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RESEARCH ARTICLE

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Immune Profiling of ICU Patients with Emphasis on Sepsis, A Pilot Study

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ABSTRACT

ICU patients suffering of multiorgan dysfunction are subject to continuous, and complex treatment based on multimodal sophisticated monitoring and frequent data analysis. Immune monitoring is applied at a minimalistic level, from research immunology standpoint, restricted to CRP, PCT, leukocyte subsets in the blood and recently IL-6 levels. The present work provides additional variables, which may serve as future targets to modify and enhance recovery.

Methods: 31 patients in total were analysed processing 36 samples. 56% of them were septic during ICU hospitalisation. Blood samples were analysed using established validated laboratory technologies.

Results: 80% of examined patients carried an immune phenotype that may be interpreted as deviance or inadequacy reflected in impaired phagocytic activity (FA), and low stimulatory indices (SI) of leukocytes, hyporesponsive phenotype in blood culture positive samples, in some cases in lower immunoglobulin numbers, in ¼ of cases enhanced T cell activation and or regulation.

Conclusions: The primary aim of this study was to raise attention to the vastly understudied immune response in sepsis, that appears to be largely deviant and little understood. The substantial number of important findings underscores the need to define immune pathology in a much more sophisticated manner in complicated clinical settings, than has been done until now. Not solely because antibiotic resistance is an emerging threat, but for the reasons of ongoing tissue damage inflicted by SIRS and a concurrent impotency of pathogen and debris clearance, a major dysbalance reflected in this work. The study is limited by the small sample size and limited resources, constraining analysis.

ARTICLE HISTORY

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KEYWORDS

ADCC- Antibody Dependent Cytotoxicity, AIPs- Autoinducible Peptides, ActA -Actin Assembly Inducing protein, BC- Blood Culture CEF- Complement Evasion factor, CRP - C Reactive Protein. PCT - Procalcitonin, FA - Phagocytic Activity, ICU – Intensive care unit, ILC1 - Innate lymphoid cell 1, Leu -Leukocytes, Ly - Lymphocytes,NADPH - Nicotinamide adenine dinucleotide phosphate, Neutro - Neutrophils, NET- Neutrophil extracellular traps, NOX (NADPH oxidase), NK - Natural killer cell, NKT - Natural killer T cell, SCIN - Staphylococcal complement inhibitor, ROS - Reactive Oxygen species, PAD4 - PEPTIDYL Arginine Deiminase 4, PCC -Pearson Correlation Coefficient, SI - Stimulatory Index, SOFA - Sequential Organ Failure Assessment Score, SIRS - Systemic Inflammatory Response Syndrome,STEMI - ST Elevation Myocardial Infarction

Introduction

This work is set to provide an observatory background on the elementary immune status of our patients based on innate and adaptive immune parameters in blood. It is a snapshot, a pilot project to pinpoint main disturbances.

The main goal of this publication is to provide evidence that the majority of our patients present with immune deviance or deficiency, and the aberrant immune behaviour may potentially worsen outcome. In order to influence the immune response, augmenting execution over blunt inflammation is a potential aspiration of future research, such effort has to be based on monitoring and understanding the reasons behind insufficient immediate responsiveness of the innate immune system. The statistical analysis provided here can offer limited value due to insufficient homogeneity stemming from small sample size of patients presenting with multiple variables.

Main Article

We observed 31 patients, 13 females, 18 males, with the characteristics depicted in table 1.:

The average age and SOFA score was comparable between two sexes, and the death rate was slightly lower among women (33 % vs 38%). In general women are known to have a more substantial antibody response leading to better opsonisation and ADCC (antibody dependent cytotoxicity) [1].

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Table 1: Age, Sex, Sofa, Comorbidity Index, Length Of ICU Stay, Death Rate Distribution of Patients, +/- Standard Errors (SE) when Applicable

	FEMALES	MALES	overall
Age	61.15+/-17.4	64.11+/-16.8	62.9+/-17.1
Sex	13	18	31
SOFA	11+/-4.15	11.65+/-4.68	11.2+/-4.4
COMORBIDITIES	6.7+/-1.64	6.5+/-1.55	6.6+/-1.58
LOS ICU	14.7+/-11.2	13.94+/-8.5	14.27+/-10.28
Death rate	33.3	38.9	36.7

Comorbidity indices were comparable, using a custom calculator, reflective in a flexible manner on the severity of comorbidities (Table 2) 56% of patients were septic, and the principal organ involvement potentially concluding in sepsis or infection was the lung in 21.2% and of abdominal origin in 30.3%, cardiovascular disease 18.2%, malignancy 18.2% and renal in 12.1% of cases (Figure 1). The average SOFA score 11.2% was predicting 50% mortality, and hospital mortality of the observed patients was 36.7%. There was a very strong significant correlation of age to comorbidity indices (Table 4, pcc:0,74, p:0.000004)

