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Research article

Prediction of short-term mortality in elderly patients with sepsis using immunoglobulin G2: An observational study

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ABSTRACT

Background: Sepsis is a global healthcare issue and continues to cause high mortality especially in elderly patients. The humoral immune system plays an important role in protecting from microbial contamination. The goal of this study is to investigate the immune status and prognostic evaluation of elderly patients with sepsis.

Methods: A single-center, prospective observational study has been conducted, with the endpoint being the 28-day mortality. Patients 65 years and older who met the diagnostic criteria of Sepsis-3 in the Emergency Department of Beijing Chao-Yang Hospital were divided into survivors and non-survivors groups. Levels of immunoglobulin (Ig) A, IgG, IgM and their subclasses as well as clinical indicators were collected upon enrollment, and the results were statistically analyzed.

Results: This study finally enrolled 106 elderly patients, including 68 survivors and 38 non-survivors. Compared with survivors, IgG2 level and IgG4 level were lower in non-survivors ($P < 0.05$). IgG2 could be regarded as an independent predictor of the 28-day mortality in elderly septic patients. IgG2 had a higher predictive value than other immunoglobulins, lactate, procalcitonin, SOFA score and APACHE II score for mortality in elderly septic patients, and the ratio of IgG2 to IgG had a slightly larger area under the ROC curve compared to IgG2 only (AUC: 0.776 v.s. 0.741).

Conclusion: IgG subclasses play important roles in the prognosis of elderly septic patients, with IgG2 being the main component. IgG2 was found to outperform other immunoglobulins, lactate, procalcitonin, SOFA score and APACHE II score in terms of predicting the mortality. A complete immunological evaluation is helpful to guide the prognosis and treatment of patients with age-related infection.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, which is often associated with high mortality and a significant consumption of healthcare resources [1, 2, 3, 4]. It is a pathology of variable continuum of overlaying immune mechanisms, triggered by an underlying infection [5]. The balance between the microbial virulence and the immunity of the host determines the process of sepsis [6]. Many studies have shown that the pathogenesis of organ failure in sepsis is associated with immune dysfunction [7, 8, 9]. When sepsis transits into septic shock, it may cause a mortality rate greater than 40% [10]. It continues to be the leading cause of death from infection especially in elderly patients [11, 12]. Elderly patients always present chronic low-level inflammation, higher infection rates, refractory infection and chronic diseases [13]. Organs of elderly patients have different degrees of degeneration, especially in the decline of immune function. In the state of severe infection, the mortality rate can be significantly increased [14]. Therefore, early recognition of sepsis and evaluation of the prognosis are of vital importance [10], especially in the emergency room [15]. Although the Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and procalcitonin (PCT) with other classic biomarkers have been commonly used in the diagnosis of sepsis [16, 17], there is still a lack of immune status and prognostic evaluation of elderly patients with sepsis.

Humoral immunity with antibodies as the protagonist plays an important role in the body's resistance to pathogens [9, 18]. Immunoglobulin can be defined into five isotypes according to their heavy chain C

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domains, namely IgA, IgD, IgE, IgG and IgM. IgG can be split into IgG1, IgG2, IgG3, and IgG4; while IgA can be split into IgA1 and IgA2. Each of these subclasses has its own biological properties [19]. When the infection occurs, microorganisms invade body's defensive mechanism, of which immunoglobulin is an important factor, especially IgA, IgG, IgM and their subclasses [20]. There have been some reports on the association between IgG levels and mortality among septic patients. The authors in [21, 22] demonstrated that low IgG levels do not discriminate between survival and nonsurvival patients with severe sepsis and septic shock. Therefore, the evidence for improved prognosis with intravenous immunoglobulin (IVIg) therapy can be deemed insufficient. In contrast, a recent study showed that low IgG level is associated with poor outcomes under severe infection [18]. Moreover, IgA may have protection function against microbial invasion of respiratory surfaces [23]. However, patients may have deficiency or excess in the subclasses of immunoglobulin regardless of the total level. There are few works in the literature that bridge the gap between the levels of immunoglobulin and its subclasses and prognosis of infection. On the other hand, protein microarray can detect low abundant proteins in clinic, which has advantages of high sensitivity and accuracy [24]. In this work, we apply a high-throughput and ultra-micro plasma microarray platform to measure the expression of IgA, IgA1-2, IgG, IgG1-4 and IgM. The main goal of this work is to study the predictive value of the levels of immunoglobulin and its subclasses on the mortality rate of elderly patients with sepsis.

