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Original Article

Increased systemic sST2 in patients with end stage renal disease contributes to milder liver damage during HCV infection

Ruzica Lukic[1], Maja Cupic[2], Nevena Gajovic[3], Milena Jurisevic[4], Zeljko Mijailovic[5], Bojana Davidovic[6], Bojan Kujundžic[6], Bojan Joksimovic[7], Nebojša Arsenijevic[3], Ivan Jovanovic[3]

[1] Department of Microbiology, Faculty of Medicine Foča, University of East Sarajevo, Foča, Bosnia and Herzegovina
[2] Department of Microbiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[3] Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia
[4] Department of clinical pharmacy, Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia
[5] Department of infectious diseases, Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia
[6] Department of Dentistry, Faculty of Medicine, University of East Sarajevo, Foča, Bosnia and Herzegovina
[7] Pediatric Department, Faculty of Medicine Foča, University of East Sarajevo, Foča, Bosnia and Herzegovina

Abstract

Introduction: Hepatitis C Virus (HCV) is the leading cause of chronic liver disease and is a serious global health problem. Hepatitis C infection is highly prevalent in patients with end stage renal disease (ESRD), due to frequent exposure to blood and blood products, nosocomial transmission of HCV, and prolong hemodialysis duration. The aim of the study was to evaluate the influence of IL-33/ST2 signaling pathway on severity of the liver disease in ESRD HCV$^+$ patients.

Methodology: Blood samples from patients with end stage renal disease (ESRD) and hepatitis C infection (HCV), 20 patients with HCV infection, 20 patients with ESRD and 20 healthy control donor patients were taken for the examination of biochemical parameters, for the determination of the serum cytokine concentration, and for the molecular diagnostics of HCV.

Results: Systemic sST2 positively correlated with serum level of urea and creatinine, respectively. Serum sST2 was significantly increased in ESRD HCV+ patients in comparison to HCV+ group. sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratios were significantly increased in serum of ESRD HCV+ patients in comparison to HCV+ patients. Significantly higher systemic level of sST2 and sST2/IL-1 and sST2/IL-4 ratios were measured in ESRD patients compared to non-ESRD patients.

Conclusion: These results suggested that elevated level sST2, as the consequence of renal failure, causes less destruction of liver in HCV infection.

Key words: HCV; end-stage renal disease; sST2.

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Introduction

Hepatitis C Virus (HCV) is the leading cause of chronic liver disease [1] and is a serious global health problem [2]. It is estimated that near 3% of the world's population (around 70 million people) have a chronic HCV infection [3,4]. Although HCV can't directly destroy hepatocytes, it can activate host's immune system, thereby facilitating liver damage [5,6].

Renal disease is one of the major health issues worldwide. Epidemiological data show that kidney disease is the 12th most common cause of death, with increased mortality by 31.7% over the last 10 years [7]. Chronic kidney disease is divided in five stages according to the level of proteinuria and renal function measured by the estimated glomerular filtration rate (eGFR) [8]. Patients with end stage renal disease (ESRD), the last stage of chronic kidney disease, with eGFR of < 15mL/minute must receive regular dialysis and are candidates for kidney transplantation [9]. Main risk factors for ESRD are smoking, obesity, hypertension and diabetes mellitus [10]. Immunosuppression is one of many consequences of chronic renal failure probably due to the effects of the so-called "uremic toxins", which include a large number of molecules such as advanced glycation endproducts or homocysteine [11,12]. B and T cell depletion and consequently reduction of humoral and

cellular immune response is main reason for prolonged immunodeficiency in ESRD patients [12].

