Early immunosuppression was associated with poor prognosis in elderly patients with sepsis: secondary analysis of the ETASS study

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Research

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Abstract

Background: Although immunosuppression has been investigated in adult septic patients, early immune status remains unclear. In this study, we aimed to assess early immune status in adult patients with sepsis stratified by age and its relevance to hospital mortality.

Methods: From post hoc analysis of a multicenter, randomized controlled trial, 273 patients whose levels of monocyte human leukocyte antigen-DR (mHLA-DR) were obtained within 48 hours after onset of sepsis were enrolled. All patients were divided into elderly (≥60yrs) group and non-elderly (<60yrs) group. Early immune status was evaluated by the percentage of mHLA-DR in total monocytes within 48 hours after onset of sepsis and it was classified as immunosuppression (mHLA-DR≤30%) or non-immunosuppression (>30%). Changes in immune status were assessed by the value change in mHLA-DR on day 3 compared with the first measurement. Three logistic regression models were conducted to test the associations between early immunosuppression and hospital mortality. We also did a sensitivity analysis to find out if the definition of early immune status (24 vs. 48 hours after onset of sepsis) affects the outcomes.

Results: Of the 181 elderly and 92 non-elderly septic patients, 71 (39.2%) elderly and 25 (27.2%) non-elderly died in hospital. The percentage of early immunosuppression in the elderly was twice of that of the non-elderly patients (32% vs. 16%, p=0.006). Immunosuppressed elderly had higher hospital mortality than the non-immunosuppressed elderly (53.4% vs. 32.5%, p=0.009), but there was no significant difference in mortality between immunosuppresed non-elderly patients and non-immunosuppressed non-elderly patients (33.5% vs. 26.0%, p=0.541). In all of the three logistic regression models, we found that early immunosuppression was independently associated with increased hospital mortality in elderly, but not in non-elderly patients. Sensitivity analysis further confirmed the definition of early immune status did not affect the outcomes. In addition, immune status improvement on day 3 was associated with reduced hospital mortality in both elderly and non-elderly patients.

Conclusion: In adult patients with sepsis, the elderly were more susceptible to early immunosuppression after onset of sepsis. Early immunosuppression was independently associated with poor prognosis in elderly patients. Trial registration: ClinicalTrials.gov NCT00711620 , 9 July 2008, https://clinicaltrials.gov/ct2/show/NCT00711620

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. After decades of effort, the mortality rate of sepsis has been decreasing; however, the absolute number of deaths is likely to continue to increase as the incidence of sepsis continues rising [2, 3]. Although sepsis has been studied for decades, its pathogenesis remains unclear. A post-mortem study of septic patients demonstrated that patients who died of sepsis were associated with widespread

immunosuppression [4]. Subsequently, numerous studies have demonstrated that immunosuppression is the main cause of high mortality in septic patients [5, 6].

Decreased expression in monocyte human leukocyte antigen-DR (mHLA-DR) is a key biomarker to assess immune status. Our previous study and other studies have revealed that both mHLA-DR and dynamic change of mHLA-DR was associated with poor prognosis in patients with sepsis [7–9]. The percentage of mHLA-DR below 30% was widely accepted as immunoparalysis or immunosuppression [9, 10]. Furthermore, mHLA-DR has been applied to select immunosuppressed septic patients in the study of immunostimulant [11]. Therefore, the use of mHLA-DR as a biomarker to assess immune status in septic patients is supported by previous research.

It is well known that the immune function declines with age, so elderly may be more susceptible to early immunosuppression than younger patients [12, 13]. Elderly patients are more susceptible to sepsis during hospitalization, and the mortality of elderly patients with sepsis was higher than that of younger patients [14–16]. Several studies found immunosuppression in elderly patient increases the risk of death and secondary infection in the course of sepsis [17, 18]. Although immunosuppression is associated with poor outcome in elderly septic patients, the timing of immunosuppression remains unclear. Recently, Muszynski et al. revealed that critically ill children with sepsis had immunosuppression from early stage (within 48 hours after onset of sepsis) [19]. However, early immune status of elderly patients with sepsis remains unclear.

In our current study, we aimed to assess early immune status in adult patients with sepsis stratified by age groups and determine their relevance to hospital mortality.

