Erythrocyte Sedimentation Rate in Patients with Renal Insufficiency and Renal Replacement Therapy

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Abstract

Background: The erythrocyte sedimentation rate (ESR) is a simple laboratory diagnostic tool for estimating systemic inflammation. It remains unclear, if renal function affects ESR, thereby compromising its validity. This pilot study aims to compare prevalence and extent of ESR elevations in hospitalized patients with or without kidney disease. In addition, the impact of renal replacement therapy (RRT) modality on ESR was determined.

Methods: In this single-center, retrospective study, patients were screened for ESR values. ESR was compared in patients with and without renal disease and/or RRT. In addition, ESR was correlated with other inflammatory markers, the extent of renal insufficiency and clinical characteristics.

Results: A total of 203 patients was identified, showing an overall elevated ESR in the study population (mean 51.7±34.6 mm/h). ESR was significantly increased in all patients with severe infection, active vasculitis or cancer, respectively, independent from renal function. Interestingly, there was no difference in ESR between patients with and without kidney disease or those having received a prior renal transplant or being on hemodialysis. However, ESRD patients treated with peritoneal dialysis presented with a significantly higher ESR (78.3±33.1 mm/h, $p<0.001$), while correlation with other inflammatory markers was not persuasive.

Conclusions: We showed that ESR: (1) does not differ between various stages of renal insufficiency; (2) may be helpful as a screening tool also in patients with renal insufficiency; and (3) is significantly increased in ESRD patients on peritoneal dialysis *per se*, while it seems not to be affected by hemodialysis or renal transplantation (see graphical abstract as supplementary material).

Background

Determination of the erythrocyte sedimentation rate (ESR) is a simple laboratory test for estimating systemic inflammation. Easy availability, simple implementation and low costs are making ESR an interesting tool in clinical practice. Acute phase proteins deplete the negative charge between erythrocytes, leading to a faster agglomeration of erythrocytes and increase of the ESR (1). Common diseases associated with ESR elevations are severe infectious diseases, tumors, vasculitis and possibly severe anemia (2). Low sensitivity and specificity however impair its validity to point out an inflammatory response, while an extremely elevated ESR is considered to be suggestive for multiple myeloma or polymyalgia rheumatica and giant cell arteritis (3) ; in fact, these disorders can be easily ruled out by a normal ESR (1). Classically, ESR is assessed after 1 and 2 hours, although it is sufficient to determine only the 1 hour value. In the literature, normal ESR values are 6–20 mm/h in women and 3–15 mm/h in, while an ESR > 70–100 mm/h is interpreted as an extremely elevated ESR (1).

Several publications suggest that renal disease may be another cause of ESR elevations (4, 5). Chronic kidney disease (CKD) affects 10–15% of the worldwide population (6), the global prevalence of end-stage renal disease (ESRD) with need of renal replacement therapy (RRT) is estimated at 0.07% (7). In Europe,

hemodialysis (HD) is by far the most common RRT (82%), followed by peritoneal dialysis (PD, 13%) and kidney transplantation (TX, 5%) (8). Signs of low-grade inflammation are commonly observed in CKD patients as well as in dialysis patients, (9), believed to be the combined result of several factors, including increased production and decreased clearance of pro-inflammatory cytokines, as well as acidosis and oxidative stress caused by uremia (10). Contact with bio-incompatible dialysis membranes may play an additional role (11).

So far, data for ESR in CKD patients and those being on RRT are insufficient or inconsistent, and the diagnostic benefit of ESR remains unclear. Furthermore, the effect of comorbidities has not been studied. *Bathon et al.* found an increased ESR in 93% of HD patients, concluding that determination of ESR is useless in this patient group, while *Brouillarid et al*. found only a normal to mildly increased ESR, values comparable to the general population (12, 13). Personal observations in our clinical practice suggest a moderately increased ESR in HD patients, independent from the underlying disease and comorbidities, but pointed to a significantly elevated ESR in patients with PD. So far, data on ESR in acute kidney injury (AKI) are sparse and mainly case-related.

The objective of this retrospective pilot study was: (1) to determine a possible correlation between ESR and the extent of renal insufficiency; (2) to see if ESR differs between patients with and without CKD; (3) to analyze if RRT modes affect ESR; and (4) to evaluate a potential correlation between ESR and other laboratory parameters as well as comorbidities.

Methods

We provide a cross sectional, descriptive study of patients admitted to the Department of of Nephrology at the University Hospital in Marburg, Germany. Inpatients between January 2019 and January 2021 were screened for an ESR value available at time of admission. Patients with and without kidney disease including those having any RRT were included. Eligible patients were classified into five groups: patients without renal disease (group 1, No-RD), patients with acute and chronic kidney disease at various stages (group 2, RD), ESRD patients receiving hemodialysis (group 3, HD), peritoneal dialysis (group 4, PD) or renal transplant recipients (group 5, TX).

