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Influence of the serum levels of immunoglobulins on clinical outcomes in medical intensive-care patients

Introduction

For more than 30 years there has been an ongoing debate about the effects of the application of intravenous immunoglobulins (IVIg) on the clinical outcomes of patients with severe infections. This research focuses on sepsis, as its incidence has been increasing in the past years, and despite all therapeutic attempts, the case fatality rate is still unacceptably high. Intravenous polyvalent immunoglobulins have seemed to be a promising therapy, but several clinical trials and meta-analyses which addressed the role of IVIg treatment in severe sepsis and septic shock came to controversial results: several studies have shown a significant reduction of mortality in septic patients, especially in those treated with IgM-enriched preparations [9, 10, 20, 23, 28] whereas in other trials and meta-analyses no such effect was found [6, 33]. Besides different methodologies, definitions of sepsis, and type of the IVIg used, the different results might be due to the relatively small number of patients included in most of the trials [17].

It seems reasonable to assume that endogenous immunoglobulin (Ig) levels before treatment could have an impact on the patients' response to immunomodulatory therapy and thereby on clinical outcomes. Two recently published studies have analyzed the endogenous levels of circulating Ig in patients during septic shock in order to reveal the relationship between Ig plasma levels and outcomes [26, 29]. In both studies diminished circulating immunoglobulin G (IgG) and immunoglobulin M (IgM) concentrations were found at the beginning of septic shock. Furthermore, in the study published by Taccone et al., patients with community-acquired septic shock and hypo-IgG had greater vasopressor requirements were more likely to develop acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and also had a higher mortality rate [26]. On the other hand in a recently published study by Vennet et al. neither mortality nor morbidity was significantly associated with hypo-IgG or hypo-IgM [29]. Furthermore, in a retrospective analysis of patients with severe sepsis and septic shock Päsler et al. found no negative influence of low IgG serum levels on 28-day mortality, but the tendency of an increased mortality in patients with low serum IgM levels [16] was present. However, as these studies only contained a small number of patients (Taccone 21 patients, Venet 62 patients, and Päsler 84 patients), larger trials would be desirable to further clarify this issue.

Although sepsis was the main focus of the studies mentioned above, the effect of immunoglobulins is not limited to the course of sepsis. Immunoglobulin A (IgA), for example, has been shown to inhibit several inflammatory diseases such as asthma and glomerulonephritis [24]. Patients with selective IgA deficiency are known to show an increased rate of infections of the respiratory and gastrointestinal tract as well as allergic disorders including arthritis, chronic active hepatitis, ulcerative colitis, and Crohn's disease [1]. IgG subclass deficiency can be associated with recurrent infections of the upper and lower respiratory tracts [1]. Additionally, it has been reported that IgM mediates atheroprotection by neutralizing proinflammatory responses of endothelial cells and macrophages [1].

Since inflammation and immunoresponse play a major role in the onset and development of many diseases, endogenous plasma levels of immunoglobulins could be useful markers of prognostic importance not only in septic patients, but in critically ill patients in general. However, this hypothesis has not yet been analyzed in the clinical setting.

The objective of this study was to examine the correlation between circulating levels of IgG, IgM, and IgA, respectively, in medical patients at intensive care unit (ICU) admission and the subsequent clinical course in these critically ill patients.

Patients and methods

This prospective, noninterventional study was realized in the Medical Intensive Care Unit (ICU) (13 beds) at the University Hospital Halle (Saale), Germany. During the observational period from May 2012 until April 2013, 618 Patients were treated at this ICU. In 340 patients, levels of IgG, IgM, and IgA were measured on arrival at ICU according to local standards. Patients