Materials And Methods

Study design

The ETASS (Efficacy of Thymosin Alpha 1 for Severe Sepsis, ETASS) study was a multi-center, randomized controlled study comparing the effect of thymosin alpha 1 (Tα 1) vs. placebo in patients with severe sepsis [20]. A full description of the methods of the ETASS study, including the full study protocol, case report form, sample size, quality control, and main results can be found in the original paper [20]. In the ETASS study, severe sepsis was defined as the presence of a proven or suspected infection in at least one site, two or more signs of a systemic inflammatory reaction, and at least one acute sepsis-related organ dysfunction. Therefore, the term ‘severe sepsis’ in our previous study is approximately equal to the definition of sepsis in Sepsis 3.0 [1]. Unless otherwise specified, ‘sepsis’ was used to replace ‘severe sepsis’ in this study. Immunotherapy in the study was defined as patients have received at least one dose of thymosin alpha 1 in the ETASS study.

In the present study, the primary outcome was to assess early immune status in adult septic patients and its relevance to hospital mortality. All adult septic patients were divided into elderly and non-elderly group. According to China Country Assessment Report on Ageing and Health from World Health Organization in

2015, elderly was defined as aged 60 years or over [21]. According to previous study, early immune status was defined as the immune status within 48 hours after onset of sepsis [19]. Immune status was measured by the expression of mHLA-DR because of its proven value in septic patients [22]. Therefore, only those patients with mHLA-DR measured within 48 hours after onset of sepsis was enrolled in this study (273/361). To assess different immune status, we divided early immune status into two categories: immunosuppression (≤ 30%) and non-immunosuppression (mHLA-DR > 30%) [10, 23]. Changes in immune status were assessed by the value change in mHLA-DR on day 3 compared with the first measurement. According to our previous study, a change of mHLA-DR value of 4.8% on day 3 compared to initial measurement allowed discrimination between survivors and non-survivors [8]. Thus, the value change over 4.8% was defined as immune status improvement, and equal or less than 4.8% was defined as immune status non-improvement.

In addition, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score with or without the age component and the Sequential Organ Failure Assessment (SOFA) score were recorded and computed during the first 24 hours after onset of sepsis. When using dichotomous variable for logistic analysis, high SOFA score was defined as the SOFA score over than 8 according to previous study [24]. Other clinical or laboratory parameters were also recorded at the same time. For prognosis, we assessed hospital mortality, 28-day mortality, ICU mortality, length of ICU stay and mechanical ventilation (MV) support days.

Because we did a second selection of patients from the ETASS study, considering of the possible selection bias, the baseline clinical characteristics between included (273/361) and excluded (88/361) patients was compared.

Statistic methods

Continuous variables with normal distribution were summarized as mean (standard deviation, SD) and compared by t-test; while non-normal distributed variables were described as median (interquartile range, IQR) and compared by the Wilcoxon rank sum test. Categorical data were presented as frequencies and percentages, and compared with Chi-squared tests. Logistic regression analysis was used to evaluate the association between early immunosuppression and mortality, stratified by age groups. In model 1, the crude odd ratios (ORs) and 95% confidence intervals (CIs) were calculated by entering only the variable for early immunosuppression. In model 2, data were adjusted for sex, age, pre-existing condition, immunotherapy, and SOFA score. Then, we further adjusted for the dichotomous variable of immune status improvement in model 3. We also did a sensitivity analysis in which only patients whose levels of mHLA-DR were obtained within 24 hours after onset of sepsis were included to find out if the definition of early immune status (24 hours vs. 48 hours after onset of sepsis) affects the outcomes. A p-value < 0.05 (two tailed) was considered statistically significant. All analyses were conducted using IBM SPSS software version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of adult patients with sepsis

Of the 361 patients, 273 patients were enrolled in this study, including 181 elderly and 92 non-elderly (Fig. 1). There was no significant difference in most clinical variables between the included and excluded patients except for the prevalence of immunotherapy (54/88 vs. 127/273, p = 0.016). The excluded patients were more likely to receive immunotherapy than those included (Table S1). Baseline clinical characteristic data of included patients are shown in Table 1. The mean APACHE II score without the age component were 18.3 (7.4) in the elderly and 17.5 (6.9) in non-elderly. The mean SOFA score was 8.0 (3.9) in the elderly and 7.5 (3.6) in non-elderly. There was no difference in the severity of sepsis between the elderly and non-elderly group, but the elderly group had a higher percentage of pre-existing conditions than non-elderly (85.1% vs. 70.7%, p = 0.006).

