Received: 14 June 2016 | Revised: 28 January 2017 | Accepted: 10 March 2017

DOI: 10.1111/iji.12318

SHORT COMMUNICATION

WILEY INTERNATIONAL JOURNAL OF IMMUNOGENETICS

Vitamin D receptor gene polymorphisms association with the risk of sepsis and mortality

K. Zeljic[1,2*] | A. Elkilany[1*] | G. Supic[2,3] | M. Surbatovic[3,4] | D. Djordjevic[3,4] | Z. Magic[2,3] | B. Bozic[1,2]

[1]Faculty of Biology, University of Belgrade, Belgrade, Serbia

[2]Institute for Medical Research, Military Medical Academy, Belgrade, Serbia

[3]Faculty of Medicine, Military Medical Academy, University of Defense, Belgrade, Serbia

[4]Clinic of Anesthesiology and Intensive Therapy, Military Medical Academy, Belgrade, Serbia

Correspondence
Katarina Zeljic, PhD (Asst. Prof.), University of Belgrade, Faculty of Biology, Belgrade, Serbia.
Emails: katarina.zeljic@bio.bg.ac.rs and katjaze@yahoo.com

Funding information
The study was financed by the Military Medical Academy Institutional Grant 06/10/A1 and the Serbian Ministry of education, science and technological development (Grant 175033).

Summary

Association of vitamin D receptor (VDR) gene polymorphisms with sepsis risk and mortality was studied. VDR FokI CC genotype was associated with increased sepsis risk (OR = 13.396, p = .000009) compared to the TT genotype. Results suggest possible role of VDR FokI (rs2228570) as a molecular biomarker of increased sepsis risk.

KEYWORDS
mortality, polymorphisms, risk, sepsis, VDR

1 | INTRODUCTION

Sepsis develops as a systemic inflammatory response of host organism on the microorganism invasion. In intensive care units, the leading cause of death in critically ill patients is still sepsis, despite advances in treatment and clinical care (Cawcutt & Peters, 2014). As genetic predisposition of premature death from severe infection was confirmed in the past (Sorensen, Nielsen, Andersen, & Teasdale, 1988), it could be assumed that genetic variations significantly contribute to sepsis development. Thus, finding novel molecular biomarkers suitable for identification of patients with higher risk of sepsis susceptibility and mortality are warranted.

Vitamin D pleiotropic functions were demonstrated in different biological processes, including inflammation and immunity (Bikle, 2014; Dusso, Brown, & Slatopolsky, 2005). Synthesis of metabolite active form of vitamin D, known as calcitriol ($1\alpha,25(OH)_2D_3$), is a complex multistep process which involves two steps of hydroxylation catalysed by members of P450 enzymes family (Dusso et al., 2005). The key point of exerting biological functions by vitamin D is its binding to vitamin D receptor (VDR) which generates signalling complex consisting of a heterodimer of the $1\alpha,25(OH)_2D_3$-liganded VDR and unoccupied retinoid X receptor (RXR). The liganded VDR-RXR heterodimer binds to the vitamin D response elements (VDRE) and regulates transcription of target genes (Bikle, 2014). Unrevealing connection between vitamin D and inflammatory diseases has attracted scientific attention after the discovery of vitamin D immunomodulating properties. It is known that VDR, coded by the VDR gene, is expressed on immune cells, such as activated B and T lymphocytes, antigen presenting cells (macrophages, dendritic cells and B cells), and is upregulated in infectious process. Vitamin D primarily influences dendritic cell maturation and macrophage differentiation, and it also reduces the release of cytokines (Cantorna, 2011; Hewison, 2010; Veldman, Cantorna, & DeLuca, 2000). In addition, previous studies reported increased mortality in severe sepsis and septic shock patients due to vitamin D deficiency (Amrein et al., 2014; Arnson, Gringauz, Itzhaky, & Amital, 2012; Braun, Gibbons, Litonjua, Giovannucci, & Christopher, 2012; Braun

*Zeljic and Elkilany have equally contributed to this study.

et al., 2011; Jeng et al., 2009; Rech, Hunsaker, & Rodriguez, 2014), which could be prevented by vitamin D supplementation during hospitalization (Rech et al., 2014).

