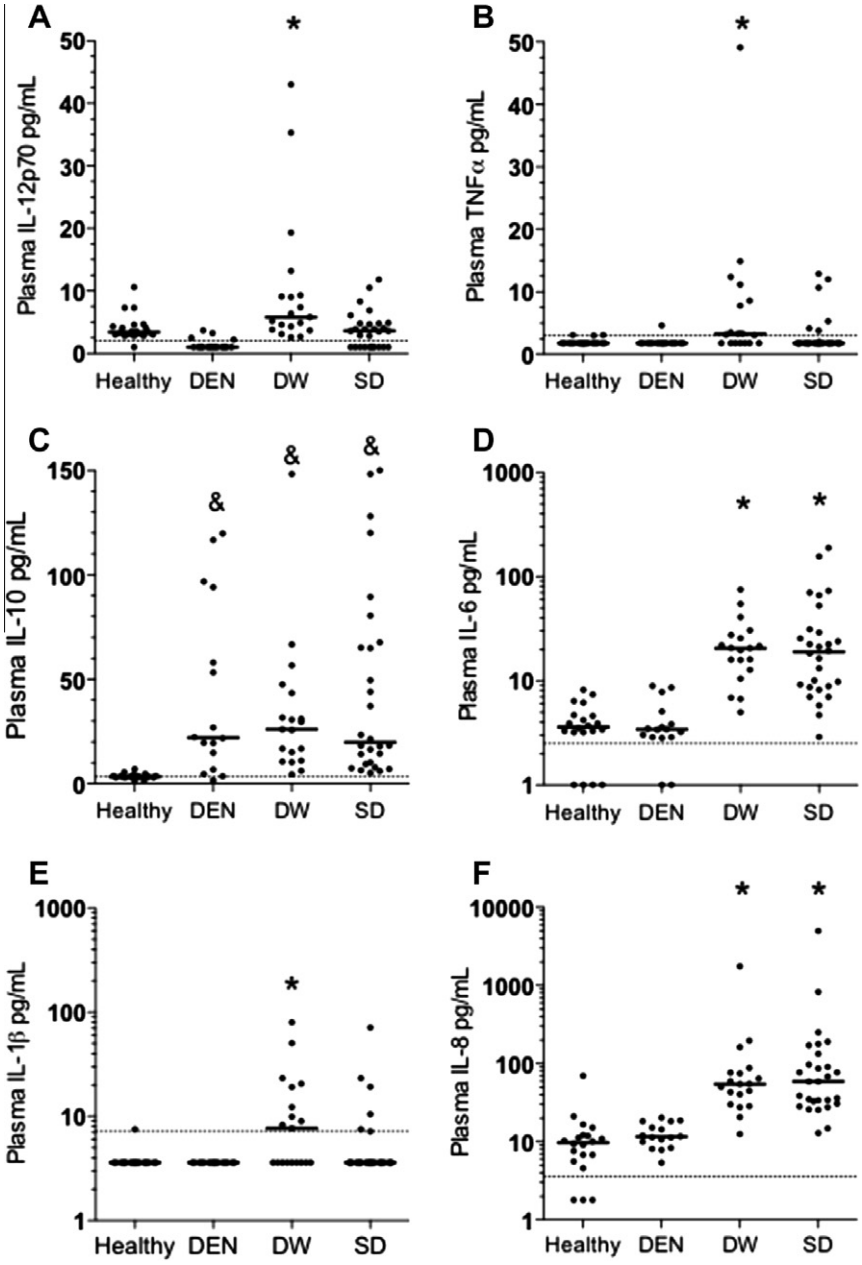

Fig. 2. Panel of cytokines present in patients with dengue (DEN, DW and SD) and in healthy volunteers. The cytokines were detected by a flow cytometry based assay. IL-12p70 (A), TNFα (B), IL-10 (C), IL-6 (D), IL-1β (E) and IL-8 (F). The dotted horizontal line represents the level of sensitivity of the test for each cytokine. Individual data are shown and horizontal lines solid represent the median value for each of the groups tested. The levels of each cytokine analyzed were different for the three dengue groups, compared to healthy group ($P < 0.01$, Kruskal–Wallis test)[&] and differences when compared with DEN group ($P \leqslant 0.01$, Bonferroni–Dunn's test)[*].

of the median of the platelet counts during the acute phase of the disease for each patient was inversely correlated with the levels of sST2 (Fig. 3C).

To determine if sST2 was associated with dengue myocarditis, we compared its plasma level with the respective levels of CK-MB isoenzyme (a marker of cardiac damage) in children with more clinically ill groups (DW and SD). As shown in Fig. 3D, a small but significant positive correlation was found between both markers. In summary, sST2 was correlated with other previously described markers of severity in dengue infection.

4. Discussion

Using the classification for dengue recommended and adopted by WHO guidelines since 2009, pediatric patients were classified accordingly in several groups, dengue (DEN), dengue with warning symptoms (DW) and severe dengue (SD). Prior published work has indicated that several cytokines are associated with the severity of DENV infection although these are not predictive makers of disease severity and may not be specific biomarkers as they are also present in other infectious diseases [40–42]. The plasma levels of sST2, IL-33, TNFα, IL-12p70, IL-10, IL-8, IL-6 and IL-1β were measured in 23 healthy children, 17 with DEN, 21 with DW and 28 children with SD, 22 of whom had dengue myocarditis.

