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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

C-reactive protein as an early marker of immune-related adverse events

Amir-Reza Abolhassani[1] · Gerold Schuler[1] · Michael Constantin Kirchberger[1] · Lucie Heinzerling[1]

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Abstract

Purpose Immune checkpoint inhibitors (ICIs) are effective against a wide variety of cancers. However, they also induce a plethora of unique immune-related adverse events (irAEs). Since for many organ systems symptoms can be unspecific, differential diagnosis with progression of disease or infection may be difficult. C-reactive protein (CRP) has been suggested as a marker for infection. The purpose of this study was to evaluate the diagnostic value of CRP in differentiating infectious causes from autoimmune side effects induced by ICIs.

Methods In order to investigate the role of CRP in irAEs, we screened our patient data base. Only events with full infectious workup were included. In total 88 events of irAEs in 37 melanoma patients were analyzed. CRP levels before and during irAEs were evaluated. Statistical analyses were conducted using the Chi-square test for categorical variables.

Results At the onset of irAE, CRP rose in 93% of cases to a mean of 52.7 mg/L (CI 35.1–70.3) from 8.4 mg/L at baseline (normal < 5 mg/L) ($P < 0.0001$). Other causes of CRP elevation including infectious diseases were excluded, and procalcitonin (PCT) levels were normal in 92% of events. Importantly, in 42% of cases CRP elevations preceded clinical symptoms.

Conclusion CRP elevation can predict the onset of irAEs in patients treated with ICIs in the absence of infectious disease.

Keywords Adverse events · C-reactive protein · Immune checkpoint inhibitors · Melanoma

Introduction

Immune checkpoint inhibitors (ICIs) are effective against a wide variety of cancers including melanoma, merkel cell carcinoma, urothelial cancer or lung cancer (Garon et al. 2015; Nghiem et al. 2016; Balar et al. 2017; Wolchok et al. 2017). However, they also induce a plethora of unique immune-related adverse events (irAEs). These occur in 70–90% of cases (Hodi et al. 2010; Brahmer et al. 2012; Topalian et al. 2012) and encompass colitis, hepatitis, endocrinopathies, pneumonitis or rarer side effects like myocarditis and neurologic side effects (Chuzi et al. 2017; Puzanov et al. 2017; Brahmer et al. 2018; Atallah-Yunes et al. 2019). When new symptoms occur during ICI therapy, other etiologies like progression of the tumor, infections, virus reactivation, or toxicity related to other drugs have to be excluded. Since for many organ systems symptoms can be unspecific differential diagnosis may be difficult.

The mainstay of treating ICI-related AEs is immunosuppression with methylprednisolone (or an equivalent) (Puzanov et al. 2017). Steroid-refractory or steroid-dependent side effects should result in prompt escalation of immunosuppression by including other immunosuppressants, such as infliximab for colitis or pneumonitis (Lankes et al. 2016; Su et al. 2019), or mycophenolate mofetil for hepatitis (Cheng et al. 2015). The majority of AEs respond well to corticosteroids and nearly all resolve with second-line immunosuppressive therapy. Because differential diagnosis is difficult and suspected irAE require immunosuppression, antibiotics are often applied to provide cover for any potential infectious focus. However, the preemptive use of antibiotics is not advisable since they might reduce diversity of the commensal microbiome and thus even diminish response to immunotherapy (Langdon et al. 2016; Derosa et al. 2018).

Michael Constantin Kirchberger and Lucie Heinzerling contributed equally to this manuscript.

✉ Lucie Heinzerling
Lucie.Heinzerling@uk-erlangen.de

[1] Department of Dermatology, Universitätsklinikum Erlangen and Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg, Ulmenweg 18, 91054 Erlangen, Germany