It is known that vitamin D biological functions could be impaired by the presence of single-nucleotide polymorphisms (SNPs) in genes involved in vitamin D metabolism and functional cascade (Whitfield et al., 2001). Numerous studies investigated the role of VDR gene polymorphisms in different pathologies such as cancer (Heist et al., 2008; Zeljic et al., 2012, 2014), autoimmune (Carvalho et al., 2015; Garcia-Martin et al., 2013; Inoue et al., 2014) and infectious diseases (Joshi et al., 2014). To date, in the current literature, there are no reports on the VDR gene polymorphisms association with sepsis risk and mortality. Thus, the aim of the study was to investigate the association between VDR gene polymorphisms, sepsis risk and mortality.

2 | MATERIALS AND METHODS

2.1 | Study group

Case groups consisted of 100 patients with severe sepsis on admission to surgical intensive care unit (ICU) at Military Medical Academy (Belgrade, Serbia) from July 2010 to May 2012. In a period of 24 hr upon ICU admission, the following scores were calculated and recorded: the Simplified Acute Physiology Score II (Le Gall, Lemeshow, & Saulnier,1993), Acute Physiology and Chronic Health Evolution II score (Knaus, Draper, Wagner, & Zimmerman, 1985) and Sequential Organ Failure Assessment score (Moreno et al., 1999). Injury Severity Score (ISS) was used to determine the severity of trauma. ISS was determined using Abbreviated Injury Scale. Great majority of trauma patients were casualties of motor vehicle accidents with blunt and/or penetrating trauma. Sepsis patients entered the study provided they had met the following criteria (according to the 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference): documented or suspected infection plus the presence of systemic inflammatory response syndrome and sepsis-associated organ dysfunction, hypotension, hypoperfusion (hyperlactatemia >2 mmol/L). The exclusion criteria included those below 18 years of age, pregnancy, severe chronic respiratory disease, severe chronic liver disease, malignancy, use of high-dose immunosuppressive therapy and AIDS. The follow-up period was 1 year.

The control group consisted of 104 healthy blood donors, Caucasians of Serbian ethnicity. Demographic and clinical characteristics of the patients with sepsis and healthy subjects are summarized in Table S1 and Table S2.

2.2 | Biological samples, DNA isolation and polymorphisms genotyping

Peripheral blood samples were collected from all individuals involved in the study and stored at −20°C until DNA isolation. DNA was isolated using the GeneJet Genomic DNA Purification Kit according to the instructions given by the manufacturer (Fermentas, St. Leon-Rot, Germany). VDR gene polymorphisms: EcoRV (rs4516035), FokI (rs2228570), ApaI (rs7975232) and TaqI (rs731236) were genotyped by real-time PCR method using the commercially available TaqMan SNP Genotyping Assays (C_2880805_10, C_12060045_20, C_28977635_10, C_2404008_10, respectively) (Applied Biosystems, Foster city, CA, USA). According to the 1000 Genomes database (www.1000genomes.org), the minor allele for each analysed VDR gene polymorphism in Europeans was referred as a rare variant and the major allele as a common variant.

2.3 | Statistical analysis

Statistical analysis was performed using the SPSS software (version 20.00, SPSS Ins., Chicago, IL, USA). Chi-square or Fisher exact tests were used for the analysis of contingency tables. Crude and adjusted odds ratios with 95% confidence interval were calculated by unconditional binary logistic regression. Adjustments were made for age and gender.

Linkage disequilibrium (LD) with D' and r^2 values and haplotype frequencies were determined by Haploview software (Barrett, Fry, Maller, & Daly, 2005). Solid spine block definition was applied in haplotype block determination. Raw and permutation (after 1,000 permutations) p values were estimated by Haploview. Association analyses of identified haplotypes were performed by Thesias software (Tregouet & Garelle, 2007).

Binary logistic regression was used in estimating independent predictors of sepsis mortality within 28-days. Tested variables reported as significant in univariate analysis were subsequently analysed in a multivariate logistic regression model.

The associations were considered as significant if p values were less than .05 ($p < .05$).