2. Material and methods

2.1. Study setting and participants

We performed a prospective observational study in the Emergency Department (ED) of Beijing Chao-Yang Hospital, Capital Medical University, from February 2017 to February 2019. Subjects who were 65 years and over, admitted to the ED and diagnosed as sepsis according to criteria in the Sepsis-3 definition [1] were eligible. The exclusion criteria were as follows: (1) were immunocompromised; (2) immunosuppressants were used for a long time; (3) were discharged within 24 hours of admission; (4) were in unrecoverable dying state; and (5) died accidentally. The design of this study was approved by the Institutional Review Board and Medical Ethics Committee of Beijing Chao-Yang Hospital (Ethical approval number: 2016-ke-173). The study was conducted in accordance with the Helsinki Declaration and its successive amendments. Informed consent was obtained from the study participants or their next of kin.

2.2. Data collection

We collected information of each eligible subject at admission, including age, sex, Body Mass Index (BMI), length of hospital stay, incidence of septic shock, SOFA score, APACHE II score and important laboratory results such as white blood cells (WBC) and platelets (PLT). All the patients were followed up for 28 days, and the endpoint was 28-day mortality.

Peripheral venous blood was collected from all study participants upon enrollment. The collected blood was then added into blood collection tubes containing heparin or Ethylene Diamine Tetraacetie Acid (EDTA) for anticoagulation. The whole blood was centrifuged at 4000 r/min × 10 mins and upper layer of plasma was sucked and left for 2 hours. Samples were marked in order and saved into a refrigerator of -80 °C until needed for experiments.

2.3. Plasma sample preparation

Microarrays preparation: Properly diluted plasma samples (from 10 to 500-fold) and serially diluted standard immunoglobulins were printed onto a 3D modified slide surface (Capital Biochip Corp, Beijing, China) in two replicas using an Arrayjet microarrayer (Roslin, UK). Phosphate-buffered saline (PBS) and bovine serum albumin (BSA, 1 mg/mL) (Sigma-Aldrich, MO, USA) were used as negative controls. After printing, the plasma microarrays were stored at -20 °C until use.

Microarrays detection: After equilibration to room temperature, the plasma microarrays were assembled into a microarray incubation tray (PEPperPRINT, Heidelberg, Germany) and blocked with 500 μL 1% BSA in each well for 1 h at room temperature. After removing the BSA, the arrays were incubated with the corresponding fluorescently-labeled antibody combinations for 1 h at room temperature. The resulting slides were washed three times with PBS containing 0.05% (w/v) Tween 20 (PBST), 5 min/each, and H_2O tk min/each. The slide was scanned using a Genepix 4000A microarray scanner (Molecular Devices, CA, USA). The fluorescent images were analyzed and the signal intensity was extracted using a GenePix Pro image analysis software (Molecular Devices, CA, USA). The plasma Ig quantification includes IgA, IgA1-2, IgG, IgG1-4 and IgM.