Organ-specific measures can guide the diagnosis of irAE; abdominal ultrasound and potentially a hepatic biopsy in case of elevated liver function tests or lab tests including electrolytes, ACTH test, fasting cortisol, TSH, fT4 for accentuated fatigue to exclude hypophysitis or hypothyroidism. In case of symptoms like fever, cough, diarrhea often infection cannot be excluded by imaging procedures or diagnosis can be delayed since the workup includes serologic (e.g. CMV-DNA in plasma) and microbiologic assessments (e.g., from bronchoalveolar lavage or blood/stool cultures) to rule out infection. However, these tests are time-consuming and often delay the initiation of immunosuppression for ICI-induced AEs. Thus, soluble markers to differentiate irAEs from infection are needed. CRP (C-reactive protein) serves as a marker for infection, most often bacterial, in approximately 80% of patients with values in excess of 10 mg/dL (100 mg/L) and in 88–94% of patients with values over 50 mg/dL (500 mg/L) (Vanderschueren et al. 2006; Le Gall et al. 2011). Elevations of CRP up to the 1000-fold of baseline value are also known to accompany acute as well as chronic inflammatory states like autoimmune disease, trauma and also malignant disease (Sproston and Ashworth 2018).

Elevated CRP levels are associated with higher mortality in patients with solid tumors as shown in a systemic literature analysis of 271 prospective and retrospective studies investigating the relationship between CRP and prognosis (Shrotriya et al. 2015). CRP expression can be due to significant tissue damage within advanced stages of cancer and as response to immunosuppressive cells such as T-regulatory lymphocytes (Tregs) and M2 macrophages in the tumor microenvironment (Ciubotaru et al. 2005; Landskron et al. 2014; Nakayama et al. 2018). In melanoma, CRP has shown to be an independent prognostic biomarker for early and advanced stage melanoma (Fang et al. 2015). However, due to its fluctuation and individual variability the significance of CRP for staging patients is limited.

Baseline and post-treatment changes in CRP levels have been identified as a promising predictive biomarker for tumor response to ipilimumab (Hopkins et al. 2017). Levels of immunological markers, particularly CRP, were assessed at baseline and weeks 4, 7, 10 and 12 after initiation of therapy. In patients with disease control CRP diminished over the course of the study, while it increased in patients with progressive disease (Simeone et al. 2014). While biological markers associated to effectiveness of ICI have been thoroughly investigated (Damuzzo et al. 2016; Jacquelot et al. 2017; Hogan et al. 2018), and research is currently focusing on factors to identify patients at a higher risk for developing irAEs, early markers for occurrence of irAEs are lacking.

CRP levels pre-therapy in combination with IL-17 and IFN-γ may predict irAE development (Callahan et al. 2011; Robert et al. 2015; Bamias et al. 2017). Nonetheless, irAEs tend to be associated with a better outcome and an improved progression-free survival implying that despite the occurrence of irAEs these patients profit from ICIs (Schadendorf et al. 2017; Indini et al. 2018; Ricciuti et al. 2018).

With the growth of the patient population under ICI therapy, optimizing outcome of induced toxicity becomes increasingly significant. The purpose of this study was to evaluate the diagnostic value of CRP in diagnosing irAEs.

Materials and methods

Potentially eligible patients were identified from the database of the skin cancer center at the University Hospital Erlangen. The following inclusion criteria were applied: (1) a diagnosis of cutaneous or uveal metastatic melanoma; (2) treatment with an anti-CTLA-4 antibody (ipilimumab), anti-PD-1 antibody (nivolumab, pembrolizumab) or a combination of these; (3) occurrence of at least 1 irAE related to treatment with ICIs; (4) sufficient blood samples to test for serum CRP levels shortly before the occurrence and during the irAEs, and (5) other causes of toxicity or infectious diseases such as pneumonia, colitis, and viral reactivation (e.g., varicella zoster, cytomegalovirus) rigorously ruled out at onset of the irAE. The exclusion criteria included: (1) patients experiencing active autoimmune disease or history of autoimmune disease; (2) history of severe hypersensitivity reaction to any monoclonal antibody; (3) treatment with corticosteroid doses exceeding physiological replacement doses before onset of irAEs, and (4) other causes of toxicity or infectious diseases such as pneumonia, colitis, and viral reactivation (e.g., varicella zoster, cytomegalovirus).

Clinical data on the disease and AEs were obtained from the electronic patient files. ICIs were administered intravenously according to standard protocols. Blood samples were collected routinely before the administration of ICIs and during the course of irAEs. CRP and procalcitonin (PCT) were measured according to laboratory standards. In patients with several irAEs with a time interval in between and available baseline CRP values for each AE, these were considered as independent events.