3 | RESULTS

3.1 | Genotype and allele distribution of studied polymorphisms in VDR gene

Genotype and allele frequency of the studied polymorphisms in the VDR gene in the patients with sepsis as well as healthy subjects are presented in Table S3. Significant difference in the genotype distribution among cases and control groups was observed for the VDR EcoRV (rs4516035) and FokI (rs2228570) polymorphisms ($p = .030$, $p = .000042$, respectively). There were no significant differences in genotype distribution among subgroups of patients with sepsis (Table S4).

3.2 | VDR gene polymorphisms association with clinicopathological characteristics and risk of sepsis

No significant associations were observed between VDR gene polymorphisms and gender, age, presence of pathogen in blood, sepsis outcome and mortality (Table S5).

The association between the studied VDR gene polymorphisms and the risk of sepsis is presented in Table 1. Adjusted odds ratio analysis

TABLE 1 Association of the studied polymorphisms in the VDR gene with the risk of sepsis

		Cases		Controls							
Gene/SNP	**Genotype**	***N***	**%**	***N***	**%**	**Crude OR (95% CI)**	***p****	***p*†**	**Adjusted OR (95% CI)[c]**	***p****	***p*†**
	TT	22	22	28	27	1.000	Reference		1.000	Reference	
VDR EcoRV	TC	60	60	44	42	1.736 (0.879–3.428)	.112	2.128	1.597 (0.783–3.257)	.198	3.762
rs4516035	CC	18	18	32	31	0.716 (0.321–1.599)	.415	7.885	0.703 (0.288–1.720)	.440	8.36
	Dominant[a]	78	78	76	73	1.306 (0.688–2.481)	.414	7.866	1.205 (0.612–2.372)	.590	11.21
	Recessive[b]	82	82	72	69	0.494 (0.256–0.954)	**.036**	0.684	0.560 (0.279–1.122)	.102	1.938
	TT	13	13	36	35	1.000	Reference		1.000	Reference	
VDR FokI	TC	53	53	55	53	2.669 (1.276–5.581)	**.009**	0.171	3.303 (1.459–7.482)	**.004**	0.076
rs2228570	CC	34	34	13	13	7.243 (2.944–17.821)	**.000016**	**0.000304**	13.396 (4.263–42.095)	**.000009**	**0.000171**
	Dominant[a]	87	87	68	65	3.543 (1.743–7.200)	**.000472**	**0.008968**	4.552 (2.069–10.014)	**.000165**	**0.003135**
	Recessive[b]	66	66	91	88	3.606 (1.767–7.359)	**.000425**	**0.008075**	4.421 (2.067–9.456)	**.000127**	**0.002413**
	CC	20	20	24	23	1.000	Reference		1.000	Reference	
VDR ApaI	CA	44	44	36	35	1.467 (0.700–3.071)	.310	5.890	1.589 (0.727–3.474)	.246	4.674
rs7975232	AA	36	36	44	42	0.982 (0.469–2.056)	.961	18.259	1.187 (0.530–2.659)	.677	12.863
	Dominant[a]	80	80	80	77	1.200 (0.614–2.344)	.593	11.267	1.376 (0.669–2.830)	.386	7.334
	Recessive[b]	64	64	60	58	0.767 (0.436–1.348)	.357	6.783	0.870 (0.478–1.583)	.649	12.331
	TT	36	36	49	47	1.000	Reference		1.000	Reference	
VDR TaqI	TC	53	53	41	39	1.759 (0.973–3.138)	.062	1.178	1.664 (0.890–3.110)	.111	2.109
rs731236	CC	11	11	14	13	1.069 (0.435–2.629)	.884	16.796	1.155 (0.451–2.959)	.764	14.516
	Dominant[a]	64	64	55	53	1.584 (0.904–2.776)	.108	2.052	1.537 (0.848–2.786)	.156	2.964
	Recessive[b]	89	89	90	87	0.795 (0.342–1.845)	.593	11.267	0.875 (0.359–2.130)	.768	14.592

N, total number of cases/controls; SNP, Single-Nucleotide Polymorphisms.
[a]Heterozygous and homozygous genotype combined vs reference genotype.
[b]Homozygous genotype vs reference and heterozygous genotypes combined.
[c]Adjustments were made for gender and age.
**p* values<.05 are given in bold.
p†: *p* values after Bonferroni correction for 19 multiple comparisons. *p* values <.05 are given in bold.

showed that homozygous CC genotype of VDR FokI (rs228570) polymorphism is associated with elevated risk of sepsis compared to TT genotype. This association was increased after adjustments for gender and age and remained significant after Bonferroni correction.