Although increase of sST2 induced by dengue has been previously reported [18,19], its levels in plasma obtained from a homogeneous pediatric population has not been done before the present study. We found significant increase of sST2 but not IL-33 in children with severe forms of dengue (Fig. 1A and B). The origin of sST2 in circulation is not known at the present time, although involve-

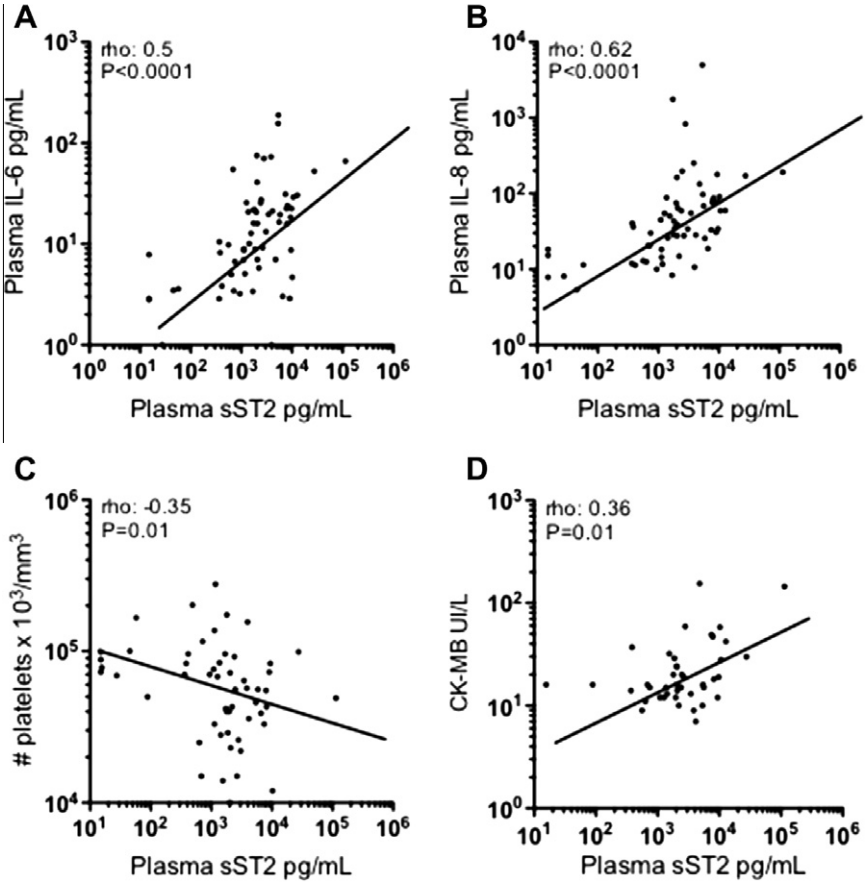

Fig. 3. Soluble ST2 correlated with IL-6 and IL-8 levels in plasma (A and B). Numbers of platelets were calculated as the median value during acute disease (hospitalization days 1 and 2 were utilized for all the patients in the study) and plotted against levels of sST2 measured by commercial ELISA test (C) and the levels of isoenzyme CK-MB are plotted against values of sST2 (D). rho: Correlation coefficient (Spearman rank test) and respective *P* values are shown.

ment of endothelial damage in dengue [43] could favor the hypothesis that sST2 is increased in vascular endothelium *in vivo* or primary endothelial cells *in vitro* [19]. Another source of sST2 could be the circulating immune cells, or peripheral blood mononuclear cells (PBMCs), but previous studies did not find significant differences in mRNA levels of sST2 between dengue fever and dengue hemorrhagic PBMCs [19]. The laboratory original data indicated that PBMCs as well as human umbilical cord endothelial cells were inducing the transcription of sST2 mRNA upon infection *in vitro* with dengue and therefore, we further studied its levels in patients' sera [9]. Future clinical research should include collection of PMBCs to be able to answer if sST2 mRNA is elevated in the immune cells. Interestingly, our preliminary data shown that the exposure of lymphocytes to sST2 will induce the synthesis of sST2 (data not shown), further amplifying the original stimulation of this factor.

Independently of the changes noted in sST2 levels, IL-33 levels were not affected (Fig. 1B). IL-33 has been associated with pro-inflammatory activity and the shift to Th2 responses [44,45]. Local, but not systemic IL-33 responses may be present in dengue, similarly to what is seen for mast cell activation models [46]. Recently, a work shows that sST2 is internalized by human monocyte-derived dendritic cells and modulates their response to lipopolysaccharides, suggesting that sST2 could acts by mechanisms other than that of sequestering the IL-33 ligand [47].

The levels of IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNFα were higher in children infected with DENV but there were no significant differences between DW and SD (Fig. 2A–F). Consistently, no tested cytokines were useful to discriminate between two the forms of clinically relevant form of dengue (Fig. 2). However, sST2 appear as exception and SD group had twofold higher levels than DW (Fig. 1A), suggesting that sST2 could be a promissory clinical correlated-biomarker in dengue infection.

In agree with previous reports, IL-6 and IL-8 were significant different in DEN and clinically more severe cases [17]. When sST2 were compared with IL-6 and IL-8 in all dengue-infected children, a strong positive correlation was found (Fig. 3A and B). Soluble ST2 was also inversely correlated with trombocytopenia, supporting the role of sST2 as severity marker. Correlations between the concentration of sST2 and pro-inflammatory cytokines have been reported in severe Leptospirosis infections and it was associated with bleeding and mortality [48].

There is a high reported incidence of mortality in severe forms of dengue infections in the pediatric cohort we studied where myocarditis was the highest causes of death [36]. A clear involvement of the sST2/IL-33 axis in heart failure and myocardial infarction has been described [49,50]. Levels of CK-MB, a marker of myocardial damage were correlated when compared with sST2 (Fig. 3D). Larger studies may be necessary to increase the level of significance of correlations between CK-MB and sST2 to myocardial damage in the context of the dengue infection.

In summary, the data shown that sST2, independently from IL-33 ligand is a biomarker of dengue infection in children. Its predictive value for severe disease should be further studied.

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