Prior to initiation of checkpoint inhibitor therapy, patients were instructed to recognize signs of irAEs and to report these immediately. Additionally, all patients completed a standardized questionnaire before each infusion to screen for irAEs. A physician reviewed the questionnaire and examined the individual patients before each infusion. Adverse events were graded according to the Common Terminology

Criteria for Adverse Events (CTCAE) v4.03 published by the National Institute of Health in 2010.

Correlation between adverse events (present/not present) and elevated serum CRP levels (present/not present) was assessed using the Chi-square test for categorical variables. Statistical differences between continuous CRP values were calculated with the paired sample *T* test. $P < 0.05$ was considered statistically significant. All analyses were performed with the GraphPad Prism version 5.01 software (GraphPad Software, La Jolla, CA, USA).

Results

This study analyzed a total of 88 events of irAEs in 37 patients with metastatic disease undergoing ICI treatment (Tables 1, 2). In 55 of these irAEs, data sets and event-related blood samples were complete and differential diagnoses such as infectious diseases were rigorously ruled out according to our study protocol. These were thus considered for further analysis. In 68% ($N = 25$) of patients, two or more irAEs occurred during treatment. Simultaneous irAEs in more than one organ system were observed in 38% ($N = 14$) of patients. The AEs comprised endocrine disorders (in 26% of patients), gastrointestinal disorders (20%), musculoskeletal disorders (11%), hepatitis (10%), cutaneous disorders (9%), neurological disorders (9%), general disorders (9%), pulmonal disorders (2%), renal disorders (1%), and cardiovascular disorders (1%). Severe irAEs, CTCAE grade 3/4, were noted in 15% ($N = 13$) of cases. The mean duration of onset for irAEs after initiation of ICI therapy was 114 days (range 6–812 days; Fig. 1).

Table 1 Characteristics of the patients included in this study

Age (years), *N*	
Mean	65
18–35	1
35–55	8
55+	28
Gender, *N* (%)	
Female	15 (40)
Male	22 (60)
Lactate dehydrogenase U/L	
Mean (range)	354 (151–1429)
AJCC stage cutaneous melanoma, *N* (%)	
Stage IIIC	2 (7)
Stage IV M1a	3 (10)
Stage IV M1b	4 (14)
Stage IV M1c	15 (52)
Stage IV M1d	5 (17)

SD standard deviation, *AJCC* American Joint Committee on Cancer

Table 2 Overview of all observed adverse events and severity grading according to the Common Terminology Criteria for Adverse Events (CTCAE)

Adverse events	*N*	CTCAE severity		
		Grade 1	Grade 2	Grade 3 or 4
Cardiovascular	1	0	0	1
Cutaneous	8	4	3	1
Endocrine	23	12	9	2
General disorders	8	5	3	0
Gastrointestinal	18	9	7	2
Hepatitis	9	0	4	5
Musculoskeletal	10	3	7	0
Neurologic	8	3	4	1
Pulmonal	2	0	2	0
Renal	1	0	0	1

Elevated levels of serum CRP were observed in 75% ($N = 41$) of cases prior to onset of irAEs in patients receiving antibodies to CTLA-4 and PD-1, either combined, or in sequence. The mean baseline CRP was 8.4 mg/L (CI 5.49–11.34). At an average of 4 days before the onset of AEs, the mean CRP was elevated to 52.7 mg/L (CI 35.1–70.3; Fig. 2). Elevation was measured at a range of 0–31 days before onset of AE. The AEs completely resolved after an average of 135 days after ICI therapy initiation (range 12–813); and the last follow-up CRP was evaluated after an average of 106 days after irAE and showed a mean of 11.1 mg/L (CI 6.6–15.7). Serum CRP levels at irAE compared to baseline was found to be significantly elevated ($P < 0.0001$). Interestingly, in the cases of endocrine disorders, complete reversion was not observed even though patients were symptom-free with hormone replacement therapy. Additionally, PCT was measured during the irAEs in 76% ($N = 42$) cases; the mean value was 0.15 µg/L (normal < 0.5 µg/L). PCT was found to be elevated in 8% ($N = 4$) of irAEs. The levels of CRP did not correlate with the severity of irAEs or organ system affected.