Table 1 Demographic data of the study population

	Total (*N* = 340)	Sepsis (*N* = 83)	Respiratory failure (*N* = 32)	Cardio-vascular diseases (*N* = 86)	Acute renal failure (*N* = 15)	Post-operative condition (*N* = 19)	State after CPR (*N* = 50)	Gastro-intestinal diseases (*N* = 29)	Others (*N* = 26)
Age	65 ± 15	62 ± 14	64 ± 17	67 ± 16	63 ± 15	72 ± 10	69 ± 13	62 ± 17	56 ± 18
Men	210 (61.8 %)	54 (65.1 %)	16 (50 %)	55 (64 %)	11 (73.3 %)	12 (63.2 %)	29 (58 %)	18 (62.1 %)	15 (57.7 %)
Women	130 (38.2 %)	29 (34.9 %)	16 (50 %)	31 (36 %)	4 (26.7 %)	7 (36.8 %)	21 (42 %)	11 (37.9 %)	11 (42.3 %)
Height (m)	1.71 ± 0.09	1.72 ± 0.09	1.7 ± 0.1	1.7 ± 0.09	1.72 ± 0.07	1.7 ± 0.1	1.7 ± 0.11	1.72 ± 0.09	1.73 ± 0.11
Weight (kg)	84.9 ± 22.1	87.7 ± 26.4	85.8 ± 21.1	83 ± 18	86.2 ± 29.6	81.5 ± 15.1	86.1 ± 24.4	82.3 ± 21.1	83.6 ± 16.7
BMI	29.1 ± 7.7	29.7 ± 9	29.5 ± 7.8	28.5 ± 6.2	28.7 ± 8.4	27.9 ± 3.6	30.7 ± 10	27.6 ± 6	28 ± 5.6
APACHE II score	24.7 ± 9.7	28.1 ± 8.3	24.9 ± 9.9	20.3 ± 9.8	26.6 ± 8.9	18.9 ± 9.5	30.5 ± 8.1	22.9 ± 8.8	21 ± 9.2
History of hypertension	197 (58.1 %)	40 (48.2 %)	20 (62.5 %)	57 (66.3 %)	13 (86.7 %)	14 (73.7 %)	27 (55.1 %)	12 (41.4 %)	14 (53.8 %)
Diabetes	125 (36.9 %)	34 (41 %)	12 (37.5 %)	33 (38.4 %)	10 (66.7 %)	5 (26.3 %)	16 (32.7 %)	7 (24.1 %)	8 (30.8 %)
Chronic dialysis	13 (3.8 %)	5 (6 %)	0	6 (7 %)	0	1 (5.3 %)	0	1 (3.4 %)	0
CHD	127 (37.5 %)	21 (25.3 %)	7 (21.9 %)	48 (55.8 %)	5 (33.3 %)	11 (57.9 %)	24 (49 %)	6 (20.7 %)	5 (19.2 %)
State after stroke	33 (9.7 %)	7 (8.4 %)	3 (9.4 %)	7 (8.1 %)	2 (13.3 %)	4 (21.1 %)	6 (12.2 %)	1 (3.4 %)	3 (11.5 %)
Heart failure	89 (26.3 %)	14 (16.9 %)	3 (9.4 %)	33 (38.4 %)	8 (53.3 %)	9 (47.4 %)	17 (34.7 %)	2 (6.9 %)	3 (11.5 %)
Pulmonary disease	55 (16.2 %)	17 (20.5 %)	15 (46.9 %)	12 (14 %)	2 (13.3 %)	1 (5.3 %)	2 (4.1 %)	3 (10.3 %)	3 (11.5 %)
Cancer	38 (11.2 %)	14 (16.9 %)	4 (12.5 %)	6 (7 %)	4 (26.7 %)	0	6 (12.2 %)	1 (3.4 %)	3 (11.5 %)

BMI body mass index, *CHD* coronary heart disease, *APACHE* acute physiology and chronic health evaluation, *CPR* cardiopulmonary resuscitation

whose Ig serum levels were not measured on arrival at ICU were excluded from the study.

Depending on the main admission diagnosis, all patients were prospectively assigned to one of eight different diagnosis groups by the treating physician based on clinical judgment (sepsis, respiratory failure, cardiovascular diseases, acute renal failure, postoperative condition, state after cardiopulmonal resuscitation, gastrointestinal diseases, others). In all patients demographic data as well as preexisting chronic diseases were recorded (see **Table 1**). The study was conducted in accordance with the standards of the local ethics committee of the Martin Luther University Halle-Wittenberg.

The patients' severity of disease was evaluated by acute physiology and chronic health evaluation (APACHE II) score [8].

All laboratory analyses were part of the ICU routine treatment and were performed by the local laboratory of the University Hospital Halle (Saale), Germany. Immunoglobulin levels on admission were measured by immunoturbidimetry (Beckman & Coulter DxC800).

Prospectively defined clinical endpoints of this observational study were ICU mortality, need for invasive mechanical ventilation, need for renal replacement therapy (RRT), substitution of coagulation factors during ICU stay (fresh frozen plasma or prothrombin complex), and need for red cell transfusion during ICU stay.

The concept of this study was submitted to the ethics committee of the Martin Luther University Halle-Wittenberg.

Due to the study's noninterventional design the need for patient consent was waived.

Statistics

SPSS (version 21) for Mac was used for statistical analyses. For all recorded metric variables descriptive statistics were calculated with the assumption of normal distribution.

A logistic regression model was computed to evaluate the influence of the immunoglobulin serum levels on dichotomous outcomes (survival, RRT, mechanical ventilation, substitution of coagulation factors, and red cell transfusion), with APACHE II score on admission included as a potential confounder. Analysis of variance (ANOVA) was used to test differences between multiple groups, followed by post hoc testing (Bonferroni).