3.3 | Haplotype analysis and linkage disequilibrium

The presence of haplotype blocks was confirmed in our study group (D' = 0.97, r^2 = .36) as well as in the cases (D' = 0.95, r^2 = .40) and control subjects (D' = 1, r^2 = .33) (Figure S1). The most prevalent is CT haplotype (cases: 42%, control: 41%), followed by AC (cases: 37%, control: 33%), while the AT haplotype is the least common (cases: 21%, control: 26%). No differences in haplotype distribution between cases and control individuals were found by raw and permutation *p* values (after the calculations for 1,000 permutations). None of the identified haplotypes was associated with the risk of sepsis (Table S6).

3.4 | Logistic regression analysis of 28-day mortality

Univariate and multivariate logistic regression analysis was used to assess independent variables that may affect early mortality during the first 28 days upon ICU admission (Table 2). The variables which entered the model as independent variables are the following: age, gender and all investigated VDR polymorphisms. In the analysis of individual variables, age (according to the median of 56 years) and dominant inheritance model of VDR FokI polymorphism, which combine heterozygous and a common variant genotype vs a rare form, were associated with higher risk of mortality within the first 28 days of admission to intensive care units. Multivariate logistic regression analysis showed that age was an independent predictor of increased 28-day mortality, while the significance for VDR FokI polymorphism was lost.

4 | DISCUSSION

Sepsis is the leading cause of morbidity and mortality among the patients in intensive care units (Cawcutt & Peters, 2014). As the statistics has remained unchanged despite the advances in the treatment and care of patients with sepsis, great efforts are made in identifying additional molecular markers which could serve as predictive and prognostic markers.

TABLE 2 Univariate and multivariate logistic regression analysis to determine independent predictors of 28-day mortality in patients with sepsis

Variables	OR (95% CI)	*p**
Univariate logistic regression		
Gender (Male vs Female)	1.934 (0.839–4.458)	.122
Age (median)	7.927 (2.729–23.033)	**.000142**
VDR EcoRV (rs4516035)	0.634 (0.223–1.801)	.392
VDR FokI (rs2228570)*	3.556 (1.064–11.878)	**.039**
VDR ApaI (rs7975232)	2.200 (0.813–5.956)	.121
VDR TaqI (rs731236)	0.891 (0.377–2.108)	.793
Multivariate logistic regression		
Age (median)	7.437 (2.533–21.835)	**.000261**
VDR FokI (rs2228570)[a]	2.880 (0.772–10.740)	.115

*p values <.05 are given in bold.
[a]Under dominant inheritance.
OR (95% CI)-Odds Ratio (95% Confidence Interval).

As far as we know, this is the first report on the association between the VDR gene polymorphism and increased sepsis susceptibility. Our main finding is that homozygous CC genotype of VDR FokI (rs2228570) polymorphism is associated with an increased risk of sepsis compared with TT genotype. These findings support the hypothesis that VDR polymorphism may play a significant role in inflammation control and maintaining homoeostasis in patients with sepsis.

Vitamin D receptor FokI polymorphism is one of the very well functionally characterized polymorphisms in the VDR gene. VDR FokI presents a non-synonymous change of thymine to cytosine in exon 2 of the VDR gene, which results in the substitution of amino acid Met to Lys and the synthesis of the receptor form shortened by three amino acids. Some functional studies demonstrated a higher activity of a changed receptor form (Uitterlinden, Fang, Van Meurs, Pols, & Van Leeuwen, 2004). Our findings highlight the possibility of using the VDR FokI polymorphism as an important molecular biomarker which could be used in the identification of critically ill patients with a higher risk of sepsis development and thus possibly implemented in the medical care practice. Functional studies reported the association among the changed FokI receptor form and increased production of IL-12 in monocytes and dendritic cells which consequently induce a strong Th1 immune response (van Etten et al., 2007). Furthermore, it has been demonstrated that the VDR, depending on the FokI genotype, differentially interacts with the transcription factors of importance within the immune system, namely NF-kB, NFAT and AP-1 (van Etten et al., 2007). Also, in inflammatory conditions, including sepsis, a higher activation of NF-kB pathway is noted (Li & Verma, 2002; Liu & Malik, 2006). Based on previously mentioned pieces of evidence, it could be assumed that individuals with CC FokI genotype are at a higher risk for sepsis development, which is supported by our results. Considering these results and literature data, we may hypothesize that adequate VDR signalling is very important for the adequate control of the immune response to microorganism or damaged cells and tissues. Thus, apart from other risk factors of importance for sepsis development, VDR FokI polymorphism could be considered as an additional confounding factor.