Courses of liquid markers of several exemplary patients are shown in Fig. 3. Patient 1 presented with fatigue and increasing CRP, and was diagnosed with hypophysitis at week 6. No additional immunosuppressant was administered with hydrocortisone replacement therapy. Multi-organ involvement with hepatitis, and thyroiditis was observed at week 9 accompanied by a further increase in CRP levels. Immunosuppression resulted in resolution of irAEs, with a decrease of serum CRP. Similarly, patient 2 presented with rising CRP, and autoimmune hepatitis was noted at week 12. Immunosuppressive therapy was initiated after infectious causes were ruled out. This led to a reduction in CRP levels. Patient 3 had initially experienced hypophysitis with syndrome of inappropriate antidiuretic hormone secretion,

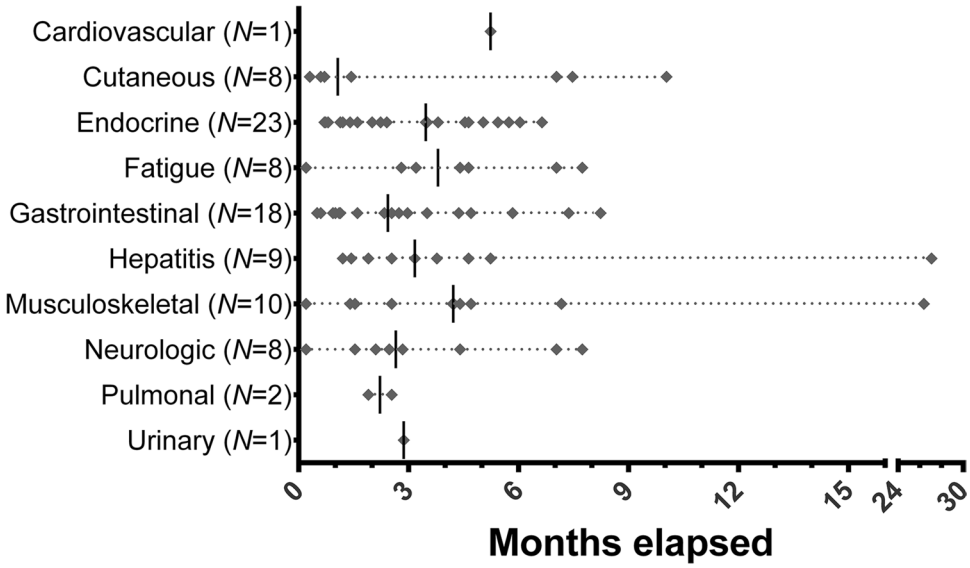

Fig. 1 Temporal occurrence of adverse events after the beginning of immune checkpoint inhibitor (ICI) therapy, as indicated by diamonds. The bar represents the time median and *N* the number of patients exhibiting the respective adverse effect