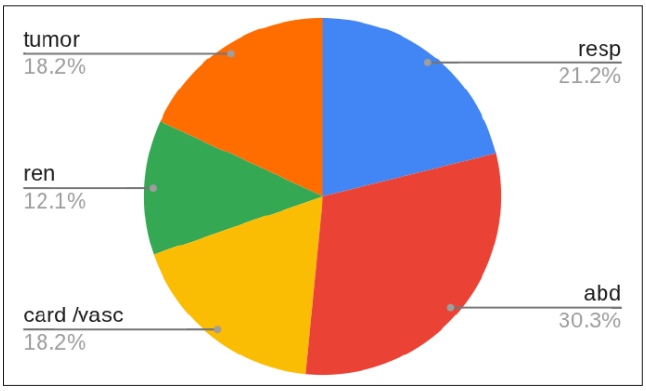


Figure 1: Organ Source of Admission, Including But Not Exclusive to Septic Patients

Resp-respiratory, ren-renal, abd-abdominal, card/vasc - cardiac and or vascular

Table 2: Comorbidity Index Calculator

POINTS	Heart Failure	COPD	Renal failure	arrhythmias	LIVER/ Tumor	CNS	Diabetes
1	DDI,II,HT	I	I	Heart rate <130/min	Steathosis inflammation	Weakness frailty	diet
2	DDIII, IV CHF EF>40%	II	II	Heart rate>130/ min	Cirrhosis	Immobility frailty	PAD
3	CHF,EF 20-40%	III	III	<40/min (pacemaker) heart blocks	Any malignancy local	coma	inzulin
4	CHF EF<20%	IV	IV	CPR	Any malignancy generalized	Any other chronic disease 1-4	Complic. of diabetes

DD-diastolic dysfunction, HT - hypertension, CHF- chronic heart failure, EF -ejection fraction, HR -heart rate, PAD- oral antidiabetics, CPR - cardiopulmonary resuscitation

Overall Immune Portrayal

Table 3 and Figure 2 demonstrate the proportion of patients with high neutrophil, low T, B, NK (natural killer) cell counts, high IgE and low IgG levels, activated T phenotype and regulation. Naturally these proportions are overlapping. While neutrophils are major contributions to immune response, functionally they disconcerted the expectation in that 80% of our patients presented with low stimulatory index, reflective of oxidative burst and in 34.2 % a phagocytic activity which was below the low norm suggesting insufficient processing of engulfed pathogen using ROS (reactive oxygen species), insufficient neutrophil stimulation. No significant correlation had been found between FA (phagocytic activity) and SOFA (sequential organ failure activity), nor between SI and SOFA indices, but age correlated to comorbidity very strongly (table 4).

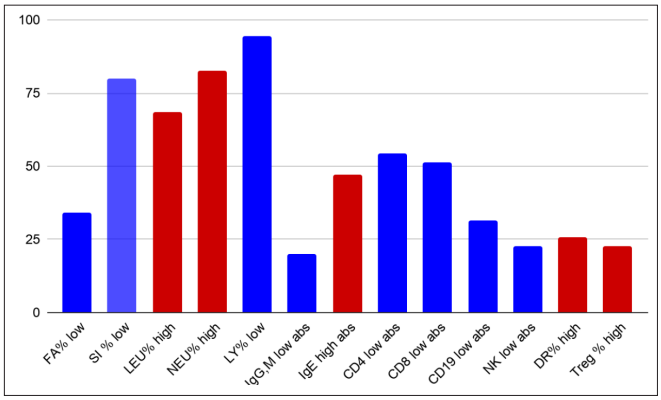


Figure 2: Proportion of Patients Representing Above Or Below Normal Levels Of Immune Parameters

Table 3: Numerical Representation, Proportion of Patients Representing with Above or Below Normal Levels of Immune Parameters

parameter	% of 100
FA% low	34.2
SI % low	80
LEU% high	68.57
NEU% high	82.8
LY% low	94.3
IgG,M low abs	20
IgE high abs	47.3
CD4 low abs	54.2
CD8 low abs	51.4
CD19 low abs	31.4
NK low abs	22.8
DR% high	25.7
Treg % high	22.85

Table 4: Pearson Correlation Between Age and Phagocytic Activity, Age and Stimulatory Index, Age and SOFA Score, as Well as Age and comorbidity index, pcc: Pearson Correlation Coefficient

	AGE/FA	AGE/SI	AGE/SOFA	AGE/CI	CI/SOFA	FA/SI
PCC	-0.1361	-0.03	0.21	0.74	0.167	0.1
p	0.48	0.89	0.28	0.000004	0.38	0.58

20% of our patients presented with low IgG or IgM numbers and 47.3% had high IgE levels which may potentially indicate a skewed Th1/Th2 phenotype, an acquired secondary hyper IgE status or hypersensitivity to some components of therapy. Monitoring the Th1 /Th17/ vs Th2 phenotype bears clinical importance in the context of pathogen and insult, in that while Th1 and Th17 enhances the antibacterial and antiviral activity of effectors (neutrophils, macrophages. NK and CD8 cells) [2,3]. Th2 response leads to the reconciliation with the potential side effects of airway hyperactivity, enhanced mucus secretion, and activation of profibrotic alternative macrophages. Th1 and Th2 are exclusive and mutually repressive [4-6].