Univariate logistic regression analysis revealed that VDR FokI polymorphism, under a dominant inheritance model, is associated with increased 28-day mortality in patients with sepsis. A multivariate model included age and VDR FokI, and revealed that age could be used as an independent predictor of mortality in patients with sepsis while the significance was lost in case of VDR FokI polymorphism. These results point out that, even though associated with higher risk odds to sepsis development, VDR FokI polymorphism association with increased mortality in patients with sepsis is overruled by confounding effectors, such as age. Our findings are in line with the results of the previous study, where an independent predictor of increased sepsis mortality was age (Rech et al., 2014). Numerous studies have reported increased mortality of patients with sepsis and vitamin D deficiency (Amrein et al., 2014; Arnson et al.,2012; Braun et al., 2011, 2012; Jeng et al.,2009; Rech et al., 2014). Also, serum level of active vitamin D form before hospitalization is associated with hospital-acquired bloodstream infections (Lange, Litonjua, Gibbons, Giovannucci, & Christopher, 2013; Quraishi et al., 2013). Moreover, vitamin D supplementation is proposed in critically ill patients as a promising prevention and the treatment agent of sepsis and septic shock (Watkins, Yamshchikov, Lemonovich, & Salata, 2011; Yilmaz et al., 2013). However, none of the mentioned studies have investigated the association of the VDR gene polymorphisms with the patients' mortality. Thus, measuring 25-hydroxyvitamin D serum level in patients with sepsis and septic shock and association studies focused on VDR gene polymorphisms as well as other relevant genes in vitamin D metabolic and functional pathways, such as CYP27A1, CYP27B1, CYP24A1, RXR, are warranted. Considering the complexity of the immune system, numerous signalling cascades and crosstalk between signal molecules involved in the inflammation, apart from the vitamin D pathway, it is also important to study signalling cascades interactions.

Vitamin D receptor gene polymorphisms were studied in numerous inflammatory diseases, such as asthma (Saadi et al., 2009) and autoimmune diseases (Carvalho et al., 2015; Garcia-Martin et al., 2013; Inoue et al., 2014). However, findings among different studies are inconsistent and inconclusive, probably as a result of various diseases analysed, sample size and population differences. For the first time, the results of our study provide the information on the VDR gene polymorphisms association with the sepsis risk and mortality, as no reports can be found in current literature.

There are several limitations of our study. First, the potential limitation includes a relatively small sample size and study results could be considered as preliminary. Second, all subjects in the study group were from the Serbian population, thus the results may not be generalized to other populations. However, we could confidently interpret our findings as a highly selected and clinically clear cohort of patients with sepsis was enrolled in the study. Third, we did not analyse RXR as well as other vitamin D related gene polymorphisms and did not measure the level of serum vitamin D.

To summarize, the results of the current study indicate the possible important role of VDR FokI (rs2228570) polymorphism in the risk of

sepsis susceptibility. Additional prospective studies on a larger homogenous group of patients with sepsis, including the serum vitamin D level, gene expression and interactions of the VDR gene with environmental factors and genes from other signalling cascades involved in inflammation, will give a full confirmation of the VDR gene role in sepsis susceptibility and patients' outcome.

ACKNOWLEDGEMENTS

Authors wish to express their gratitude to Dr Svetlana Bojic for help and consultations in statistical analysis.

ETHICS

The Ethics Committee of the Military Medical Academy approved the conduction of the study according to the Helsinki Declaration (2008) (approval decision made on 21.06.2012.). All individuals involved in the study provided informed consent or it was given by a first-degree relative.

DISCLOSURES

The authors state that there is no conflict of interest.