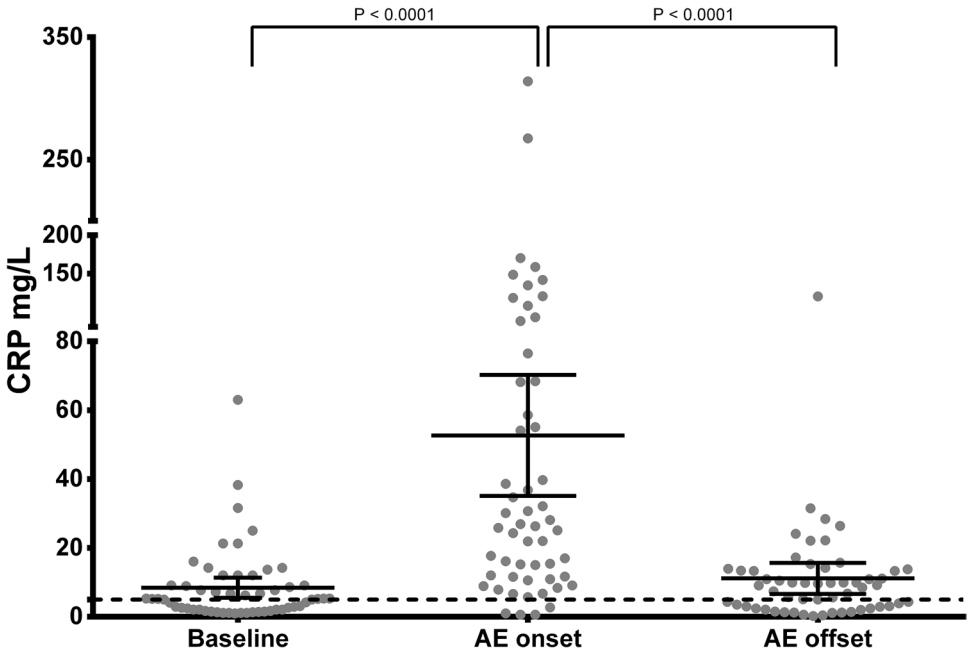

Fig. 2 C-reactive protein (CRP) values (mg/L) for all 55 immune-related adverse events (irAEs) at baseline, onset and resolution of adverse events (ULN 5 mg/L). The bars represent the median and respective 95% confidence intervals

22 days after ICI initiation. Symptoms resolved, and CRP levels normalized after initiating immunosuppression with glucocorticoids. Addison disease was noted on day 14 while immunosuppressive glucocorticoids were being gradually tapered. Reinstitution of glucocorticoids at previous doses improved the symptoms and normalized CRP levels. Patient 4 presented with autoimmune colitis 37 days after ICI initiation (CTCAE grade 3). Immunosuppression with glucocorticoids was initiated 7 days after diagnosis of the irAE. Escalating immunosuppression with infliximab was necessary due to the severity and steroid-refractory nature of the colitis; the symptoms and CRP levels subsequently resolved. Patient 5 was diagnosed with autoimmune diabetes (CTCAE grade 4) 72 days after initiating ICIs. Therapy with pembrolizumab was withheld and insulin was initiated. Interestingly, in the first 4 cases, CRP levels declined within 8 days (range 5–11 days) after initiation of glucocorticosteroids, with resolution of symptoms. In the last case, however, the irAE was managed with discontinuation of treatment and the CRP remained elevated for more than 18 days after the onset of the AE.

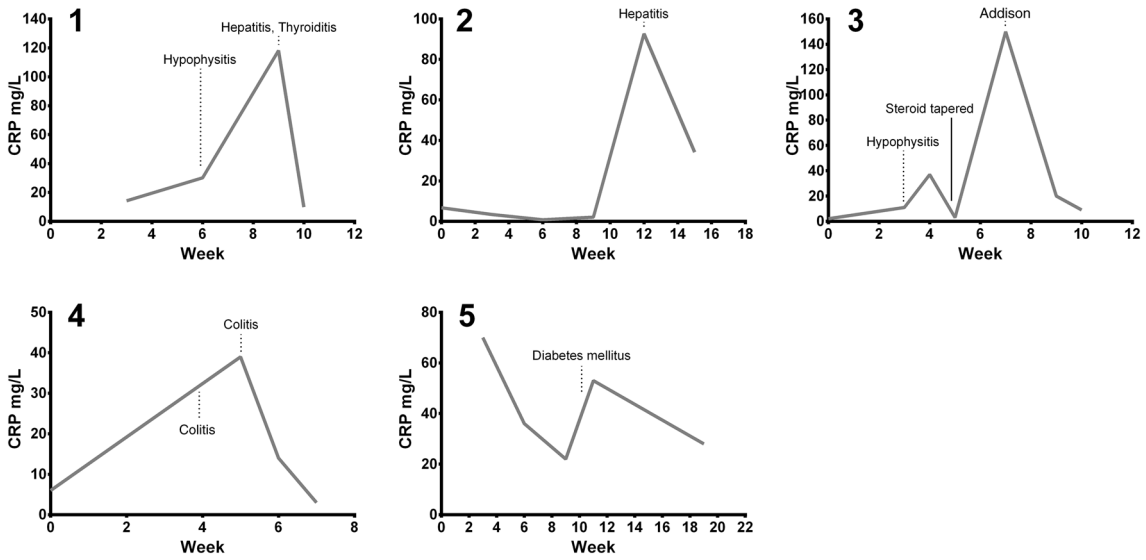

Fig. 3 C-reactive protein (CRP) values (mg/L) over time after the beginning of ICI therapy, and their correlation with the occurrence of adverse events in five representative patients (ULN 5 mg/L). The specific time of occurrence of each adverse event is indicated by a dashed line

