Early Severe Lymphopenia in Critically Ill Emergency Surgical Patients is Associated with Disease Severity and Outcome

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Introduction

• A state of 'lymphocyte exhaustion,' characterized by reduced numbers of circulating cells with reduced functional and proliferative capacity, has been described in critically ill patients [1]

• Prolonged lymphopenia has been postulated to be a simple marker of lymphocyte dysfunction and immunosuppression [2]

• Lymphopenia which persists for several days after the onset of critical illness is associated with increased mortality in patients with sepsis [3] and following major trauma [4]

• However, the relationship between lymphocyte counts early in the course of critical illness and outcome is not clear

• The aim of this study was to investigate the relationship between early lymphocyte count and outcome in a cohort of critically ill Emergency General Surgical patients, a complex group who account for substantial a number of ICU admission and among whom mortality rates remain high [5]

• Specifically, we hypothesized that severe lymphopenia within the first 48 hours of admission would be associated with poor outcome

Method

• Retrospective cohort study of ICU admissions to a single centre between 2002-2013

• **Inclusion Criteria:**
 - Adult emergency general surgical admission
 - Sequential Organ Failure Assessment (SOFA) score ≥5 at admission (indicating dysfunction in at least two organ systems)

• **Exclusion Criteria:**
 - Trauma patients, vascular emergencies and acute pancreatitis
 - Inherited or acquired immunosuppression
 - Pregnancy

• Demographics, primary diagnosis and outcome data were collected and recorded prospectively

• Illness severity was assessed using Acute Physiology and Chronic Health Evaluation (APACHE) 2 Score and SOFA score at admission

• Differential white blood cell counts measured over the first 48 hours of admission were recorded

• The cohort was divided into three groups based on the lowest lymphocyte count observed in this period, according to previously defined criteria [3]:
 - No lymphopenia (>0.9x10^9/L)
 - Moderate lymphopenia (0.5-0.9x10^9/L)
 - Severe lymphopenia (<0.5x10^9/L)

• Multivariate logistic regression was performed, incorporating all variables associated with mortality on univariate analysis into the final model

Results

Table 1: Demographics of the study cohort

	All patients (n=173)
Demographics	
Male gender, n (%)	88 (51%)
Age, median (IQR)	69 (56-78)
Days to ICU admission, median (IQR)	1 (0-3)
Surgical procedure, n (%)	159 (92%)
Midline laparotomy, n (%)	139 (80%)
APACHE II score, median (IQR)	17 (12-21)
SOFA score, median (IQR)	8 (7-10)
Lymphocyte Profile	
No lymphopenia	23 (13%)
Moderate lymphopenia	70 (41%)
Severe lymphopenia	80 (46%)
Outcome	
ICU LOS, median (IQR)	3.0 (1.7-6.7)
In-hospital mortality, n (%)	71 (41%)

Figure 1: Severe lymphopenia is associated with greater disease severity, as measured by APACHE 2 and SOFA scores at admission
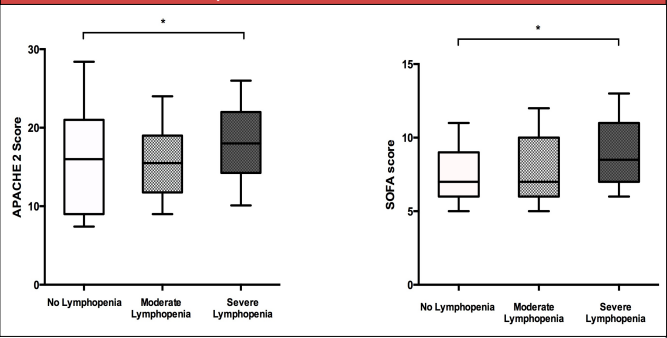

Figure 2: Lymphopenic patients exhibit a signature white cell profile, characterized by low monocyte and neutrophil counts, which is proportional to the severity of lymphopenia
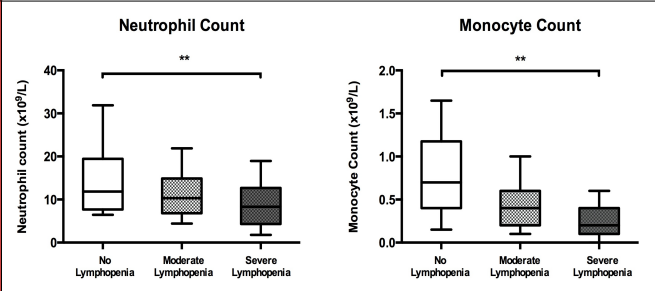

Figure 3: Non-survivors exhibit lower lymphocyte counts in the first 48 hours of admission compared to survivors
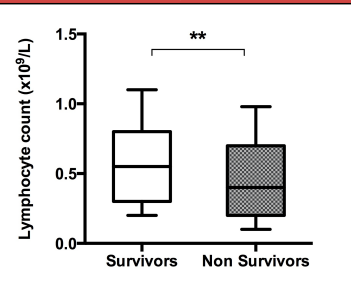

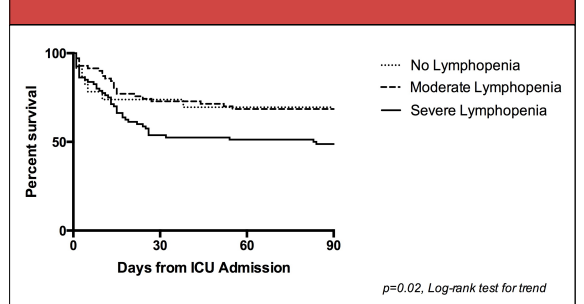**Figure 4:** Severe lymphopenia, but not moderate lymphopenia, is associated with increased mortality

p=0.02, Log-rank test for trend

Figure 5: Multivariate Regression Analysis[1]

Variable	Odds Ratio	p-value
Age	1.042 (1.015-1.071)	0.002
APACHE 2	1.098 (1.019-1.184)	0.015
SOFA	1.207 (1.029-1.415)	0.021
Severe Lymphopenia	**2.105 (1.010-4.388)**	**0.047**

All box plots demonstrate median with interquartile range; whiskers represent 10th-90th percentiles
*p<0.05 **p<0.01
[1]Only variables with statistically significant association with mortality on multivariate analysis are shown; values in parentheses correspond to 95% confidence intervals

Conclusion

• This study supports previous evidence from other cohorts of critically ill patients suggesting that lymphopenia is associated with poor outcome

• A novel observation is that severe lymphopenia at an early stage of critical illness, rather than lymphopenia which persists for several days, is associated with higher mortality; this was not true of patients with only moderate lymphopenia

• Lymphopenia is also associated with a reduction in monocyte and neutrophil counts, which is proportional to the severity of lymphopenia

• Although patients with severe lymphopenia tend to be more unwell, it remains an independent risk factor for poor outcome

• The question of whether therapeutic strategies to increase lymphocyte count and function could improve outcome in critically ill patients is an important areas for further study

References

1. Monneret G, Venet F. A rapidly progressing lymphocyte exhaustion after severe sepsis. *Crit Care* 2012;16(4):140.
2. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol*. 2013;13(12):862-74
3. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM Hotchkiss RS Persistent lymphopenia after diagnosis of sepsis predicts mortality. *Shock*. 2014;42(5):383-91.
4. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, Ayala A. Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. *Crit Care*. 2012 Jan 20;16 (1):R12.
5. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, Grounds RM, Bennett ED. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care*. 2006;10(3):R8

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