ESR was determined by the Westergren method in an S-sedivette by Sarstedt, being read after 60 minutes of sedimentation at room temperature. Increased ESR elevation was defined as ≥ 25 mm/1h, values ≥ 80 mm/1h were considered to be extremely elevated. ESR values were correlated with the following laboratory parameters: C-reactive protein (CRP), leucocytes, creatinine, estimated glomerular filtration rate (eGFR; as determined by the MDRD formula), urea, hemoglobin, and protein. Additionally, information on the underlying renal disease and comorbidities was assessed. Data were analyzed using SPSS and Excel; correlation between BSG and laboratory parameters and comorbidities, respectively, including calculation of a correlation coefficient was analyzed in a linear model regarding. One-way ANOVA and Tukey post-hoc analysis were used to compare different groups. Normal distribution was assessed by Shapiro-Wilk test, homogeneity of variances was asserted using Levene's test. Data are represented as mean ±

standard deviation, unless otherwise stated. The study was given a waiver by the Ethics Committee, Philipps University, Marburg, Germany.

Results

Overall, 203 patients (mean age 63.1 ± 18.6 years; median 65.0 years; range 18–95 years) were included in this study with comparable numbers of male (n = 104, 51.2%) and female patients (n = 99, 48.8%, Table 1). Eighty-two individuals had CKD stage 1–5, of whom 36 presented with additional AKI, 9 patients showed AKI without preexisting CKD. Hypertensive and/or diabetic nephropathy was the predominant cause for CKD and ESRD (41,8%) followed by glomerulonephritis (21,5%). The remaining individuals had a variety of underlying renal diseases. Seventy-six patients had ESRD with 28 patients receiving HD, 19 were treated with PD and 29 patients had a kidney transplant as RRT; forty-five patients had no kidney disease. Arterial hypertension was the most common comorbidity with highest prevalence in patients with RRT. HD patients represented the oldest population (70.1 ± 13.7 years), while PD patients were significantly younger (48.3 ± 11.8 years). Kidney transplant recipients were the longest time on RRT (151.5 ± 203.5 months). Mean ESR of the total population was elevated (51.8 ± 34.6 mm/h, range 0-150 mm/h): ESR was normal in 54 patients (< 25 mm/h), while 54 patients had an extremely elevated ESR (> 80 mm/h).

Table 1
Baseline characteristics of the study population

	No-RD	RD	HD	PD	TX	Total
number (n)	45	82	28	19	29	203
male/female	20/25	39/43	20/8	12/7	13/16	104/99
age (years)	60.7 ± 20.3	67.5 ± 18.5	70.1 ± 13.7	48.3 ± 11.8	57.3 ± 17.1	63.1 ± 18.6
diabetes	8 (17.8%)	23 (28.0%)	14 (50%)	5 (26.3%)	10 (34.5%)	60 (29.6%)
hypertension	30 (66.7%)	63 (76.8%)	28 (100%)	19 (100%)	24 (82.8%)	164 (80.8 %)
coronary heart disease	8 (17.8%)	26 (31.7%)	15 (53.6%)	4 (21.0%)	6 (20.7%)	59 (29.1%)
vasculitis	3 (6.7%)	4 (4.9%)	2 (7.1%)	1 (5.2%)	3 (10.3%)	13 (6.4%)
GCA/PMR	4 (8.9%)	4 (4.9%)	0 (0%)	0 (0%)	0 (0%)	8 (3.9%)
active tumor	3 (6.7%)	9 (11.0%)	2 (7.1%)	0 (0%)	3 (10.3%)	17 (8.4%)
severe infection	15 (33.3%)	18 (21.9%)	7 (25.0%)	0 (0%)	8 (27.5%)	48 (23.7%)
time from start RRT (months)	n/a	n/a	15.6 ± 16.9	31.0 ± 32.8	151.5 ± 203.5	26.7 ± 92.6

GCA; giant cell arteritis; PMR, polymyalgia rheumatic; RRT, renal replacement therapy; n/a, not applicable