Table 1

Baseline clinical characteristics of adult patients with sepsis

Characteristics	N (%)		p value
	Non-elderly (< 60 year, n = 92)	Elderly (≥ 60 year, n = 181)	
Age	54 (48, 57)	75 (68, 80)	< 0.001
Sex (male)	67 (72.8)	138 (76.2)	0.538
Immunotherapy	44 (48)	83 (46)	0.798
Pre-existing conditions	65 (70.7)	154 (85.1)	0.006
Congestive cardiomyopathy	1 (1.1)	8 (4.4)	0.145
Hypertension	25 (27.2)	97 (53.6)	< 0.001
Coronary heart disease	4 (4.3)	27 (14.9)	0.009
Liver disease	9 (9.8)	3 (1.7)	0.002
COPD	5 (5.4)	38 (21.0)	0.001
Diabetes	12 (13.0)	41 (22.7)	0.058
Recent trauma	5 (5.4)	4 (2.2)	0.158
Cancer	36 (39.1)	57 (31.5)	0.208
Recent surgical history			0.064
No history of surgery	40 (43.5)	103 (56.9)	
Elective surgery	24 (26.1)	43 (23.8)	
Emergency surgery	28 (30.4)	34 (18.8)	
Other indicators of disease severity			
Mechanical ventilation	64 (69.6)	150 (82.9)	0.012
Shock	36 (39.1)	72 (39.8)	0.917
Use of vasopressor	37 (40.2)	75 (41.4)	0.847
RRT	11 (12.0)	27 (14.9)	0.312
Low dose corticoid	12 (13.0)	16 (8.8)	0.279

Values are described by number (percentage), mean ± standard deviation or median (interquartile range). COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

Characteristics	N (%)		p value
	Non-elderly (< 60 year, n = 92)	Elderly (≥ 60 year, n = 181)	
Blood transfusion	36 (39.1)	46 (25.4)	0.019
Acute organ dysfunctions			
Pulmonary	85 (92.4)	174 (96.1)	0.185
Renal	24 (26.1)	51 (28.2)	0.715
Cardiovascular	57 (62.0)	133 (73.5)	0.050
Haematologic	42 (45.7)	65 (35.9)	0.119
Hepatic	17 (18.5)	32 (17.7)	0.871
Number of acute organ dysfunctions			0.531
1	17 (18.5)	23 (12.7)	
2	35 (38.0)	79 (43.6)	
3	27 (29.3)	49 (27.1)	
4	8 (8.7)	23 (12.7)	
5	5 (5.4)	7 (3.9)	
Site of infection			
Lung	58 (63.0)	141 (77.9)	0.009
Abdomen	35 (38.0)	44 (24.3)	0.018
Positive blood culture	4 (4.3)	12 (6.6)	0.448
Urinary tract	0	5 (2.8)	0.108
Other	11 (12.0)	12 (6.6)	0.134
Result of pathogens			0.714
Gram negative	24 (26.1)	37 (20.4)	
Gram positive	7 (7.6)	14 (7.7)	
Fungus	7 (7.6)	22 (12.2)	
Mixed	31 (33.7)	64 (35.4)	

Values are described by number (percentage), mean ± standard deviation or median (interquartile range). COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

Characteristics	N (%)		p value
	Non-elderly (< 60 year, n = 92)	Elderly (≥ 60 year, n = 181)	
No	23 (25.0)	44 (24.3)	
APACHE II score	19.6 ± 6.8	23.5 ± 7.5	< 0.001
APACHE II score (without age)	17.5 ± 6.9	18.3 ± 7.4	0.378
SOFA score	7.5 ± 3.6	8.0 ± 3.9	0.327
C reactive protein (mg/L)	127.0 (83.4, 198.0)	133.0 (71.2, 195.5)	0.701
White blood cell count ($\times 10^9$/L)	14.1 (8.6, 19.2)	14.2 (9.8, 18.0)	0.979
Neutrophil (%)	86.3 (80.0, 90.7)	85.5 (80.7, 90.9)	0.939
Monocyte (%)	4.5 (2.9, 7.9)	5.0 (3.0, 7.2)	0.743
Lymphocyte count ($\times 10^9$/L)	0.96 (0.62, 1.64)	0.84 (0.49, 1.29)	0.091
Platelet count ($\times 10^9$/L)	160.0 (82.2, 282.8)	162.7 (101.7, 235.3)	0.816
Lactate (mmol/L)	2.2 (1.2, 3.5)	2.3 (1.4, 3.8)	0.304