The prevalence of hepatitis C infection (HCV) in patients with the final stage of renal disease is higher than in the general population and amounts to 3% in Western European countries, up to 20% in southern European countries [13,14]. HCV induced liver disease significantly increases morbidity and mortality in patients with end-stage renal disease (ESRD) treated with dialysis or kidney transplantation [15]. It is confirmed that HCV infections is highly prevalent in ESRD patients, due to frequent exposure to blood and blood products, nosocomial transmission of HCV, and prolong hemodialysis duration [16]. Absence of symptoms and clinical signs, alanine aminotransferase (ALT) below reference range accompanied with false-negative serologic test are the main reasons of the delayed diagnosis of HCV infection in ESRD patients [17]. Our previous study demonstrate less liver destruction in ESRD HCV^+ patients in comparison to HCV^+ patients, indicating on immunosuppressive and hepatoprotective influence of chronic renal failure [5].

ST2 is a member of the interleukin (IL)-1 cytokine family and it has two isoforms (transmembrane and secretory) [18]. While transmembrane form of ST2 is expressed on Th2 lymphocytes, macrophages, mast cells, basophils, eosinophils, dendritic cells, NK and iNKT cells, soluble form of this molecule is mainly produced by fibroblasts and epithelial cells [18]. As decoy receptor for IL-33, sST2 inhibits IL-33/ST2 signaling pathway and inhibits inflammation [19,20]. Previous investigations confirmed involvement of IL-33/ST2 signaling pathway in different liver diseases such as fatty liver disease, hepatitis, liver fibrosis, and cirrhosis. It is shown that serum concentration of IL-33 positively correlated with serum HCV RNA [21]. Animal study indicated that more severe form of hepatitis is detected in ST2-deficient mice, followed by higher number of mononuclear cells in the liver and predomination of proinflammatory cytokines [22].

The aim of the study was to evaluate the nature of influence of IL-33/ST2 signaling pathway on severity of the liver disease in ESRD HCV^+ patients.

Methodology

Ethical approvals

Ethical approvals were obtained from the Ethical Committee of the University Hospital Foca, Bosnia and Herzegovina, as well as from the University Medical Center Kragujevac, University of Kragujevac, Serbia, where the study was conducted. All patients gave an informative consent to participate in the study. All research procedures were made according to the principle of Good Clinical Practice and the Declaration of Helsinki.

Patients

This study included 40 patients with end stage renal disease (ESRD) and hepatitis C infection (HCV), 20 patients with HCV infection and without ESRD, 20 patients with ESRD and without HCV infection. The control group consisted of 20 voluntary blood donors, were selected at the University Hospital of Foca, Bosnia and Herzegovina and matched with experimental groups by gender.

From all participants during the course of our research, on the day of admission were taken blood samples for the examination of biochemical parameters, for the determination of the serum cytokine concentration, and for the molecular diagnostics of HCV (proving the presence of HCV nucleic acid, genotyping).

Serum levels of biochemical parameters

Serum levels of urea and creatinine were examined on the Abbott Architec c4000 apparatus in the biochemical laboratory at the University Hospital Foca, Bosnia and Herzegovina. Urea was processed by the Jaffa method; creatinine by enzymatic, spectrophotometric kinetic method.

Measurement of HCV RNA

The HCV gene was detected by a commercial PCR test with reverse transcription - RT-PCR (Amplicor Hepatitis C virus test, version 2.0, Roche diagnostics systems, Mannheim, Germany). After the presence of viral RNA in the sample has been established, the amount of it is calculated. The quantitative analysis of HCV RNA was performed by "real time-PCR commercial quantitative kit (CobasAmplicor HCV monitor test, version 2.0 - Roche diagnostics systems, Mannhaim, Germany) at the COBAS® TaqMan® 48 Analyzer, according to the manufacturer's instructions analytical sensitivity from 25 IU/mL to more than 100,000,000 IU/mL, and in accordance with the international standard for HCV RNA NAT analysis. The HCV genotype was determined by using the Linear Array Hepatitis C Virus Genotyping Test (Amplicor and CobasAmplicor HCV Test, version 2.0), a reverse hybridization method based on the blotting principle, after pterno-derived PCR test amplification. Genotyping was done using primers specific for the core region.