Assessment of ESR in the five different subject groups showed comparable values in the No-RD group (48.2 ± 30.1 mm/h), the RD group (51.5 ± 35.3 mm/h), the HD group (45.8 ± 31.8 mm/h) and the TX group (46.4 ± 37.1 mm/h), but ESR was significantly higher in PD patients (78.3 ± 33.1 mm/h, $p < 0.001$) with only two outliers in the latter population (Fig. 1). Equal variances being assumed ($p = 0.237$ based on mean), ESR was normally distributed for No-RD and PD, but not for RD, HD and TX ($\alpha = 0.05$). The level of ESR differed statistically significant for the different populations, ($F(4.198) = 3.44$, $p = 0.01$, $\eta^2=0.065$). Tukey post-hoc analysis revealed a significant difference ($p < 0.05$) between ESR levels of the PD group individually compared with all other groups: PD vs. No-RD (30.02, 95%-CI[4.55–55.39]), PD vs. RD (26.81, 95%-CI[3.11–50.51]), PD vs. HD (32.44, 95%-CI[4.77–60.11]), PD vs. TX (31.85, 95%-CI[4.37–59.33]). In fact, there was a significant difference comparing the PD patients with all other groups (78.3 ± 33.1 mm/h vs. all other patients 49.0 ± 33.7 mm/h, $p < 0.001$). Most biochemical parameters (leucocytes, C-reactive protein, protein, hemoglobin) did not differ significantly between the groups (Table 2). As expected, urea was significantly higher in patients with RD or RRT when compared to patients without RD (96.1 ± 73.3 mg/dL vs. 48.3 ± 68.4 mg/dL; $p < 0.001$). Of note, ESR significantly correlated with CRP in all

subgroups but not in patients with HD or PD as RRT (Table 3). As expected, ESR was higher in patients with vasculitis, active tumors, giant cell arteritis and polymyalgia rheumatica or multiple myeloma; however, this was not true for the PD group (data not shown).

Table 2
Laboratory parameters of the study participants (n = 203)

	No-RD	RD	HD	PD	TX	Total
ESR (mm/h)	48.2 ± 30.2	51.45 ± 35.3	45.8 ± 31.8	78.3 ± 33.1	46.4 ± 37.1	51.7 ± 34.6
leucocytes (G/µL)	8.7 ± 3.8	8.3 ± 4.0	7.0 ± 2.2	8.9 ± 2.9	7.9 ± 3.3	8.2 ± 3.6
C-reactive protein (mg/L)	71.0 ± 84.6	40.2 ± 56.4	61.0 ± 76.5	38.1 ± 36.4	54.3 ± 92.0	51.6 ± 71.3
creatinine (mg/dL)	0.7 ± 0.2	2.7 ± 2.2	6.1 ± 2.3	10.9 ± 4.6	2.6 ± 1.3	3.7 ± 3.9
urea (mg/dL)	48.3 ± 68.4	109.5 ± 82.9	114.5 ± 59.9	111.7 ± 32.1	101.9 ± 52.1	95.7 ± 73.3
protein (g/L)	64.0 ± 8.8	62.6 ± 10.3	61.7 ± 7.5	66.1 ± 5.4	66.7 ± 7.9	63.7 ± 9.0
hemoglobin (g/dL)	11.4 ± 2.2	11.4 ± 2.7	9.9 ± 2.1	10.0 ± 1.4	10.6 ± 2.1	11.2 ± 1.7
Data are depicted as mean ± SD						

Table 3
Correlation of ESR with laboratory parameters

	No RD	RD	HD	PD	NTX	Total
C-reactive protein	0.471**	0.308**	0.253	0.428	0.534**	0.338**
leucocytes	0.156	0.140	-0.007	0.219	-0.014	0.141*
Creatinine	-0.05	0.27	-0.040	0.212	0.345	0.221
urea	0.024	0.216	-0.150	0.071	0.201	0.134*
protein	0.047	-0.151	0.093	-0.076	-0.096	-0.044
hemoglobin	-0.258	-0.300**	-0.392*	-0.501*	-0.567**	-0.024
time from start RRT	n/a	n/a	0.007	-0.017	0.315	0.086
Data are depicted as Pearson correlation coefficient r; *significant correlation (p < 0,05, 2-tailed);						
**significant correlation (p < 0.01, 2-tailed); n/a, not applicable						