2.4. Statistical analysis

All continuous variables were first used for normality test. Measurement data conforming to the normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$). Two independent sample t-test was then used for comparison between survivors and non-survivors. Non-normally distributed measurement data were used in the non-parametric test. The count data were expressed as the number of cases (percentage) using chi-square test. Variables with a P-value less than 0.05 were considered potential predictors of death and were imported into a multivariate logistic regression model. The resulting model was analyzed by the regression coefficient (β), adjusted odds ratio (aOR), and 95% confidence interval (CI). The receiver operating characteristic curve (ROC) was used to evaluate the predictive effect of each independent factor on death. The area under the ROC curve (AUC), 95% CI, P-value, cut-off, sensitivity, and specificity were also calculated. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 24.0.

3. Results

3.1. Patient characteristics

A total of 106 eligible subjects were screened, out of which 62 (58.5%) were male. The averaged (±SD) age was 78.31 ± 10.86 years and averaged BMI was 23.34 ± 4.65 kg/m^2. According to the 28-day mortality, 68 patients (64%) were categorized as survivors and the rest 38 patients were non-survivors. The basic characteristics of the study population and the comparison of important laboratory values are shown in Table 1. One striking observation was that the age did not differ between the two groups, which is probably because our study has a relatively small sample size and about half of enrolled patients were 80 years and over. As expected, survivors had longer average hospital stay ($P = 0.001$) and lower incidence of septic shock ($P = 0.001$). Besides, non-survivors showed higher lactate level ($P = 0.029$), PCT level ($P = 0.025$), SOFA score ($P = 0.001$), and APACHE II score ($P = 0.015$). However, there were no statistically significant differences in other clinical characteristics between the two groups such as BMI ($P = 0.059$), albumin ($P = 0.608$), WBC ($P = 0.715$) and PLT ($P = 0.300$).

We investigated the immunoglobulin quantification of IgA, IgA1-2, IgG, IgG1-4 and IgM and compared their levels between the two groups in the study population. As shown in Table 2, IgG2 and IgG4 were significantly higher in survivors compared to non-survivors ($P < 0.05$). All other classes of immunoglobulins did not differ between the two groups. We further used the ratio IgG2/IgG as another parameter for analysis, and it turned out that there was significant difference in this parameter between survivors and non-survivors (0.0055 ± 0.0048 v.s. 0.0026 ± 0.0011, $p < 0.001$).

Table 1. Clinical characteristics of the study patients.

	Total ($n = 106$)	Survivors ($n_1 = 68$)	Non-survivors ($n_2 = 38$)	P-value
Age (years, $\bar{x} \pm s$)	78.31 ± 10.86	78.57 ± 10.62	77.84 ± 11.39	0.741
Male (# of cases (%))	62 (58.5%)	38 (55.9%)	24 (63.2%)	0.76
BMI (kg/m^2, $\bar{x} \pm s$)	23.34 ± 4.65	23.97 ± 4.98	22.19 ± 3.78	0.059
Incidence of septic shock (%)	18.7	7.35	39.47	0.001*
Lactate (mmol/L, $\bar{x} \pm s$)	2.30 ± 2.16	1.93 ± 1.80	2.98 ± 2.57	0.029*
PCT (ng/mL, M (P_{25}, P_{75}))	0.69 (0.18, 8.35)	0.52 (0.10, 6.74)	1.85 (0.50, 13.82)	0.025*
Albumin (g/L, $\bar{x} \pm s$)	34.85 ± 5.39	35.06 ± 5.36	34.49 ± 5.48	0.608
SOFA ($\bar{x} \pm s$)	5.00 ± 2.56	4.34 ± 2.01	6.18 ± 3.00	0.001*
APACHE II ($\bar{x} \pm s$)	15.77 ± 7.88	14.24 ± 6.52	18.53 ± 9.34	0.015*
Length of hospital stay ($\bar{x} \pm s$)	6.66 ± 6.35	7.93 ± 7.01	4.39 ± 4.12	0.001*
WBC (×10^9/L, $\bar{x} \pm s$)	12.04 ± 8.28	11.82 ± 7.22	12.44 ± 10.04	0.715
PLT (×10^9/L, $\bar{x} \pm s$)	180.69 ± 95.54	187.85 ± 96.19	167.51 ± 94.21	0.300

* $P < 0.05$ means the difference is statistically significant.