Measurement of cytokine values

Blood samples from patients with ESRD HCV+ and ESRD patients were collected prior to dialysis. Control groups consist of HCV+ patients and healthy donors. Blood samples were collected from each participant in the study and the blood was centrifuged to separate the serum and all serum samples were stored at -20°C before use. Serum cytokine concentrations were measured [23] using a sensitive immunoassay test (ELISA) of kits (R & D Systems Minneapolis, MN, USA) for IL-1β, IL-4, IL-23, IL-33, sST2; carried out according to the manufacturer's recommendations

Statistical analysis

The data were analyzed using the IMB SPSS Statistics software package (v.20.0, SSR Inc., Chicago, IL, USA). Statistically significant difference between the means of two groups was determined using Student's t-test for independent samples if the data had normal distribution or Mann-Whitney U-test for data without normal distribution and Kruskal-Wallis one way analysis or ANOVA. The results are shown as mean values and standard errors. Strength of Spearman's correlation was defined as negative or positive weak (-0.3 to -0.1 or 0.1 to 0.3), moderate (-0.5 to -0.3 or 0.3 to 0.5) or strong (-1.0 to -0.5 or 0.5 to 1). P-value of 0.05 was considered as statistically significant.

Results

The study included 100 patients: 40 ESRD and HCV^+ patients, 20 HCV^+ patients without ESRD, 20 ESRD patients without HCV infection and 20 healthy patients for control group. There was no significant difference between the defined groups in terms of gender and age.

sST2, but not IL33 correlates with ESRD parameters

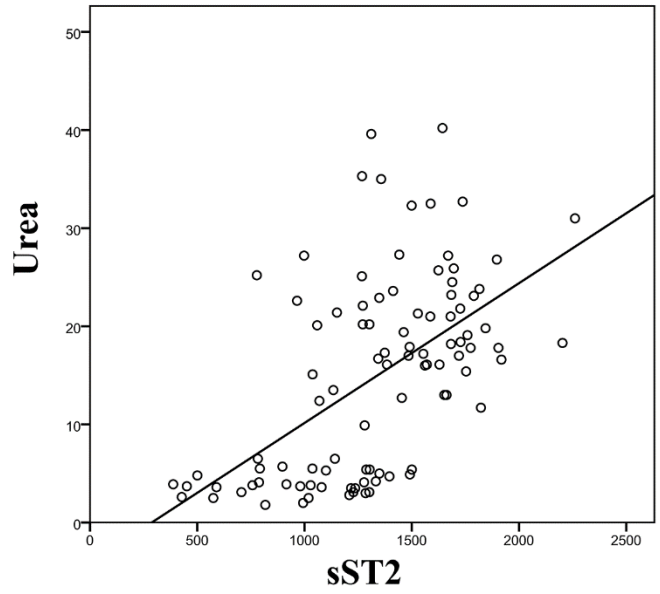
In order to elucidate importance of different cytokines in pathogenesis of ESRD in patients infected with HCV, relationships between soluble mediators and biochemical parameters of kidney functions have been analyzed. Interestingly, we did not find correlation between serum IL-33 and biochemical parameters of kidney function (data not shown). Strong positive correlations were detected between serum concentration of sST2 and serum level of urea (r = 0.562; p = 0.001) as well as between serum concentration of sST2 and serum level of creatinine (r = 0.563; p = 0.001) (Figure 1A, 1B).