A value of p less than 0.05 was considered statistically significant.

Results

In 340 out of 618 patients that were admitted to our ICU within 1 year, levels of IgG, IgM, and IgA were measured on arrival. Clinical data for these patients is shown in **Table 1**.

Table 2 shows the mean serum levels of the immunoglobulins depending on the different admission diagnoses.

Table 3 shows the patients outcome separated by admission diagnoses.

As seen from **Table 4**, a significant difference in IgM levels was found between men and women whereas no significant differences regarding immunoglobulin levels could be detected in different age groups. Additionally, we found no correlation between low Ig levels and hypoalbuminemia (not shown) as described before [26, 29].

In order to evaluate the prognostic value of the Ig serum levels, several approaches

were used. First, the mean Ig levels between surviving and non-surviving patients were compared (**Fig. 1**) but no difference could be detected. Additionally, logistic regression models were established to analyze the influence of the Ig levels on the predefined binaric outcomes (mortality, RRT, invasive ventilation, substitution of coagulation factors, and red cell transfusion) both in a univariate way (data not shown) as well as with the consideration of APACHE II score as a potential confounder (**Table 5**). In these regression models, the entire cohort of all patients was analyzed as well as two independent subgroups of patients: the first subgroup contained all patients suffering from sepsis or respiratory failure whereas the second subgroup contained patients with cardiovascular diseases. As seen from **Table 4**, no effect of the Ig levels on mortality could be detected in any of the groups. However, when looking at patients who were admitted to the ICU because of cardiovascular diseases we found that a low serum level of IgG was significantly linked to an increased risk of mechanical ventilation (odds ratio 0.794; $p = 0.037$). On the contrary, in patients suffering from sepsis or respiratory failure high initial IgM serum levels were significantly associated with more frequent need for substitution of coagulation factors (odds ratio 2.761; $p = 0.039$)—an effect that could also be observed in the overall study population (odds ratio 1.886; $p = 0.011$). Furthermore, we found that patients with acute renal failure had significantly higher IgA levels than patients in all other groups (see **Table 2**).

Discussion

Although the important role of endogenous immunoglobulins as part of the host defense in acute infections is beyond doubt, the question whether or not the therapeutic administration of Ig preparations might also have beneficial effects has been discussed controversially.

Circulating Ig levels are often diminished after severe infections and in the lower normal range in patients with sepsis [31, 32]. In a recently published study, survivors of sepsis showed a greater generation of IgM than non-survivors [5].

Abstract · Zusammenfassung

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Influence of the serum levels of immunoglobulins on clinical outcomes in medical intensive-care patients

Abstract

Introduction. Endogenous immunoglobulins (Igs) are of fundamental importance in the host defense after microbial infections. However, the therapeutic administration of intravenous IgG (IVIgG) has not yet been shown to improve clinical outcomes in patients suffering from sepsis, and in the case of IgM-containing preparations (IVIgGMA) the positive evidence is only weak. Recently published studies implicate that Ig levels on admission could have an impact on the patient's response to IVIg treatment and on outcomes of critically ill patients.

Methods. In this noninterventional study, the serum levels of IgG, IgM, and IgA were determined in 340 medical patients on ICU admission, and clinical outcomes were prospectively recorded (ICU mortality, need for renal replacement therapy (RRT), need for mechanical ventilation, substitution of coagulation factors, and amount of red cell transfusions). Patients were prospectively grouped according to their main reason for ICU admission (sepsis, respiratory failure, cardiovascular diseases, acute renal failure, postoperative condition, state after cardiopulmonal resuscitation, gastrointestinal diseases, and others).

Results and discussion. There was no correlation between the Ig levels on admission and ICU mortality neither in the total cohort of medical ICU patients nor in any prespecified subgroup. However, in a logistic regression model that was adjusted for APACHE II score on admission, an increase in serum IgG was associated with a reduced need for mechanical ventilation in patients suffering from cardiovascular disease. On the other hand, in patients suffering from sepsis, an increased level of IgM was linked to an increased administration of coagulation factors.

Conclusion. Our data do not support the hypothesis that serum levels of immunoglobulins are linked to mortality in medical ICU patients.

Keywords

Immunoglobulins · Immune system · Intensive care · Clinical outcome · Sepsis · Mortality

Einfluss der Immunglobulin-Spiegel im Serum von Patienten auf Intensivstation auf deren klinisches Outcome

Zusammenfassung

Hintergrund. Endogene Immunglobuline spielen eine bedeutende Rolle in der Immunabwehr von mikrobiellen Infektionen. Kürzlich veröffentlichte Studien legen nahe, dass die Immunglobulinspiegel bei stationärer Aufnahme eine prognostische Bedeutung bei Intensivpatienten haben könnten.