Table 2. Comparison of plasma immunoglobulin quantification.

Immunoglobulin (μg/mL, $\bar{x} \pm s$)	Total ($n = 106$)	Survivors ($n_1 = 68$)	Non-survivors ($n_2 = 38$)	P-value
IgA	4539.50 ± 2552.42	4288.07 ± 2593.53	4989.41 ± 2446.18	0.176
IgA1	3524.02 ± 2896.55	3376.62 ± 3051.19	3787.80 ± 2615.31	0.486
IgA2	268.46 ± 129.10	266.68 ± 127.77	271.63 ± 133.10	0.851
IgG	26914.69 ± 11653.09	25525.30 ± 10026.11	29400.96 ± 13908.22	0.101
IgG1	8282.61 ± 7448.68	7316.07 ± 4515.42	10012.20 ± 10758.31	0.148
IgG2	102.14 ± 71.21	120.40 ± 79.34	69.45 ± 35.77	<0.001*
IgG3	15.50 ± 23.48	17.77 ± 27.84	11.44 ± 11.61	0.184
IgG4	16.50 ± 27.67	20.29 ± 33.12	9.73 ± 10.59	0.018*
IgM	3099.15 ± 889.92	3051.71 ± 793.47	3184.05 ± 1046.83	0.465

* $P < 0.05$ means the difference is statistically significant.

Table 3. Risk factors for 28-day mortality of elderly septic patients using 6 factors.

	β	Wald	aOR	95% CI	P-value
IgG2 (μg/mL)	-0.023	8.704	0.978	0.963-0.992	0.003*
IgG4 (μg/mL)	-0.017	0.751	0.983	0.946-1.022	0.386
Lactate (mmol/L)	0.084	0.396	1.087	0.838-1.411	0.529
PCT (ng/mL)	-0.004	0.454	0.996	0.983-1.008	0.501
SOFA	0.217	2.563	1.243	0.952-1.622	0.109
APACHE II	0.073	2.780	1.076	0.987-1.173	0.095

* $P < 0.05$ means the difference is statistically significant.

Table 4. Risk factors for 28-day mortality of elderly septic patients using 5 factors.

	β	Wald	aOR	95% CI	P-value
IgG2 (μg/mL)	-0.025	10.885	0.975	0.961-0.990	0.001*
Lactate (mmol/L)	0.085	0.414	1.088	0.841-1.409	0.520
PCT (ng/mL)	-0.004	0.387	0.996	0.984-1.008	0.534
SOFA	0.221	2.756	1.248	0.961-1.621	0.097
APACHE II	0.070	2.608	1.072	0.985-1.168	0.106

* $P < 0.05$ means the difference is statistically significant.

3.2. Risk factors

We first selected the six biomarkers from Table 1 and Table 2 that are statistically significant between the two groups for multivariate stepwise logistic regression analysis. As illustrated in Table 3, Lower IgG2 (aOR: 0.978, 95% CI: 0.963 – 0.992, $P = 0.003$) was found to be one independent predictor for the 28-day mortality in elderly patients with sepsis. Based on the regression coefficient (β), we could infer that a higher IgG2 was associated with a better outcome. Meanwhile, the risk of mortality of elderly sepsis increased by 97.8% for each 1 μg/mL decrease in IgG2 level. The sensitivity of this model was 0.579 and the specificity was 0.897. We then further excluded IgG4 and used the remaining five factors for sepsis prognostic evaluation and the coefficients are summarized in Table 4. As expected, the sensitivity was increased to 0.605, whereas the specificity was decreased to 0.868.