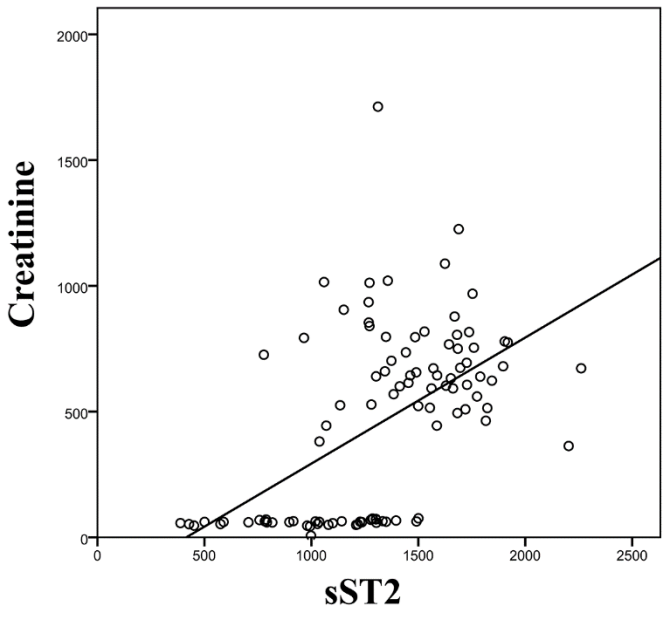
Predomination of sST2 over proinflammatory cytokines in ESRD HCV+ patients

Further, serum concentration of IL-33 and sST2 were measured in serum of patients of all four defined groups. ESRD HCV+ patients had significantly higher

Figure 1. Positive correlation between serum levels of sST2 and markers of renal function.

Variables	sST2	
	Spearman's rho	p value
Urea	0.562	0.001
Creatinine	0.563	0.001





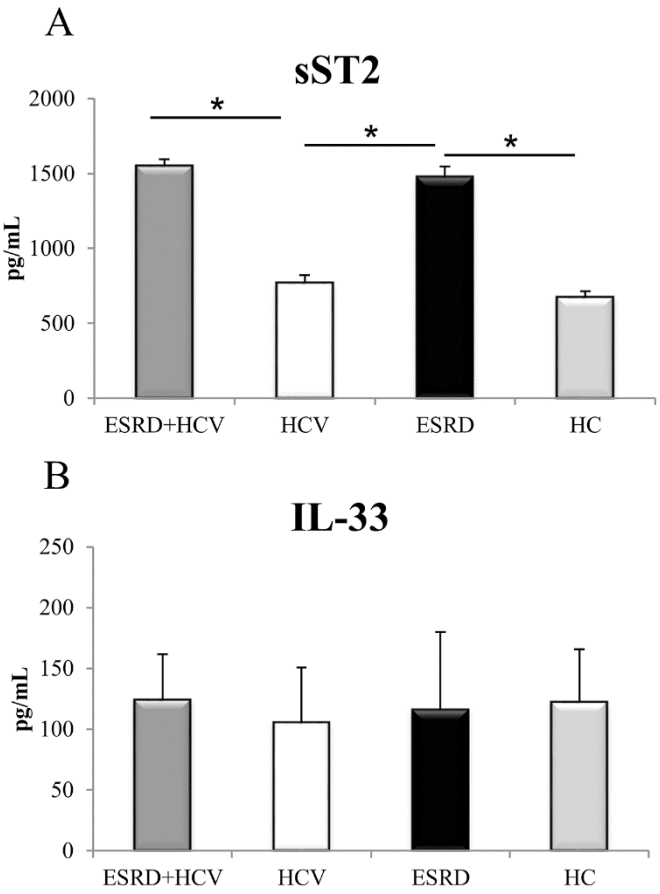
Serum level of sST2 was measured by ELISA. Strong positive correlation was detected between serum sST2 and urea and between sST2 and creatinine. Strength of correlation was determined using Spearman's test.

systemic concentration of sST2 compared to HCV+ patients (p = 0.001) (Figure 2A). Additionally, serum concentration of sST2 was significantly elevated in ESRD patients in comparison to healthy control group (p = 0.005) (Figure 2A). Analysis of systemic concentration of IL-33 didn't reveal statistical significance between all four defined groups of patients (Figure 2B). Further, we have analyzed ratios of different pro- inflammatory cytokines in defined groups of patients. There were no significant differences in IL-33/IL-1, IL-33/IL-4 nor IL-33/IL-23 ratios between four groups of patients (data not shown). However, sST2/IL-1 (p = 0.001), sST2/IL-4 (p = 0.003) as well as sST2/IL-23 (p = 0.044) ratios were significantly increased in serum of ESRD HCV+ patients in comparison to HCV+ patients (Figure 3A, 3B, 3C).