Discussion

In this study, the correlation between elevations in CRP levels and the occurrence of ICI-induced toxicity was assessed in patients with advanced melanoma. We could show that CRP represents an early marker for irAE and additionally possesses the potential of an early marker for recurrence of irAE while tapering corticosteroids. Since CRP is a non-specific marker indicating infections, inflammatory conditions or high tumor burden (Haas et al. 2013; Sproston and Ashworth 2018) it has to be assessed in the context and is not diagnostic on its own. In several cancer entities, CRP elevation was associated with poor prognosis such as head and neck squamous cell carcinoma, pancreatic cancer, and melanoma (Haas et al. 2013; Tarhini et al. 2014; Andersson et al. 2014; Heppt et al. 2017a). It has also been shown to be associated with response to ICI with improved diseases control and survival (Simeone et al. 2014). Additionally, the normalization of an elevated CRP at baseline in the course of treatment is associated with significantly better overall survival (Okuhira et al. 2018).

The prediction of irAEs has been an important topic in research with some recent findings. Patients with increased IL-17 levels might be more likely to develop immune-mediated AEs (Joshi et al. 2011; Stucci et al. 2017). Besides implications on treatment response, the gut microbiota can influence the probability and onset of AEs (Vétizou et al. 2015; Roy and Trinchieri 2017). Pro-inflammatory intestinal microenvironments lead to Th-17 cell expansion and are associated with an increased risk of colitis. Additionally, increased eosinophil counts are associated with the occurrence of AEs in melanoma patients treated with ipilimumab (Schindler et al. 2014). In terms of body composition, sarcopenia has been found to be associated with high-grade AEs in patients treated with ipilimumab for metastatic melanoma (Daly et al. 2017). However, these predictors have not entered standard clinical care routines. The relevance of CRP in the prediction or diagnosis of irAEs has not been studied until now. While studies to characterize the risk of occurrence of irAEs exist (Hopkins et al. 2017) to our knowledge, this is the first study to demonstrate an association between early CRP elevation and the occurrence of checkpoint inhibitor-induced toxicity. Precise and early diagnosis of irAEs in the setting of ICI therapy requires experience and a thorough assessment of the differential diagnoses, particularly tumor progression and infectious diseases. CRP elevation does not necessarily indicate an infectious etiology for the patient's symptoms. In patients presenting with rising CRP and low PCT levels, and no evidence of infectious diseases (negative cultures and serology) it can be predictive of an irAE. Other biomarkers may be used to support the diagnosis. Additionally, recurrence of irAE upon tapering steroids is a frequent phenomenon. Potentially, monitoring of CRP could guide the speed of steroid reduction. However, in several inflammatory diseases such as rheumatoid arthritis, steroid treatment can lead to a decrease of CRP values but not to a significant disease modification (Mysler et al. 2004). To what extent this is transferable to the management of irAEs remains unclear.

Our study has several shortcomings. Firstly, the study design was retrospective; therefore, a control group without AEs was not included. Secondly, simultaneous infectious diseases could have possibly been overlooked despite

thorough workups. PCT had also been assessed to potentially screen for nonspecific infectious diseases. Notably, the mean PCT was 0.15 µg/L, which was lower than the established cut-off limits for several infections (Schuetz et al. 2011). Lastly, the number of patients ($N=37$) in this study was small; still, a total of 55 cases of irAEs were assessed in this cohort. Furthermore, data from large prospective clinical trials may elaborate the predictive role of CRP for irAE and be able to suggest thresholds or the combination of multiple markers.

The scope for the clinical use of ICIs is expanding and thus predicting and identifying irAEs early is an unmet need. The plethora of potential pathways and biomarkers associated with tumor microenvironments and ICIs is likely to yield multiple predictors of toxicity and response (Martens et al. 2016; Weide et al. 2016; Heppt et al. 2017b; Hopkins et al. 2017). Our study provides important insights into the significance of early CRP elevation in ICI therapy-induced AEs. Measurement of CRP is readily available and can help to monitor patients during therapy, events of irAE and the subsequent taper of steroids and can thus contribute to better patient management under immunotherapy. We suggest prospective measurement of CRP in future trials to determine the exact timing of CRP elevation with respect to irAEs.

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Compliance with ethical standards

Study participants gave written consent for anonymous analyzation of data. This study was approved by the institutional review board of the medical faculty of the University Erlangen and all procedures performed in studies were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declarations.

Conflict of interest The authors declare that they have no conflict of interest.

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