Discussion

ESR is an unspecific, but easy, quick and cheap diagnostic test to screen for systemic inflammation. Despite its lack of specificity, an elevated ESR may point to an underlying disorder and/or inflammatory problem, while an extremely elevated ESR is helpful in establishing the diagnosis of polymyalgia rheumatica and giant cell arteritis, or multiple myeloma, respectively. So far, there is conflicting data whether chronic kidney disease affects the ESR, thereby compromising its validity. Indeed, previous publications suggest a general ESR increase in CKD patients (12, 14), possibly caused by decreased clearance of pro-inflammatory cytokines, oxidative stress, metabolic acidosis but also by dialysis-related factors, such as extracorporeal membranes, impurities in dialysis water or foreign material, like hemodialysis or peritoneal dialysis catheters. Chronic inflammation is considered to have an impact on cardiovascular mortality (15); in fact, patients with CKD and ESRD are at significantly higher risk for cardiovascular events (10, 16). A recent publication claimed an extremely elevated ESR in 1 out of 3 patients with ESRD (17). Conversely, other studies could not find any significant higher ESR values in CKD patients (13). Furthermore, patients with AKI consistently have a likelihood for impaired outcome with respect to mortality and kidney function, independent from comorbidities (18). It is conceivable that an associated inflammatory response may contribute to this.

In the present study, we investigated ESR in 45 patients without and 158 patients with a renal disease, including those being on RRT. In contrast to our previous impressions, we could not find any evidence for significant higher ESR values in patients with renal disease when compared to those with normal kidney function, suggesting that ESR may also be used as a valuable screening tool in this population. Prevalence of an extremely elevated ESR is comparable in patients with and without renal insufficiency, including ESRD patients with HD or a kidney transplant. However, ESR values in the PD group were ordinarily extremely elevated. Prior data suggest that chronic inflammation caused by a combination of systemic and intraperitoneal inflammation could lead to elevated levels of acute phase proteins, thereby also raising the ESR (9). Conceivably, intraperitoneal catheters, exposure to endotoxins and high glucose concentrations *via* the dialysate and complement activation result in an inflammatory response, as previously suggested by elevated CRP levels in 12–65% of PD-patients (19). However, we were unable to confirm significantly higher CRP levels in the PD group, rather showing a trend to levels below average (38.1 ± 36.4 mg/l vs. 51.6 ± 71.3 mg/l; n.s.). These findings are supported by a study of *Haubitz et al.*, showing chronically elevated CRP levels in ESRD patient with HD but not in those with PD (20). However, comparing HD- and PD-patients may be problematic due to different baseline characteristics, e.g., PD patients in general are significantly younger and have less comorbidities than HD patients. In fact, it would be interesting to see if switching the RRT mode has an effect on ESR levels.

Kidney transplant recipients are considered to have less acute-phase-proteins, possibly as a result from the immunosuppressive therapy (11). Nevertheless, our study does not confirm a notable impact on ESR. Of interest, we noticed a significant negative correlation between ESR and hemoglobin levels in all renal patients (correlation coefficient − 0,30, $p < 0.01$), while this could not be seen in patients without renal disease, consistent with previous studies (21, 22). It is possible that renal anemia contributes to this observation since ESR is affected by increased velocity of the upward plasma flow and faster fallout of red blood cells (23). Neither etiology of the renal disease nor time on RRT correlated with ESR. Leucocytes

and CRP showed a weak correlation only in the No-RD and RD group ($p < 0.001$), while this could not be seen in patients on RRT (n.s.). This is consistent with data from *Panichi et al.*, showing a stronger correlation in patients without CKD ($r = 0.46$ in patients with a creatinine clearance > 20 ml/min vs. $r = 0.32$ in those with a creatinine clearance < 20 ml/min, 19).

Limitations of the present study are the retrospective study design, the monocentric data acquisition, as well as missing ESR values in a large number of individuals, thereby minimizing the eligibility for the study. In addition, data were assessed only in hospitalized patients, possibly tampering the transferability of the study results on an outpatient population. An elevated CRP in most of the patients (70,2 %) may suggest an acute problem. Thus, data from a healthy control group, patients with defined stable CKD or those with ESRD and ambulatory RRT would be interesting. Furthermore, a longitudinal study design with repeatedly measured ESR in the same patient population could clarify if elevated ERS levels are rather due to an acute situation or result from chronic inflammation.

Conclusions

In conclusion, we showed that ESR: (1) does not differ between various stages of renal insufficiency; (2) can be used as a screening tool without restriction in patients with renal insufficiency; and (3) is significantly increased in ESRD patients on PD, while it seems not to be affected by HD and in renal transplant recipients. Further studies would be helpful to understand these observations and to define the possible role of RRT choice in ESRD.

Abbreviations

ESR erythrocyte sedimentation rate

RRT renal replacement therapy

CKD chronic kidney disease

ESRD end-stage renal disease

HD hemodialysis

PD peritoneal dialysis

TX kidney transplantation

AKI acute kidney injury

CRP C-reactive protein

eGFR estimated glomerular filtration rate

Declarations

Ethics approval and consent of participate:

The ethics committee of the University of Marburg was notified regarding this study. They ruled, that according to the university standard no formal approval was necessary and that consent from participants was not required as this was a retrospective study using anonymized data collected for routine clinical practice.