ESRD, but not HCV infection significantly increases sST2 in sera

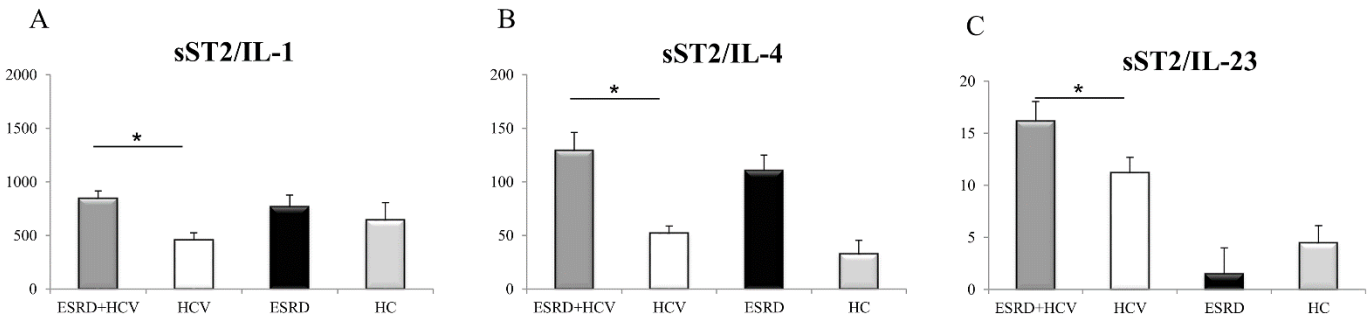
Further, ESRD HCV+ patients were divided in two groups on the basis of detection RNA of HCV virus: ESRD HCV RNA+ and ESRD HCV RNA- patients. There was no difference in the serum concentration of sST2 and IL-1 (Figure 4A). However, significantly lower serum concentration of IL-4 was detected in ESRD patients with detectable RNA compared to ESRD RNA- patients (p = 0.049) (Figure 4A). Serum level of IL-23 was higher in ESRD HCV RNA+ patients, however this difference didn't reach statistical significance (Figure 4A). Analysis of ratios of counter regulatory cytokines was also made. sST2/IL-4 ratio was significantly higher in serum of ESRD RNA+ patients compared to ESRD RNA- groups of patients (p = 0.049) (Figure 4A). There were no statistical differences in sST2/IL-1, sST2/IL-23 ratios between defined groups (Figure 4A).

Figure 2. Increased concentration of sST2 in serum of patients with ESRD.