Methodik. In einer nicht-interventionellen Studie wurden die Serumspiegel von IgG, IgM und IgA von 340 Patienten bei Aufnahme auf die Intensivstation sowie das Auftreten klinischer Endpunkte (Mortalität auf ITS, Nierenersatzverfahren, invasive Beatmung, Substitution von Gerinnungsfaktoren, Gabe von Erythrozytenkonzentraten) erfasst. Abhängig von der Hauptursache für den Intensivaufenthalt wurden die Patienten prospektiv einer der folgenden Gruppen zugeordnet: Sepsis, respiratorische Insuffizienz, kardiovaskuläre Erkrankung, akutes Nierenversagen, Zustand nach Operation, Zustand nach CPR, gastrointestinale Erkrankung, sonstige Erkrankungen.

Ergebnisse und Diskussion. Es findet sich weder in der Gesamtkohorte noch in einer der prädefinierten Subgruppen eine Korrelation zwischen den Immunglobulinspiegeln bei Aufnahme und der Mortalität während des Aufenthaltes auf der Intensivstation. In einer logistischen Regression unter Berücksichtigung des Confounders APACHE-II-Score bei Aufnahme findet sich eine Korrelation zwischen erhöhten IgG-Spiegeln und geringerem Bedarf von invasiver Beatmung bei der Patientengruppe mit kardiovaskulären Erkrankungen. Andererseits besteht bei Patienten mit Sepsis ein Zusammenhang zwischen erhöhten IgM-Spiegeln und erhöhter Substitution von Gerinnungsfaktoren.

Schlussfolgerung. In unserer Studie kann kein Zusammenhang zwischen den Immunglobulinspiegeln im Serum und der ITS-Mortalität nachgewiesen werden.

Schlüsselwörter

Immunglobuline · Sepsis · Intensivmedizin · Klinische Endpunkte · Mortalität

Table 2 Serum levels of immunoglobulins in medical ICU patients according to admission diagnosis

	Total (*N* = 340)	Sepsis (*N* = 83)	Respiratory failure (*N* = 32)	Cardiovascular diseases (*N* = 86)	Acute renal failure (*N* = 15)	Post operative condition (*N* = 19)	State after CPR (*N* = 50)	Gastro-intestinal diseases (*N* = 29)	Others (*N* = 26)	*p* (ANOVA)
Ig total (g/l)	13.6 ± 7.1	14.9 ± 9.8	14.2 ± 6.7	12.5 ± 3.8	18.5 ± 11.9*	13.5 ± 5.3	11.9 ± 4.7	15.1 ± 7.9	11.3 ± 3.3	0.008
IgG (g/l)	9.6 ± 5.6	11.1 ± 9.3	9.6 ± 3.7	9.1 ± 3.1	9.3 ± 4.7	9.9 ± 4.3	8.6 ± 3.4	10.1 ± 4.5	8.2 ± 2.5	0.184
IgM (g/l)	0.8 ± 0.6	0.8 ± 0.5	0.9 ± 0.4	0.8 ± 0.5	0.9 ± 0.8	0.9 ± 0.4	0.7 ± 0.4	1.1 ± 1.1	0.8 ± 0.4	0.174
IgA (g/l)	3.1 ± 3.9	3 ± 2.2	3.7 ± 5.6	2.6 ± 1.2	8.3 ± 13.7**	2.7 ± 1.2	2.6 ± 1.6	3.9 ± 3.3	2.3 ± 1.3	0.000

CPR cardiopulmonary resuscitation, *ANOVA* analysis of variance
*$p < 0.05$ versus "CPR" and "Others"; **$p < 0.05$ versus all other groups