REFERENCES

Amrein, K., Zajic, P., Schnedl, C., Waltensdorfer, A., Fruhwald, S., Holl, A., … Dobnig, H. (2014). Vitamin d status and its association with season, hospital and sepsis mortality in critical illness. *Critical Care*, *18*, R47.

Arnson, Y., Gringauz, I., Itzhaky, D., & Amital, H. (2012). Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients. *QJM*, *105*, 633–639.

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of ld and haplotype maps. *Bioinformatics*, *21*, 263–265.

Bikle, D. D. (2014). Vitamin D metabolism, mechanism of action, and clinical applications. *Chemistry & Biology*, *21*, 319–329.

Braun, A., Chang, D., Mahadevappa, K., Gibbons, F. K., Liu, Y., Giovannucci, E., & Christopher, K. B. (2011). Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. *Critical Care Medicine*, *39*, 671–677.

Braun, A. B., Gibbons, F. K., Litonjua, A. A., Giovannucci, E., & Christopher, K. B. (2012). Low serum 25-hydroxyvitamin D at critical care initiation is associated with increased mortality. *Critical Care Medicine*, *40*, 63–72.

Cantorna, M. T. (2011). Why do t cells express the vitamin D receptor? *Annals of the New York Academy of Sciences*, *1217*, 77–82.

Carvalho, C., Marinho, A., Leal, B., Bettencourt, A., Boleixa, D., Almeida, I., … Silva, B. M. (2015). Association between vitamin D receptor (vdr) gene polymorphisms and systemic lupus erythematosus in portuguese patients. *Lupus*, *24*, 846–853.

Cawcutt, K. A., & Peters, S. G. (2014). Severe sepsis and septic shock: Clinical overview and update on management. *Mayo Clinic Proceedings*, *89*, 1572–1578.

Dusso, A. S., Brown, A. J., & Slatopolsky, E. (2005). Vitamin D. *American Journal of Physiology. Renal Physiology*, *289*, F8–F28.

van Etten, E., Verlinden, L., Giulietti, A., Ramos-Lopez, E., Branisteanu, D. D., Ferreira, G. B., … Mathieu, C. (2007). The vitamin D receptor gene foki polymorphism: Functional impact on the immune system. *European Journal of Immunology*, *37*, 395–405.

Garcia-Martin, E., Agundez, J. A., Martinez, C., Benito-Leon, J., Millan-Pascual, J., Calleja, P., … Jimenez-Jimenez, F. J. (2013). Vitamin D3 receptor (vdr) gene rs2228570 (fok1) and rs731236 (taq1) variants are not associated with the risk for multiple sclerosis: Results of a new study and a meta-analysis. *PLoS One*, *8*, e65487.

Heist, R. S., Zhou, W., Wang, Z., Liu, G., Neuberg, D., Su, L., … Christiani, D. C. (2008). Circulating 25-hydroxyvitamin d, vdr polymorphisms, and survival in advanced non-small-cell lung cancer. *Journal of Clinical Oncology*, *26*, 5596–5602.

Hewison, M. (2010). Vitamin D and the immune system: New perspectives on an old theme. *Endocrinology and Metabolism Clinics of North America*, *39*, 365–379, table of contents.

Inoue, N., Watanabe, M., Ishido, N., Katsumata, Y., Kagawa, T., Hidaka, Y., & Iwatani, Y. (2014). The functional polymorphisms of vdr, gc and cyp2r1 are involved in the pathogenesis of autoimmune thyroid diseases. *Clinical and Experimental Immunology*, *178*, 262–269.

Jeng, L., Yamshchikov, A. V., Judd, S. E., Blumberg, H. M., Martin, G. S., Ziegler, T. R., & Tangpricha, V. (2009). Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. *Journal of Translational Medicine*, *7*, 28.

Joshi, L., Ponnana, M., Penmetsa, S. R., Nallari, P., Valluri, V., & Gaddam, S. (2014). Serum vitamin D levels and vdr polymorphisms (bsmi and foki) in patients and their household contacts susceptible to tuberculosis. *Scandinavian Journal of Immunology*, *79*, 113–119.

Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). Apache ii: A severity of disease classification system. *Critical Care Medicine*, *13*, 818–829.