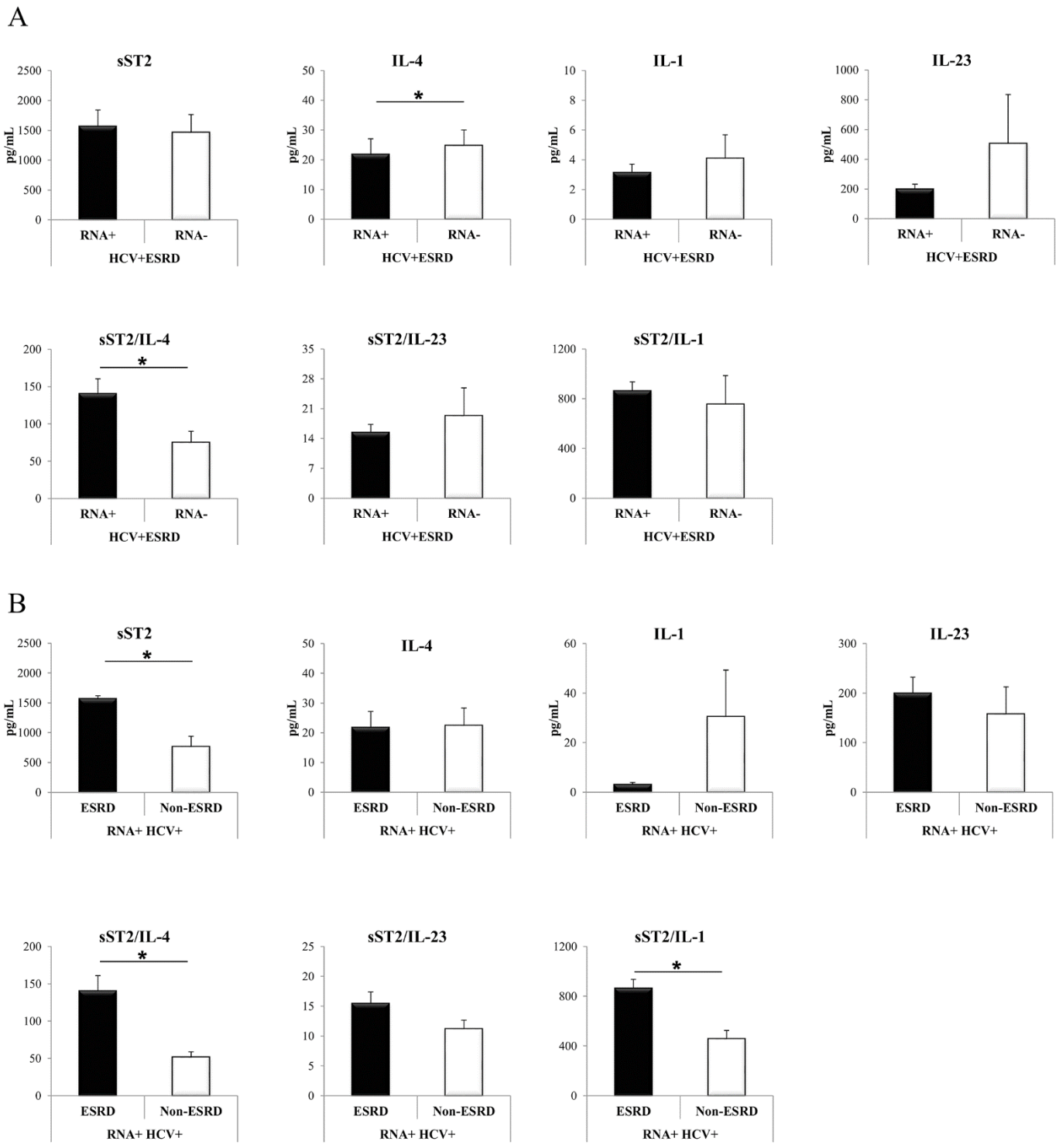
Patients were divided in four groups: 40 patients with end-stage renal disease and hepatitis C viral infection (ESRD+ HCV), 20 hepatitis C-positive patients (HCV), 20 patients with end-stage renal disease (ESRD), and 20healthy control individuals. A: significantly higher concentration of sST2 was detected in patients with ESRD+HCV in comparison to HCV+ patients as well as in ESRD patients compared to HC individuals. B: There was no significant difference in serum level of IL-33 between all four defined groups of patients. The serum levels of all mentioned biomarkers were determined by ELISA. The statistical significance was tested by Mann–Whitney Rank Sum test.

Figure 3. Increased sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratios in serum of ESRD HCV+ patients.



Patients were divided in four groups based on the presence of HCV infection and renal function. A, B, C: sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratios were significantly increased in serum of patients with ESRD HCV+ compared to HCV+ patients. The serum levels of all mentioned biomarkers were determined by ELISA. The statistical significance was tested by Mann–Whitney Rank Sum test.

Figure 4. Increased sST2 in sera of ESRDHCV+ in comparison to non-ESRD HCV+ patients.