Values are described by number (percentage), mean ± standard deviation or median (interquartile range). COPD, chronic obstructive pulmonary disease; RRT, renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

Prognosis of adult patients with sepsis

In our study, 71 (39.2%) elderly and 25 (27.2%) non-elderly died in hospital (Table 2). The elderly patients received more days of mechanical ventilation support than the non-elderly patients (6.2 vs. 4.8; p = 0.009), but there was no difference in the length of ICU stay days (10.3 vs. 9.0; p = 0.103) between elderly and non-elderly patients (Table 2).

Table 2
Prognosis of adult patients with sepsis

Characteristics	N (%)		p value
	Non-elderly (< 60 year, n = 92)	Elderly (≥ 60 year, n = 181)	
ICU mortality	15 (16.3)	50 (27.6)	0.038
Hospital mortality	25 (27.2)	71 (39.2)	0.049
28-day mortality	22 (23.9)	62 (34.3)	0.081
Days of MV (Median, IQR)	4.8 (1.6, 7.7)	6.2 (2.7, 14.2)	0.009
MV free days (Median, IQR)	23.3 (20.3, 26.4)	21.8 (13.8, 25.4)	0.009
ICU stay days (Median, IQR)	9.0 (5.5, 14.7)	10.3 (5.6, 20.7)	0.103
ICU-free days (Median, IQR)	19.0 (13.3, 22.6)	17.8 (7.3, 22.4)	0.112

Values are described by number (percentage) or median (interquartile range). 'Free days' were calculated as the number of days that the patient was alive and free of specified intervention (ventilator use and ICU stay) during the 28-day study period. IQR, interquartile range; MV, mechanical ventilation.

Immune status in adult patients with sepsis

The percentage of early immunosuppression (mHLA-DR ≤ 30%) in the elderly was twice of that in the non-elderly (32% vs. 16%, p = 0.006) patients (Fig. 2A). The immunosuppressed elderly patients had higher hospital mortality than the non-immunosuppressed ones (53.4% vs. 32.5%, p = 0.009), but there was no significant difference in hospital mortality between the immunosuppressed non-elderly and the non-immunosuppressed non-elderly (33.5% vs. 26.0%, p = 0.541) patients (Fig. 3A). To detect the change of immune status, 239 septic patients (80 non-elderly and 159 elderly) whose mHLA-DR was measured on day 3 were included. In these patients, about half of the elderly (82/159, 52%) and the non-elderly (38/80, 47%) patients had immune status improvement on day 3 (Fig. 2B). We also found that patients with immune status improvement on day 3 had lower hospital mortality than those without immune status improvement in both the elderly (21/82 vs. 35/77) and the non-elderly (4/38 vs. 16/42) group (Fig. 3B).

Early immunosuppression was associated with increased mortality in elderly patients

In univariate logistic regression analysis (model 1), early immunosuppression was associated with increased hospital mortality in elderly (ORs: 2.382; 95% CIs: 1.257 ~ 4.514; p = 0.008), but not in non-elderly (ORs: 1.425; 95% CI 0.434–4.676; p = 0.559) patients (Table 3). Adjusted by age, sex, pre-existing

conditions, immunotherapy and SOFA score in model 2, early immunosuppression was independently associated with increased hospital mortality in elderly (ORs: 2.257; 95% CI 1.130–4.506; p = 0.021), but not in non-elderly (ORs: 1.074; 95% CI 0.242–4.763; p = 0.925) patients (Table 3). Then, we conducted another model (model 3) that added the immune status improvement on day 3 into model 2. In model 3, early immunosuppression was also only associated with increased hospital mortality in elderly (ORs: 2.684; 95% CIs: 1.224 ~ 5.883; p = 0.014), but not in non-elderly (ORs: 1.604; 95% CI 0.351–7.331; p = 0.542) patients (Table 3). In addition, we also found that immune status improvement on day 3 was associated with reduced hospital mortality in both elderly (ORs: 0.335; 95% CI 0.159–0.706; p = 0.004) and non-elderly (ORs: 0.131; 95% CI 0.029–0.584; p = 0.008) patients.