Finally, we plotted ROC curves for various indicators which differed significantly between the two groups to evaluate their predictive values on 28-day mortality of elderly patients with sepsis. It could be seen from Table 5 and Fig. 1 that the AUC of IgG2 was 0.741 (Sensitivity: 64.7%, Specificity: 76.3%, 95% CI: 0.644 – 0.837, $P < 0.001$), and it outperformed IgG4, lactate, PCT, SOFA and APACHE II scores in 28-day mortality prediction. We also used the cut-off method to obtain IgG2 < 77.9311 μg/mL as the threshold for predicting 28-day mortality in elderly patients with sepsis. More interestingly, it showed that IgG2/IgG even outperformed IgG2 in terms of the predictive capability (AUC: 0.776, $P < 0.001$). This suggested that IgG2/IgG was a promising parameter for predicting the 28-day mortality of elderly patients with sepsis.

4. Discussion

A dysregulated host response to an infection is known as the essence of sepsis [1, 4, 25]. Organ dysfunction and death often occur at the phase when pro-inflammatory response and anti-inflammatory response are out of balance [26, 27]. Several studies had revealed that clinical biomarkers and warning scores are useful tools for risk stratification and sepsis screening for adult sepsis patients. Lactate is currently the most commonly used biomarker to identify sepsis and is an independent predictor of mortality in patients with sepsis and septic shock [12, 28, 29]. SOFA score was designed to evaluate sepsis-associated organ dysfunction, which is related to the prognosis of septic patients [30]. A study enrolled in 742 septic patients showed that SOFA score had a moderate prognostic stratification ability [31]. APACHE II score was first developed in 1985 for critically ill patients [32, 33]. However, the prediction capability of the mortality rate in sepsis using APACHE II score is still under investigation [17, 34].

Elderly patients may have a blunted host inflammatory response that could increase the complexity of the sepsis process and over 60% sepsis diagnoses are attributed to patients aged greater than or equal to 65 years [35]. PCT was found to be a valuable marker for the discrimination of elderly patients with sepsis [36]. However, few studies had specifically focused on biomarkers of elderly sepsis prognosis. Elderly individuals display increased mortality caused by immunosenescence, which may affect almost all cell types in the immune systems [37]. It

Table 5. Predictive values of different indicators on 28-day mortality of elderly patients with sepsis.

	Cutoff	AUC	P-value	95% CI	Sensitivity (%)	Specificity (%)
IgG2 (μg/mL)	77.9311	0.741	<0.001	0.644-0.837	64.7	76.3
IgG4 (μg/mL)	5.9012	0.637	0.020	0.530-0.745	70.6	55.3
IgG2/IgG	0.0036	**0.776**	<0.001	0.688-0.863	61.8	86.8
Lactate (mmol/L)	1.35	0.676	0.003	0.573-0.780	78.9	55.9
PCT (ng/mL)	0.495	0.631	0.025	0.524-0.739	78.9	45.6
SOFA score	5.5	0.688	0.001	0.585-0.791	52.6	70.6
APACHE II score	18.5	0.636	0.020	0.521-0.752	47.4	79.4