A: ESRD HCV+ patients were divided in two groups based on detection of RNA of HCV virus: ESRD HCV RNA+ and ESRD HCV RNA- patients. Decreased serum level of IL-4 while increased sST2/IL-4 ratio was detected in ESRD patients with detectable RNA.B: HCV RNA+ patients were divided in two groups based on renal function: ESRD HCV RNA+ and non ESRD HCV RNA+. sST2, sST2/IL-1 and sST2/IL-4 ratio were significantly higher in ESRD patients compared to non-ESRD patients. The serum levels of all mentioned biomarkers were determined by ELISA. The statistical significance was tested by Mann–Whitney Rank Sum test.

Next, analysis included patients with detectable HCV RNA. Significantly higher serum concentration of sST2 was detected in ESRD patients compared to non-ESRD patients ($p = 0.001$) (Figure 4B). There was no difference in serum levels of IL-1, IL-4 and IL-23 between defined groups. sST2/IL-1 ratio ($p = 0.001$) andsST2/IL-4 ratio ($p = 0.001$) were significantly higher in ESRD patients in comparison to non-ESRD patients (Figure 4B). sST2/IL-23 ratio was also higher in serum of ESRD patients, but the difference didn't reach statistical significance.

HCV RNA genotype does not affect sST2 in sera

HCV RNA was detected in 34 (85%) patients on dialysis, while it did not in 6 (15%). 11 of the patients (27.5%) on hemodialysis have high viremia $>8\times10^5$ IU/mL, 23 (57.5%) of them have a low viremia of less than 8×10^6IU/mL, and 6 of them (15%) have no viraemia. In 6 of the patients (15.15%) with detected HCV RNA, due to the extremely low viremia value, <25 IU/mL, it was not possible to determine the genotype. The average value of the quantitative test "viral load-on viral RNA for genotype 1 was 1,879,035 IU/mL, and for genotype 4 it was 1,478,187 IU/mL. 18 patients had genotype 1, 2 patients had genotype 3, while genotype 4 had 8 patients. Further analyses revealed there was no significant difference in serum concentration of IL-33 as well as sST2 between groups divided acording to genotype and viral load, respectively (data not shown).

Discussion

Recently, we have shown that patients with ESRD HCV+ had significantly decreased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) compared to HCV+ patients, implicating on less level of hepatic destruction [5]. In the present study, we tested the potential connection of the IL-33/ST2 signal pathway with the severity of the disease in HCV+ patients with and without ESRD. Although linkage between systemic values of IL-33 with parameters of disease severity was not found, positive correlation was detected between systemic values of sST2 and urea and creatinine, respectively (Figure 1). For the first time, we demonstrated that systemic values of sST2 were significantly increased in ESRD HCV+ patients in comparison to HCV+ group of patients (Figure 2).

Previous studies confirmed that renal dysfunction changes several components of innate and adaptive immunity, thus suppressing immune response on different microorganisms [24,25]. As it is also known that the ratio of counterregulatory cytokines is a reliable marker of the disease process, we have further analyzed the ratio of sST2 with proinflammatory cytokines. IL-1, as member of IL-1 family of cytokines, is known as one of the major factors important for initiation and maintaining the process of damaging inflammation [26]. IL-1 released from infected or damaged cells triggers inflammation via stimulation of production of chemokine that further recruit and attract leukocytes to the damaged tissue [27]. In addition to the importance of the innate and cellular immune response in HCV infection, humoral immunity is also important in the fight against viral infections [28]. IL-4 is one of the major stimulations of Th2 cellular and humoral immune response [29]. IL-23 is a pro-inflammatory cytokine involved in differentiation of naive $CD4^+$ T cells into Th-17 cells that further by producing several proinflammatory cytokines facilitates tissue destruction [30]. The goal was to cover all three types of the aquired immune response (Th1, Th2 and Th17) involved in eliminating HCV infection. Significantly increased sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratios were detected in serum of ESRD HCV+ patients in comparison to HCV+ patients (Figure 3). Our previous study revealed that attenuated ongoing proinflammatory process in ESRD HCV+ patients prevents liver destruction, implicating on immunosuppression as one of the key mechanisms [5]. In line with these, predomination of sST2 over proinflammatory cytokines of interest in these patients suggests on possible immunosuppressive role of sST2 targeting innate as well as acquired anti HCV immune response.