Table 3 Patient outcomes separated by admission diagnoses

	Total	Sepsis	Respiratory failure	Cardiovascular diseases	Acute renal failure	Post operative condition	State after CPR	Gastro-intestinal diseases	Others
Death	103/340 (30.3 %)	35/83 (42.2 %)	9/32 (28.1 %)	18/86 (20.9 %)	3/15 (20.0 %)	1/19 (5.3 %)	24/50 (48.0 %)	8/29 (27.6 %)	5/26 (19.2 %)
RRT	95/340 (27.9 %)	41/83 (49.4 %)	5/32 (15.6 %)	16/86 (18.6 %)	10/15 (66.7 %)	4/19 (21.1 %)	10/50 (20.0 %)	7/29 (24.1 %)	2/26 (7.7 %)
Mechanical ventilation	214/340 (62.9 %)	70/83 (84.3 %)	23/32 (71.9 %)	36/86 (41.9 %)	7/15 (46.7 %)	7/19 (36.8 %)	47/50 (94.0 %)	11/29 (37.9 %)	13/26 (50.0 %)
Substitution of coagulation factors	42/340 (12.4 %)	15/83 (18.1 %)	1/32 (3.1 %)	6/86 (7.0 %)	3/15 (20.0 %)	1/19 (5.3 %)	5/50 (10.0 %)	8/29 (27.6 %)	3/26 (11.5 %)
Transfusion	113/340 (33.2 %)	42/83 (50.6 %)	10/32 (31.2 %)	13/86 (15.1 %)	5/15 (33.3 %)	5/19 (26.3 %)	18/50 (36.0 %)	16/29 (55.2 %)	4/26 (15.4 %)

CPR cardiopulmonary resuscitation, *RRT* renal replacement therapy

Table 4 Serum levels of immunoglobulins in medical ICU patients according to sex or age, respectively

			Ig total (g/l)	IgG (g/l)	IgM (g/l)	IgA (g/l)
Sex	**Men**	*N* = 210	14.1 ± 7.8	9.9 ± 6.2	0.8 ± 0.5*	3.4 ± 4.7
	Women	*N* = 130	12.8 ± 5.7	9.2 ± 4.3	0.9 ± 0.7*	2.7 ± 1.8
Age (years)	< 60	*N* = 116	13.6 ± 7.6	9.1 ± 4.3	0.9 ± 0.6	3.6 ± 5.6
	60–75	*N* = 131	13.3 ± 7.2	9.6 ± 6.4	0.8 ± 0.4	2.9 ± 3
	> 75	*N* = 92	14 ± 6.4	10.3 ± 5.8	0.8 ± 0.7	2.9 ± 1.7

*$p < 0.05$

In the study by Taccone patients suffering from septic shock which presented with low IgG levels more frequently developed ALI/ARDS had fewer vasopressor-free days and a higher mortality than patients with normal IgG plasma levels [26]. However, this negative effect of hypo-IgG immunoglobulinemia on mortality could not be significantly reproduced in a study by Venet, although a trend to the same effect was described [29]. These findings suggest that endogenous plasma levels of immunoglobulins could have an impact on patient's outcomes at the ICU and that it could be a therapeutic strategy to normalize the Ig plasma levels in order to improve clinical outcomes in critically ill patients. Despite this, one of our major findings is that no difference was found between endogenous Ig levels on admission in survivors and non-survivors as [29] has been described, meaning that our data do not support the assumption of IgG's prognostic relevance [2, 26]. This finding has to be considered in the light of previous interventional studies: neither in the score-based immunoglobulin G therapy of patients with sepsis (SBITS) study on patients with severe sepsis [33] nor in the Early Supplemental Severe SIRS Treatment With IVIG in Score-Identified High-Risk Patients After Cardiac Surgery (ESSICS) study on patients with escalating systemic inflammatory response syndrome (SIRS) after cardiac surgery [34] the therapeutic administration of IVIgG could be shown to improve morbidity or mortality.

The objectives of this study were to compare the Ig plasma levels between patients with different ICU admission diagnoses and to link the Ig serum levels to the patient's prognosis. Although we did not detect major differences between the majority of diagnosis subgroups (e.g., between patients presenting with sepsis or with cardiovascular disease, respectively) we measured significantly higher IgA levels in patients presenting with acute renal failure than in all other groups. This supports the hypothesis that the high IgA levels might be caused by patients with renal failure as a consequence of IgA nephropathy. It has been reported that patients with IgA nephropathy have significantly higher IgA serum levels, so the serum level of IgA is used as one of four clinical markers for diagnosis [11, 13, 15, 27]. In mice which spontaneously suffer from IgA nephropathy, serum levels of IgA rose up to 850 % of the initial state during onset of nephropathy [7] and among mice that develop IgA nephropathy spontaneously, those with high IgA serum levels had a higher incidence of nephropathy and developed the disease earlier than mice from the same strain with lower IgA serum levels