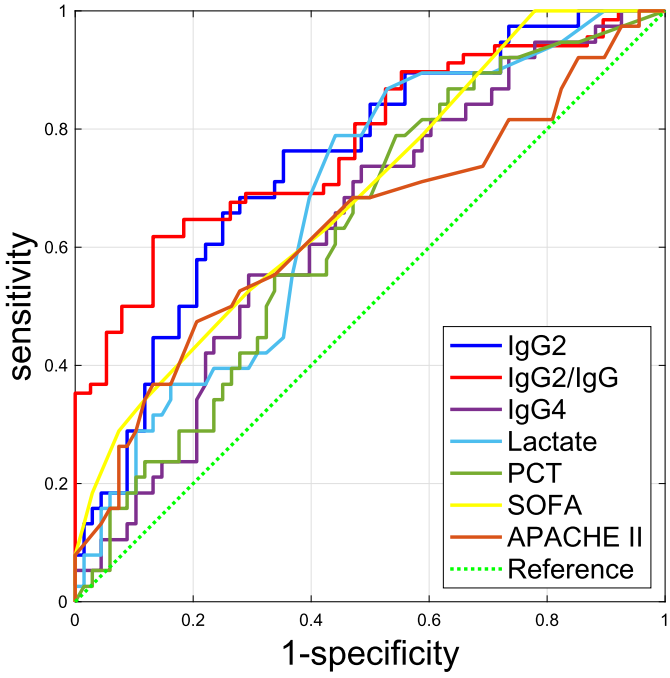

Fig. 1. ROC evaluation of the predictive values of different indicators for 28-day mortality of elderly septic patients.

has been concluded that sepsis can affect both innate and adaptive immune cells in elderly mice and patients [37]. In this regard, our study focused mainly on immunoglobulin, an important part of adaptive immunity, and its relationship with the short-term mortality of elderly septic patients.

Our first finding is that non-survivors of elderly septic patients often exhibit higher lactate level, PCT level, SOFA score and APACHE II score than survivors. We found that the levels of IgG2 and IgG4 had been significantly declined in non-survivors. The most severe infected patients may show signs of capillary leakage with resultant low albumin levels and decreased immunoglobulin levels, which may also affect the levels of the subclasses of immunoglobulin. However, we did not see any significant difference in either the albumin or the total IgG level between the two groups from Table 1 and Table 2. Further statistical analysis showed that IgG2 outperforms other immunoglobulins, lactate, PCT, SOFA and APACHE II scores in predicting the mortality of elderly septic patients (AUC: 0.741) and the ratio IgG2/IgG further increased the AUC to 0.776, which suggested that IgG2 is a moderate mortality biomarker of elderly septic patients.

Even though there are few works that explicitly investigate the relationship between immunoglobulin subclasses and sepsis mortality, our results are consistent with some previous studies in some aspects. It has been shown in [38] that low IgG2 level is significantly related to abnormal lung function. IgG2 level was also found to be significantly lower in patients with methicillin-resistant Staphylococcus aureus infections after esophageal surgery [39]. Some studies have evidenced that IgG2 is a specific immunoglobulin against pneumococcal polysaccharides, leading to a subclass-specific inducing mechanism for human response to polysaccharide antigens [40, 41]. It has been speculated in [42] that levels of IgG1, total IgG, IgM and IgA might play a beneficial role in septic shock. However, there is still insufficient evidence for the mechanism research.

In this work, we developed a large-scale, ultra-micro plasma immunoglobulin quantification chip to identify the immunoglobulin and its subclasses' levels in the body, which has high reproducibility and high sensitivity. Using this platform, we were able to screen the immunoglobulin concentration of all the enrolled patients within 20 minutes. Nonetheless, there are some limitations within this study. First, the observations are from a single-center and the number of subjects was relatively insufficient to make a comprehensive conclusion about the connections between the prognoses of elderly patients with sepsis and the levels of the immunoglobulin and its subclasses. Second, the limited follow-up time may cause bias in our analysis. Third, the study did not assess all immune status such as cellular immunity and innate immunity. Our future work will include multi-center studies and large-scale data analysis.

5. Conclusion

In this paper, we have investigated the relationship between the immunoglobulin level and the 28-day mortality of elderly septic patients. The major finding of this study showed that IgG and its subclasses play important roles in the prognosis of sepsis in elderly patients. In particular, IgG2 can be used as a prognostic biomarker of short-term mortality in elderly septic patients. A comprehensive immunological evaluation may be helpful to guide the prognosis evaluation of patients with age-related infection.

Ethics approval and consent to participate

The Institutional Review Board and Medical Ethics Committee of Beijing Chao-Yang Hospital approved the protocol and consent forms (No. 2016-ke-173).

Declarations

Author contribution statement

Fang Zhang: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data; Wrote the paper.

Tiantian Wan; Xin Liu: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Shu-Bin Guo, M.D: Conceived and designed the experiments.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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