There are few possible mechanisms of immunosuppressive effect of sST2 molecule. The one possible immunosuppressive effect of sST2 relies on previous studies showing that sST2 by binding to the surface of macrophages significantly reduces the production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, and the expression of Toll-like receptor 1 (TLR1) and TLR4. At the same time, sST2 does not disrupt the production of anti-inflammatory mediators IL-10 and TGF-β, as well as production of NO [31]. One of the acceptable models of the anti-inflammatory role of soluble sST2 is that microorganism products induce cascade production of pro-inflammatory cytokines, adhesion molecules and other inflammatory mediators by innate immunity cells to [32]. PAMPs stimulate macrophages, fibroblasts, and other cell types to produce sST2. Further, sST2 binds directly to innate immunity cells and inhibits the pro-inflammatory response by negative feedback, most likely by inactivation of TLRs [33]. Thus, sST2 acts as

significant participant in negative feedback to prevent an uncontrolled inflammatory reaction.

IL-33, member of IL-1 family of cytokines, is constitutively expressed by different non-hematopoietic cells such as endothelial cells and epithelial cells [26]. In mostly cases, IL-33, known as alarmin, is released after cell damage and facilitates both innate and acquired immune response [34]. Soluble form of ST2 molecule serves as decoy receptor for IL-33 that blocks IL-33/ST2 signaling and NFκB transcriptional factor,andsubsequently inhibits inflammation [20]. Our results revealed significant increment of systemic values of sST2 molecule as well as sST2/IL-1, sST2/IL-4 and sST2/IL-23 ratios in sera of ESRD HCV+ patients in comparison to HCV+ patients (Figures 2 and 3). These results are suggesting on predomination of immunosupressive effect of sST2 over IL-33 and subsequent lower grade inflamation in liver.

Absence of difference in the serum concentration of sST2 between ESRD HCV RNA+ and ESRD HCV RNA- patients (Figure 4) implicates that virus activity does not affect systemic values of sST2. In line with this finding, differences in genotype as well as viral load also did not affect systemic concentration of sST2.

Interestingly, sST2 positively correlated with markers of severity of renal disease and ESRD patients had significantly higher level of sST2 compared to healthy control group of patients (Figure 2). This soluble marker is higher in sera of HCV+ patients with renal disease in comparison to HCV+ patients without renal disease. This trend was confirmed in ESRD vs. non-ESRD patients, both with detectable HCV RNA (Figure 4). Taken together, these results suggest that elevation of serum sST2 is consequence of renal disease not HCV infection.

Presented data make new insight in modulation of anti HCV immune response in patients with renal failure introducing sST2 as new player in this phenomenon, besides previously discussed galectin-3 and IL-6 as immunosuppressive and hepatoprotective factors in ESRD HCV+ patients [5].

Conclusion

Collectively, increased serum level of sST2 in ESRD HCV+ may be considered as the cause of less destruction of liver. Higher systemic values of sST2 in ESRD patients suggest that elevation of sST2 is due to renal disease, not HCV infection. Predomination of sST2 over IL-1, IL-4 and IL-23 in ESRD HCV+ may suggest on immunomodulatory role of sST2 followed by suppression of inflammatory process in liver. These results implicate on protective role of sST2 in HCV infection in patients with renal failure.

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Authors' contributions

RL, IJ, ZM, and MC designed the study. NG, MJ, BD performed the study. BK, BSM and BJ collected data, and NA, NG and RL analyzed data. MJ, IJ, NA and RL wrote the paper. All authors discussed the results and implications and commented on the manuscript at all stages.

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Corresponding author

Nevena Gajovic, MD, PhD
Center for Molecular Medicine and Stem Cell Research
Faculty of Medical Sciences University of Kragujevac
SvetozaraMarkovica 69, 34000 Kragujevac, Serbia
Tel +38134306800,
Fax. +38134306800112
E-mail: gajovicnevena@yahoo.com

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