Consent to publication:

Not applicable.

Availability of data and material:

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest:

The authors declare that they have no competing interest.

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Not applicable.

Authors' contributions:

AB, data collection and analysis, first and final draft of manuscript and review; LD, data collection; JH, critical review of manuscript; SK, study design and critical review of manuscript ; CSH; study idea and over-sight; data analysis and interpretation; manuscript revision

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Consent for publication:

All authors gave consent to publication of this work.

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Figures

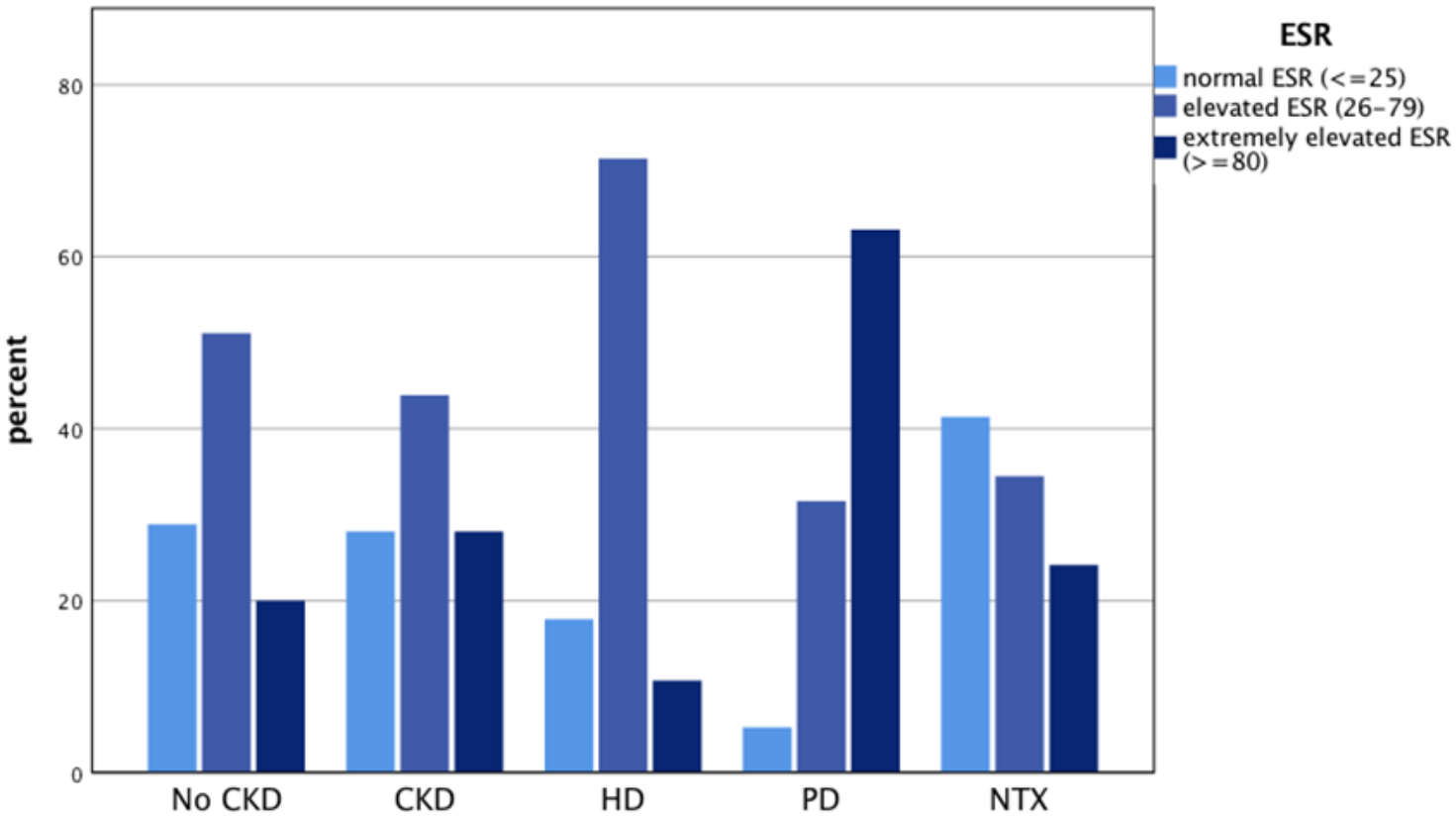

Figure 1

Prevalence of ESR levels (normal, elevated, extremely elevated)

Supplementary Files

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