Table 3
Early immunosuppression was associated with increased hospital mortality in elderly patients

Subgroup	Model 1	Model 2 [a]	Model 3 [b]
Non-elderly			
Sample size (n)	92	92	80
Early immunosuppression	1.425 (0.434–4.676)	1.074 (0.242–4.763)	1.604 (0.351–7.331)
Immune status improvement	-	-	0.131 (0.029–0.584)
Elderly			
Sample size (n)	181	181	159
Early immunosuppression	2.382 (1.257–4.514)	2.257 (1.130–4.506)	2.684 (1.224–5.883)
Immune status improvement	-	-	0.335 (0.159–0.706)
Values are odds ratios (95% confidence intervals) unless stated otherwise			
a, Adjusted for sex, age (per 10 years), pre-existing condition, immunotherapy, and SOFA score (high vs. low).			
b, Adjusted for covariates in model 2 and the dichotomous variable of immune status improvement on day 3 (yes vs. no).			

The definition of early immune status is a controversial issue, and early immune status was defined as immune status within 48 hours after onset of sepsis in our study. To evaluate whether the definition of early immune status was driving our results, we performed a sensitivity analyses in which early immune status was measured within 24 hours after onset of sepsis. Consistently, early immunosuppression was independently associated with increased hospital mortality in elderly (ORs: 5.507; 95% CIs: 1.497 ~ 20.2584; p = 0.010), but not in non-elderly (ORs: 1.536; 95% CI 0.236–10.023; p = 0.654) patients (Figure S1).

Discussion

The present study is, to the best of our knowledge, the first one to evaluate early immune status in elderly septic patients. Our study has a few important findings. First, our data indicated the elderly had greater risk of developing immunosuppression within 48 hours after onset of sepsis, and the rate was twice of that of the non-elderly. Secondly, early immunosuppression in elderly was associated with poor prognosis, but not in non-elderly patients. Thirdly, immune status improvement was associated with reduced mortality in both elderly and non-elderly.

Immunosuppression was associated with increased mortality and secondary infection, prolonged length of ICU stay and aggravated organ dysfunction in adult and children with sepsis [18, 19, 25, 26]. However, the timing of immunosuppression remains controversial, so it is difficult to determine when to administer immune monitoring and immunotherapy. A recent study demonstrated that septic paediatric patients were immunosuppressed within the first 48 hours after sepsis, and such early immunosuppression was significantly associated with prolonged organ dysfunction time [19]. In our study, about one-third of the elderly (58/181) had early immunosuppression within 48 hours, and more than half of the immunosuppressed patients (31/58) died in hospital. All these results displayed that elderly were more susceptible to immune dysfunction early after onset of sepsis. Therefore, the immune status of elderly patients needs to be monitored from the early stage of sepsis.

Consistent with previous studies, we found elderly patients with sepsis have higher mortality than non-elderly [2, 27]. However, it appears that it is not the age per se but rather the associated factors, such as severity of illness or immune status, contribute to the increased mortality rate [28]. In our study, the severity of sepsis (SOFA score and APACHE-□ score without an age component) was similar in the elderly and non-elderly, but the percentage of early immunosuppression in the elderly was twice of that of the non-elderly patients. We also found that more than half of the immunosuppressed elderly (31/58, 53%) died in hospital, but only one third of the non-elderly (5/15, 33%) died during hospitalization. Furthermore, immunosuppression was associated with increased hospital mortality in the elderly, but not in the non-elderly patients. That is to say, immunosuppression may be responsible for the increased mortality in elderly patients with sepsis.