Lange, N., Litonjua, A. A., Gibbons, F. K., Giovannucci, E., & Christopher, K. B. (2013). Pre-hospital vitamin D concentration, mortality, and bloodstream infection in a hospitalized patient population. *American Journal of Medicine*, *126*(640), e19–e27.

Le Gall, J. R., Lemeshow, S., & Saulnier, F. (1993). A new simplified acute physiology score (saps ii) based on a european/north american multicenter study. *JAMA*, *270*, 2957–2963.

Li, Q., & Verma, I. M. (2002). Nf-kappab regulation in the immune system. *Nature Reviews Immunology*, *2*, 725–734.

Liu, S. F., & Malik, A. B. (2006). Nf-kappa b activation as a pathological mechanism of septic shock and inflammation. *American Journal of Physiology. Lung Cellular and Molecular Physiology*, *290*, L622–L645.

Moreno, R., Vincent, J. L., Matos, R., Mendonca, A., Cantraine, F., Thijs, L., … Willatts, S. (1999). The use of maximum sofa score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working group on sepsis related problems of the esicm. *Intensive Care Medicine*, *25*, 686–696.

Quraishi, S. A., Litonjua, A. A., Moromizato, T., Gibbons, F. K., Camargo, C. A. Jr, Giovannucci, E., & Christopher, K. B. (2013). Association between prehospital vitamin D status and hospital-acquired bloodstream infections. *American Journal of Clinical Nutrition*, *98*, 952–959.

Rech, M. A., Hunsaker, T., & Rodriguez, J. (2014). Deficiency in 25-hydroxyvitamin D and 30-day mortality in patients with severe sepsis and septic shock. *American Journal of Critical Care*, *23*, e72–e79.

Saadi, A., Gao, G., Li, H., Wei, C., Gong, Y., & Liu, Q. (2009). Association study between vitamin D receptor gene polymorphisms and asthma in the chinese han population: A case-control study. *BMC Medical Genetics*, *10*, 71.

Sorensen, T. I., Nielsen, G. G., Andersen, P. K., & Teasdale, T. W. (1988). Genetic and environmental influences on premature death in adult adoptees. *New England Journal of Medicine*, *318*, 727–732.

Tregouet, D. A., & Garelle, V. (2007). A new java interface implementation of thesias: Testing haplotype effects in association studies. *Bioinformatics*, *23*, 1038–1039.

Uitterlinden, A. G., Fang, Y., Van Meurs, J. B., Pols, H. A., & Van Leeuwen, J. P. (2004). Genetics and biology of vitamin D receptor polymorphisms. *Gene*, *338*, 143–156.

Veldman, C. M., Cantorna, M. T., & DeLuca, H. F. (2000). Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Archives of Biochemistry and Biophysics*, *374*, 334–338.

Watkins, R. R., Yamshchikov, A. V., Lemonovich, T. L., & Salata, R. A. (2011). The role of vitamin D deficiency in sepsis and potential therapeutic implications. *Journal of Infection*, *63*, 321–326.

Whitfield, G. K., Remus, L. S., Jurutka, P. W., Zitzer, H., Oza, A. K., Dang, H. T., … Haussler, M. R. (2001). Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. *Molecular and Cellular Endocrinology*, *177*, 145–159.

Yilmaz, H., Sahiner, E., Darcin, T., Celik, H. T., Bilgic, M. A., & Akcay, A. (2013). Is vitamin D supplementation a new hope for the therapy of the septic shock? *Endocrine Regulations*, *47*, 133–136.

Zeljic, K., Kandolf-Sekulovic, L., Supic, G., Pejovic, J., Novakovic, M., Mijuskovic, Z., & Magic, Z. (2014). Melanoma risk is associated with vitamin D receptor gene polymorphisms. *Melanoma Research*, *24*, 273–279.

Zeljic, K., Supic, G., Stamenkovic Radak, M., Jovic, N., Kozomara, R., & Magic, Z. (2012). Vitamin D receptor, cyp27b1 and cyp24a1 genes polymorphisms association with oral cancer risk and survival. *Journal of Oral Pathology and Medicine*, *41*, 779–787.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Zeljic K, Elkilany A, Supic G, et al. Vitamin D receptor gene polymorphisms association with the risk of sepsis and mortality. *Int J Immunogenet*. 2017;44:129–134. https://doi.org/10.1111/iji.12318