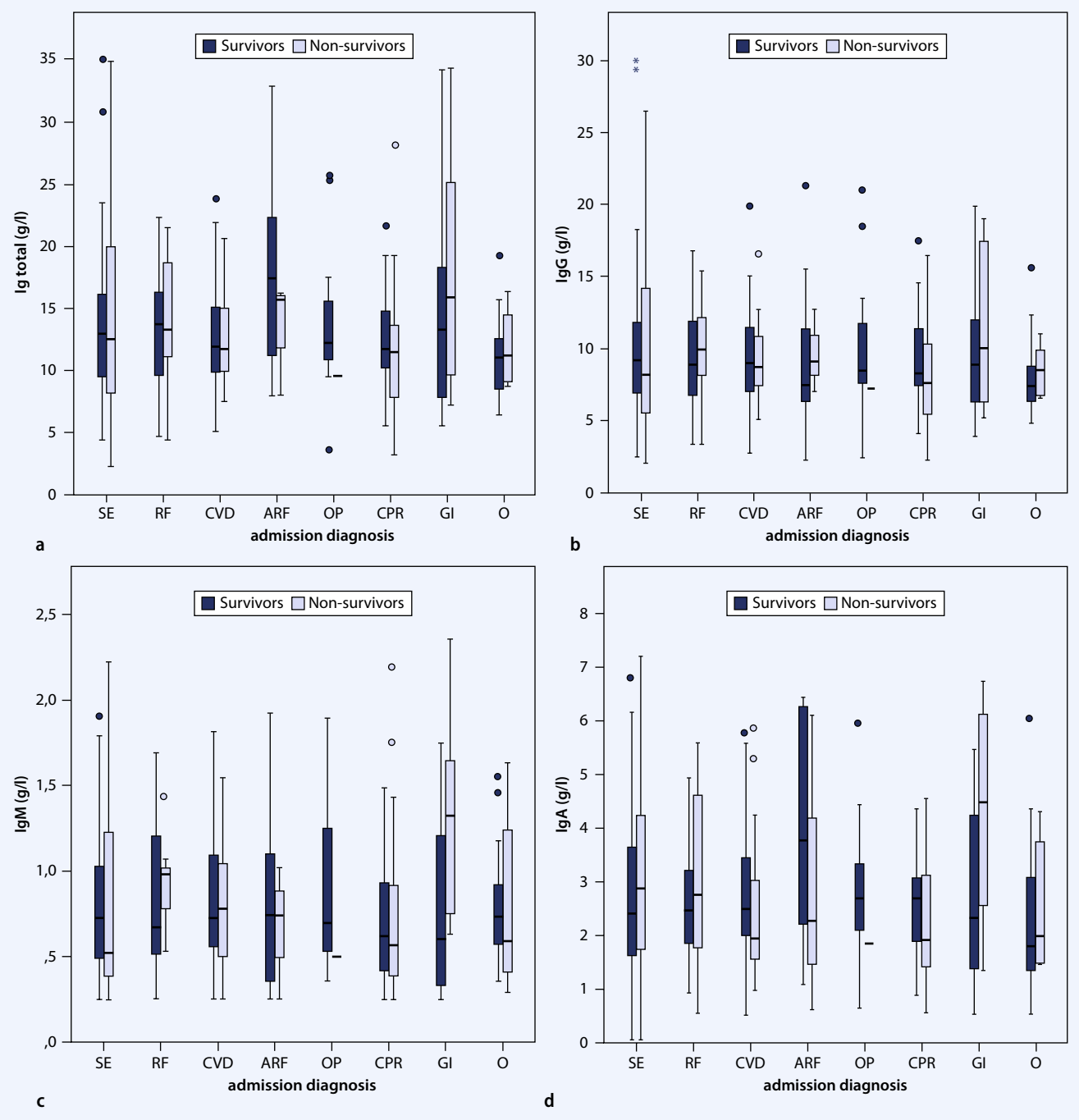

Fig. 1 ▲ **a** Serum immunoglobulin levels Ig total on ICU admission in surviving (S) and non-surviving (NS) medical patients depending on admission diagnosis. $p > 0.05$ (not significant) for all comparisons between S and NS. **b** Serum immunoglobulin levels Ig G on ICU admission in surviving (S) and non-surviving (NS) medical patients depending on admission diagnosis. $p > 0.05$ (not significant) for all comparisons between S and NS. **c** Serum immunoglobulin levels Ig M on ICU admission in surviving (S) and non-surviving (NS) medical patients depending on admission diagnosis. $p > 0.05$ (not significant) for all comparisons between S and NS. **d** Serum immunoglobulin levels Ig A on ICU admission in surviving (S) and non-surviving (NS) medical patients depending on admission diagnosis. $p > 0.05$ (not significant) for all comparisons between S and NS. *SE* sepsis, *RF* respiratory failure, *CVD* cardiovascular disease, *ARF* acute renal failure, *OP* postoperative condition, *CPR* cardiopulmonary resuscitation, *GI* gastrointestinal diseases, *O* other diseases

[14]. However, due to the nature of our study, we cannot confirm the clinical diagnosis of IgA nephropathy in our study patients. This hypothesis therefore remains speculative.