Numerous studies revealed that mHLADR can be used to predict prognosis and to select immunosuppressed patients who needed immunostimulant [8, 9, 29]. Monneret and his colleagues previously found that mHLA-DR decreased in septic patients on days 1–2 and days 3–4 after onset of sepsis, but only low mHLA-DR (≤ 30%) on days 3–4 was independently associated with increased 28-day mortality in patients with sepsis [10]. However, Perry and his colleagues reported a different result that mHLADR on days 1–3 cannot help to predict outcome in sepsis [30]. In Perry' research, the median age of septic patients was about 56 with a range from 20 to 84, while in Monneret' study, the median age was 64 (IQR: 48 ~ 75), the age differences in septic patients may be the cause of the opposite outcomes in the two studies. In current study, our results indicated that early low mHLA-DR expression was an independent risk factor for poor outcome in elderly, but not in non-elderly septic patients. Our previous study demonstrated that dynamic change of mHLA-DR was a reliable predictor for mortality in septic patients [8]. Then, we combined early immune status with changes of immune status to evaluate hospital

mortality. In this study, early immunosuppression was associated with increased hospital mortality in elderly, and immune status improvement on day 3 was associated with reduced hospital mortality in both elderly and non-elderly patients. Therefore, monitoring of early immune status should be carried out in elderly patients, and it may be beneficial to monitor the dynamic changes of immune status in both elderly and non-elderly patients.

Several limitations should be noted in our study. Firstly, our data came from a clinical study of immunotherapy for patients with sepsis. Considering the interference of immunotherapy in our study, we took immunotherapy as a fixed covariate in multivariate logistic regression analysis for mortality and found immunotherapy did not affect the prognosis of elderly patients. Secondly, only 15 non-elderly septic patients with early immunosuppression were included in our study, so a larger study is needed to further verify the results that early immunosuppression was not associated with poor prognosis in non-elderly patients.

Conclusions

In adult patients with sepsis, the elderly were more susceptible to early immunosuppression after onset of sepsis. Early immunosuppression was associated with poor prognosis in elderly patients.

Abbreviations

APACHE II = Acute Physiology and Chronic Health Evaluation II; CIs = confidence intervals; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ETASS = Efficacy of Thymosin Alpha 1 for Severe Sepsis; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial pressure; mHLA-DR = monocyte human leukocyte antigen-DR; MV = mechanical ventilation; ORs = odds ratios; RRT = renal replacement therapy; SBP = systolic blood pressure; SD = standard deviation; SOFA = sequential organ failure assessment; SSC = surviving sepsis campaign; Tα 1 = thymosin alpha 1.

Declarations

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Availability of data and materials: The data used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Figures

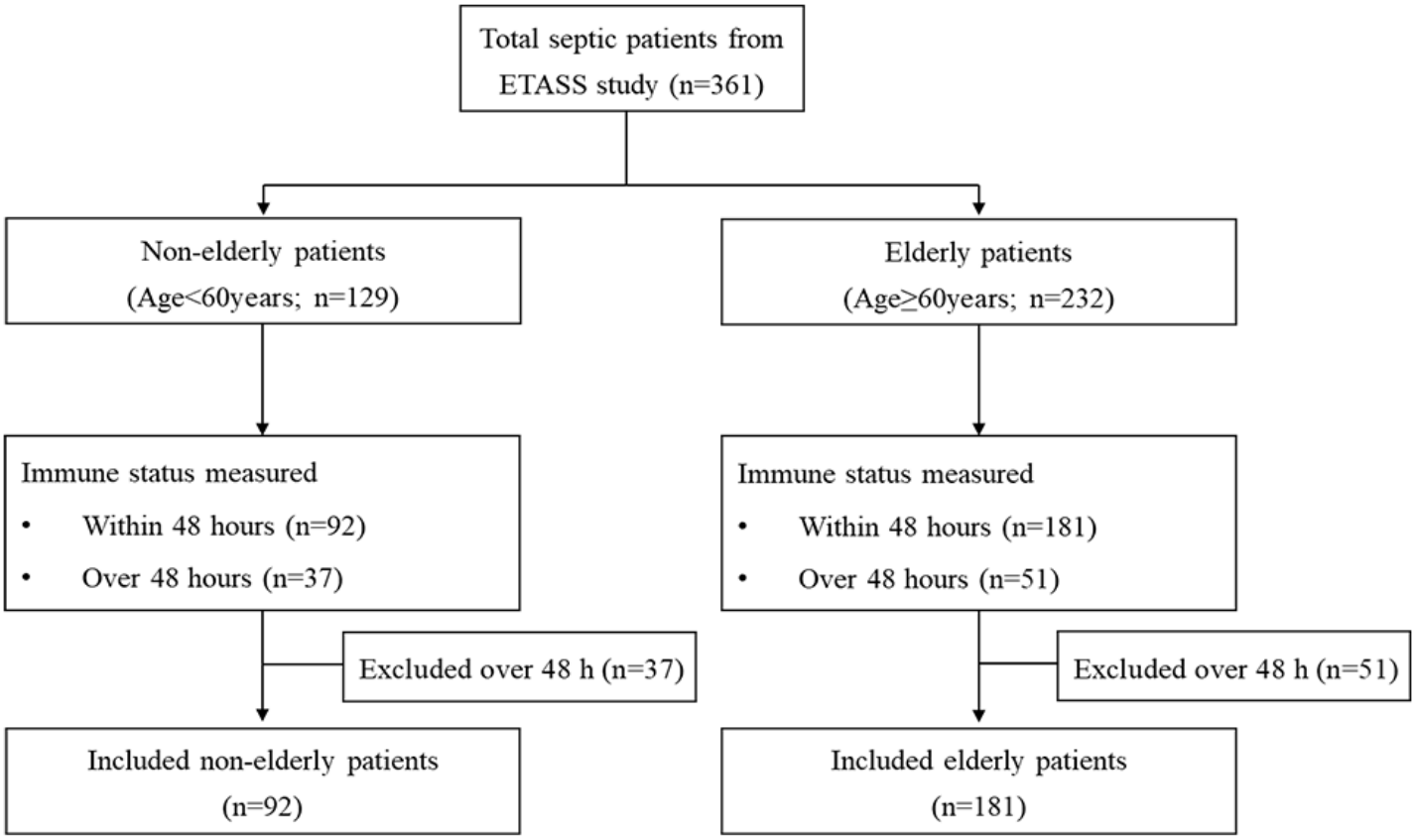

Figure 1

Flow chart In this study, 181 elderly and 92 non-elderly septic patients whose mHLA-DR was obtained within 48 hours after onset of sepsis were enrolled.