Although it is well known that several functions of the acquired immune system decline with age, we found no differences

Table 5 Influence of serum immunoglobulin levels on clinical outcomes in medical ICU patients

			Death		Mechanical ventilation		RRT		Substitution of coagulation factors		Transfusion	
			OR	*p*	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Ig total	Total	*N* = 302	1.008	0.676	1.009	0.721	1.035	0.054	1.027	0.191	1.022	0.210
	Sepsis + RF	*N* = 106	1.016	0.494	1.046	0.341	1.021	0.372	1.004	0.883	1.016	0.496
	CVD	*N* = 70	1.004	0.968	0.855	0.057	0.928	0.385	1.104	0.673	0.928	0.452
IgG	Total		1.016	0.519	1.012	0.726	1.038	0.129	0.997	0.927	1.021	0.367
	Sepsis + RF		1.012	0.641	1.038	0.542	1.024	0.402	1.000	0.992	1.021	0.454
	CVD		1.022	0.844	0.794	0.037	0.953	0.649	1.142	0.688	0.877	0.317
IgM	Total		1.347	0.176	1.031	0.909	1.028	0.902	1.886	0.011	0.919	0.707
	Sepsis + RF		1.669	0.220	1.829	0.389	1.343	0.470	2.761	0.039	1.108	0.797
	CVD		1.343	0.650	1.441	0.593	0.682	0.578	0.215	0.326	0.474	0.370
IgA	Total		0.989	0.734	1.007	0.861	1.041	0.218	1.068	0.069	1.032	0.323
	Sepsis + RF		1.028	0.616	1.137	0.476	1.014	0.802	1.007	0.928	0.999	0.979
	CVD		0.841	0.558	0.801	0.441	0.668	0.171	1.366	0.527	1.160	0.600

Logistic regression model including the confounder APACHE II score

CVD cardiovascular diseases, *Ig* immunoglobulin, *OR* odds ratio, *RF* respiratory failure, *RRT* renal replacement therapy

in immunoglobulin levels in patients of different age groups (< 60, 60–75, and > 75 years). Additionally, we also could not confirm a correlation between low plasma levels of albumin and low immunoglobulins in the way it has been described by Taccone and Venet [26, 29]. Certainly, one major difference between these two studies and our own findings is the fact that the former study populations consisting only of patients with septic shock whereas our analysis included patients with different diagnoses.

The present study found no significant correlation between endogenous immunoglobulin levels on ICU admission and mortality. Despite this, we found several indications that other clinical outcomes such as the need for mechanical ventilation or the substitution of coagulation factors might be linked to Ig plasma levels.

During disseminated intravascular coagulopathy (DIC) as a typical severe complication of sepsis (and other diseases), a consumption of coagulation factors can occur, and it ultimately results in severe disturbances of coagulation tests and the onset of diffuse bleeding [12, 36]. As a surrogate parameter for the severity of clotting disturbances we collected data about substitution of coagulation factors and red cell transfusion. We found a positive correlation between higher plasma levels of IgM and the substitution of coagulation factors in patients with admission diagnosis sepsis or respiratory failure (odds ratio (OR) 2.761; $p = 0.039$) as well as in the total group of our medical intensive-care patients (OR 1.886; $p = 0.011$). Thus, patients with higher IgM levels on admission were more likely to receive substitution of coagulation factors during their ICU stay (see **Table 5**). This finding is somewhat surprising as it has been reported that IgM is correlated with an increased coagulation potential and that patients with acute venous thromboembolism have higher levels of special IgM antibodies [4, 22, 35]. So far, there are no studies that argue for the rather speculative hypothesis that IgM might promote the onset of disseminated coagulation, so that patients with lower IgM plasma levels might have a reduced risk of developing DIC and the resulting loss of coagulation factors. Our findings are especially surprising as it has been shown in different studies that IgM enriched IVIG is a potent inhibitor of complement activation [21, 30]. For a better understanding of the connection between IgM and coagulation in ICU patients further research is required.

We found that hypo-IgG is associated with an increased need for mechanical ventilation (OR 0.794; $p = 0.037$) in patients with cardiovascular diseases (CVD). It is certainly plausible that patients with cardiovascular diseases carry an increased risk of acquiring infections of the respiratory tract-like hypostatic pneumonia during their ICU stay and that higher IgG levels could have a protective effect in this context. However, the data from our study are at best hypothesis-generating and are not sufficient to establish a pathophysiological concept that reliably explains this association of IgG and the need for mechanical ventilation.