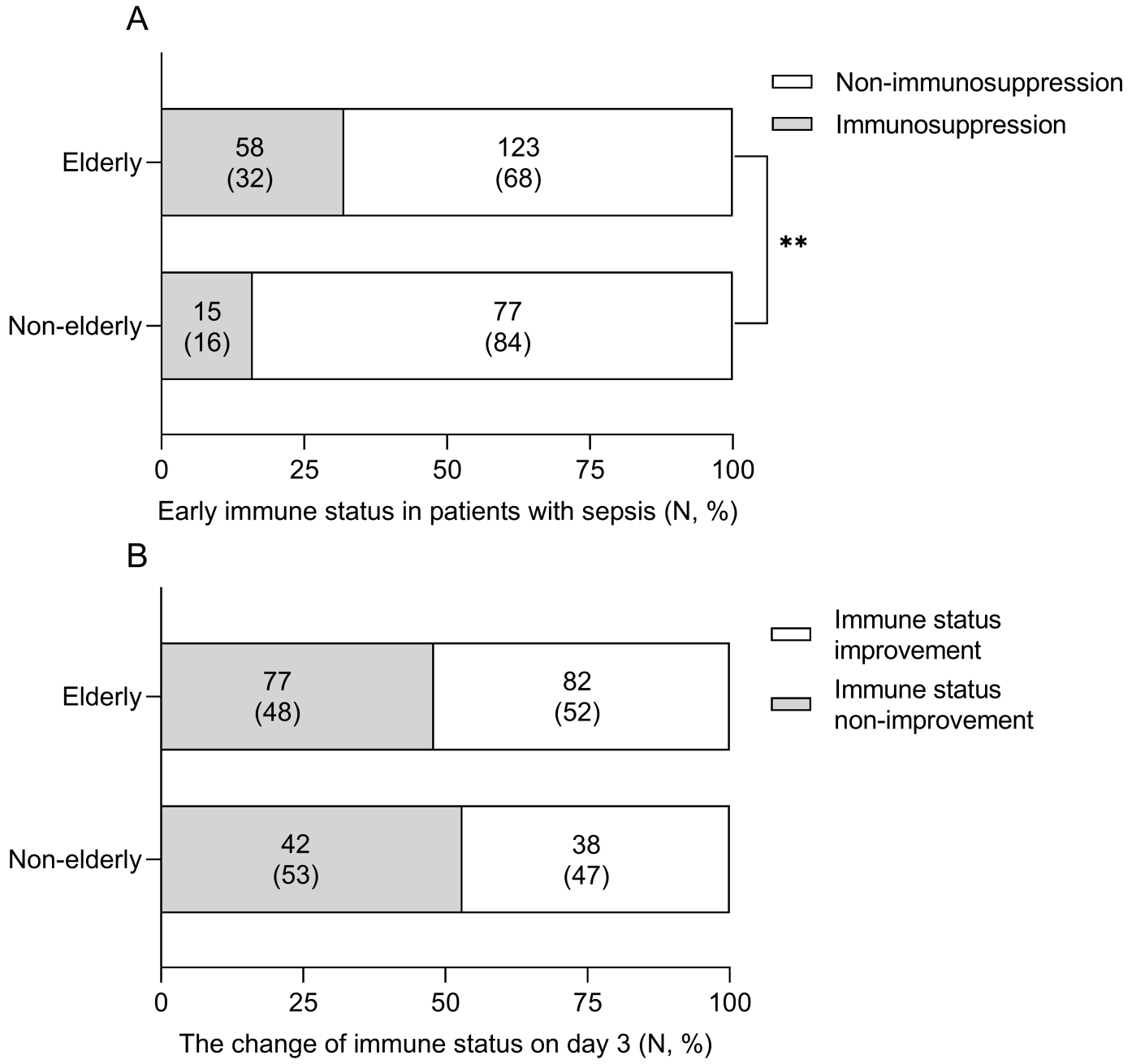

Figure 2

Early immune status and change of immune status in patients with sepsis A. The percentage of early immunosuppression in elderly patients was twice of that of non-elderly patients (32% vs. 16%, p=0.008). B. About half of elderly (82/159, 52%) and non-elderly (38/80, 47%) patients had immune status improvement on day 3. (**, p value <0.01)

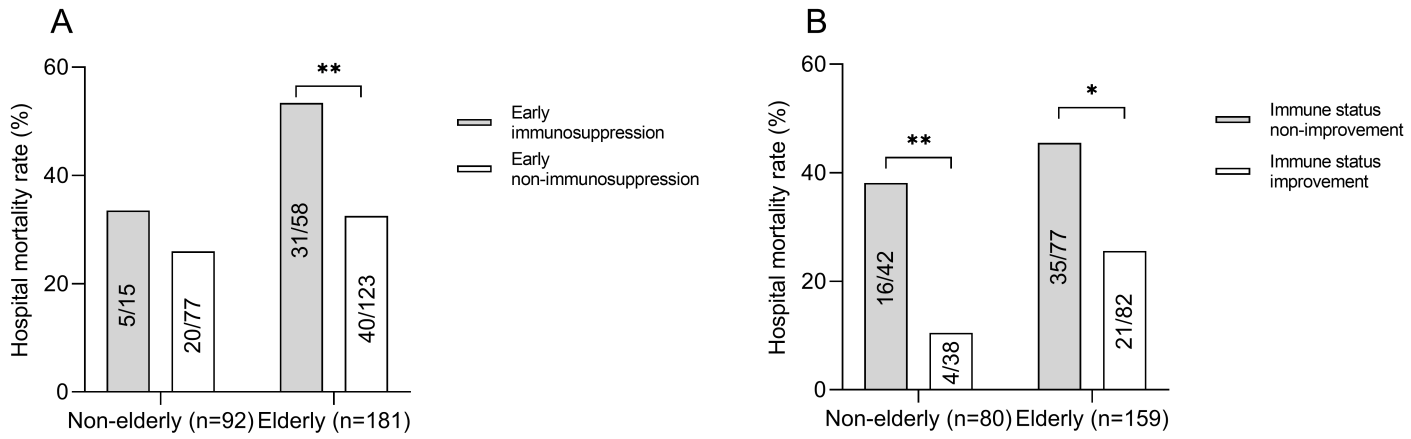

Figure 3

Immune status and hospital mortality A. Elderly patients with immunosuppression had higher hospital mortality than elderly patients without immunosuppression (31/58 vs. 40/123), but there was no significant difference between immunosuppresive group and non-immunosuppresive group in non-elderly (5/15 vs. 20/77) patients. B. Septic patients with immune status improvement on day 3 had lower hospital mortality than patients with non-improvement in both elderly and non-elderly. (*, p value <0.05; **, p value <0.01)

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