Limitations of the study

Our prospective nonintervention study has several limitations. First, we can only present data from a single ICU with a limited number of patients. Additionally, we measured all outcome parameters only during the ICU stay, meaning that effects occurring later on would be undetected. Furthermore, we did not differentiate between patients coming to the ICU from other hospital wards and patients coming directly from the emergency department. This might be of relevance as there could exist an influence of previous medical treatment on the patient's outcome as well as on immunoglobulin levels. So far, no conclusions regarding the potential effects of a therapeutic IVIG administration can be drawn from our data. Additionally, the study was not designed to find patients with immunodeficiency syndromes or to establish a role of Ig serum levels as potential biomarkers but to search for a possible link between Ig serum levels on patient's outcomes.

Abbreviations

ALI	acute lung injury
ANOVA	analysis of variance
APACHE score	acute physiology and chronic health evaluation score
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
BMI	body mass index
CHD	coronary heart disease
CPR	state after cardiopulmonary resuscitation
CVD	cardiovascular diseases
DIC	disseminated intravascular coagulopathy
GI	gastrointestinal diseases
ICU	intensive care unit
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IVIg	intravenous immunoglobulin
N	number
NS	non-surviving
O	other diseases
OP	postoperative condition
OR	odds ratio
RF	respiratory failure
RRT	renal replacement therapy
S	surviving
SE	sepsis
SIRS	systemic inflammatory response syndrome
Y	years

Conclusion

In conclusion, we did not find a correlation between circulating levels of IgG, IgM, or IgA on ICU admission and mortality in patients treated at a medical ICU. However, in patients with cardiovascular diseases hypo-IgG was associated with an increased need for mechanical ventilation. Patients with sepsis or respiratory failure had a significantly lower substitution of coagulation factors when they presented with low IgM serum levels.

Key messages

- **In a cohort of 340 medical ICU patients, no correlation was found between circulating levels of IgG, IgM, or IgA on ICU admission and mortality.**
- **In the predefined subgroup of patients with acute cardiovascular diseases a reduced serum level of IgG could be shown to be associated with an increased risk of mechanical ventilation.**
- **Low serum levels of IgM were linked to a reduced need for the substitution of coagulation factors in patients suffering from sepsis or respiratory failure.**

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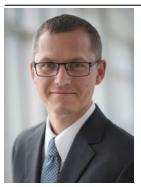

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Compliance with ethical guidelines

Conflict of interest. C. Geier, J. Schröder, A. Tamm, S. Dietz, S. Nuding, K. Holder, and Ö. Khandanpour state that there are no conflicts of interest.

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The study was conducted in accordance with the standards of the local ethics committee of the Martin Luther University Halle-Wittenberg.

Due to the study's noninterventional design the need for patient consent was waived.

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Fachnachrichten

Neuer Ansatz zur Früherkennung der Sepsis

Die wirksamste Maßnahme, um Patienten mit einer gesicherten Sepsis erfolgreich zu behandeln, ist eine rechtzeitige und adäquate Antibiotika-Therapie. Dies setzt die frühe und verlässliche Diagnose einer Sepsis bei Intensivpatienten voraus. Ein an der Universitätsmedizin Mannheim entwickelter neuartiger Ansatz zur Früherkennung der Sepsis könnte die Prognose der Betroffenen verbessern.

Die Wissenschaftler stellen in der aktuellen Ausgabe der *Critical Care Medicine* einen Computeralgorithmus vor, der die laufend erhobenen und in der elektronischen Patientenakte gespeicherten Routinedaten zur individuellen, minutengenauen Abbildung des sogenannten „Systemischen Inflammatorischen Response Syndroms" (SIRS), eines wichtigen Merkmals der Sepsis, nutzt. Auf dem Algorithmus aufbauend definierten die Wissenschaftler zur Erfassung der Dynamik des SIRS intuitive Maße, etwa den Durchschnitt und die Änderung der Anzahl der SIRS-Kriterien über ein Zeitfenster von 24 Stunden.

Bei der praktischen Anwendung dieser SIRS-Deskriptoren zeigte sich, dass diese der üblichen punktuellen Erhebung des SIRS deutlich darin überlegen sind, eine Sepsis bei Polytrauma-Patienten vorauszusagen. Ihre Trennschärfe bei der Diagnose der Sepsis im Intensivverlauf reichte sogar an jene von derzeitigen Sepsis-Biomarkern heran, ohne den zusätzlichen Testaufwand zu erfordern.

Literatur: Lindner HA, Balaban Ü, Sturm T et al. (2016) An algorithm for systemic inflammatory response syndrome criteria-based prediction of sepsis in a polytrauma cohort. Critical Care Medicine, 44:2199, 2016

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