Comparison Based on Bacteremia, the Positivity of Blood Culture for Pathogens

When local defenses are subdued by the pathogen and sepsis culminates in positive blood cultures, direct interaction between the pathogen and innate immune cells betides. Patients in whom positive blood cultures(BC+) were obtained were found to have neutrophil phagocytic activity significantly lower (68.75%+/-7.3, BC+ vs 86.5%+/-3.2, BC-,p:0,038) (table 5 , figure 3) than in the patient population, not bacteremic , while stimulatory indices were not notably different between bacteremic and non bacteremic patients(22.74% +/- 5.18, BC+ vs 17.8% +/- 3.08, BC-,p:0,39). Age (63.3+/-5.13 vs 63.56+/-4.16), SOFA(12+/-1.36 vs 10.5 +/-1.1) and comorbidity index scores(5.9+/-0.86 vs 5.4+/- 0.62) were not different, mortality was higher in BC+group without capacity to drawing statistical conclusions (30.7% vs 25%), PCT(29.1+/-4.9 vs. 15.5+/-25.9 ug/l), CRP(168+/-11.6mg/l vs 162.9+/-10.76mg/l) and neutrophil counts (16.46+/- 4,38 vs 14.35+/-2.56 x10*9/l) were not significantly different among the two groups, sample size was lower in the positive blood culture group (13 vs 18) and in general, relatively low. The plausible theoretical explanation may be an impaired phagocytic responsiveness of neutrophils enabling measurable bacteremia to take place. Neutrophil stimulation transpires upon contact with opsonized pathogens using immune globulins, complement and various pattern recognition receptors, the process is enhanced by proinflammatory cytokines. To decipher why neutrophils, present with a repressed phagocytic phenotype unexpectedly in bacteremia should be subject to further research. The apprehended pathogens are shown in table 6. Among the pathogens members of the seven critical priority opportunistic pathogens emphasized by WHO, with emerging potential of carrying carbapenemase resistance genes ESKAPE have been encountered -1,3,4,6,13 [7].

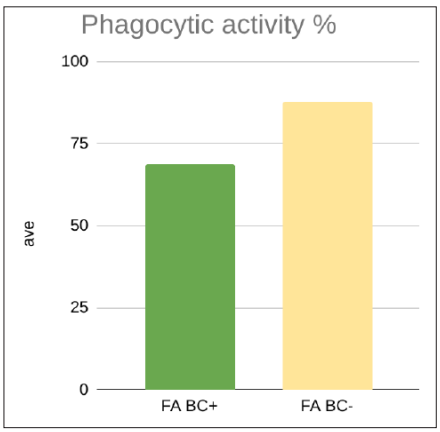


Figure 3: Average Phagocytic Activity of Neutrophils in Patients from Positive and Negative Blood Cultures for Pathogens (%)

Table 5: Average (ave,mean) Phagocytic Activity and Stimulatory Index of Neutrophils in Patients from Positive and Negative Blood Cultures for Pathogens, with Standard Errors (se) and Statistical Comparison Based on Welch t-test

	FA BC+	FA BC-	SI BC+	SI BC-
ave	68.75	86.5	22.74	17.8
se	7.3	3.2	5.18	3.08
welch t test		0.038		0.39

Table 6: Bacteria Cultivated from Blood Cultures, with Respective Phagocytic and Stimulatory Activities. Yellow - Gram Negative, Purple - Anaerobic, Pink- Obligatory Intracellular., MRSA –Methicillin Resistant Staphylococcus Aureus, MSSA- Methicillin Sensitive Staphylococcus Aureus

	pathogen	FA(80-100%)	SI(30-100%)
1	Klebsiella pneumoniae	72.86	8.28
2	Cutibacterium acne	98.9	11.21
3	MRSA	38.7	16.9
4	Enterococcus faecium	51.7	10.1
5	Clostridium perfingens	98.8	15.03
6	MSSA	74.37	4.48
7	Staphylococcus hominis	90.42	20.46
8	Streptococcus pyogenes	85.07	19.03
^9	Streptococcus dysgalactiae	15.09	22.93
10	Listeria monocytogenes	51.8	56.99
11	Streptococcus dysgalactiae	91	15.02
12	MSSA	56.3	18.9
13	Enterobacter cobei	99	36.84
average		71.08	19.7
se		7.36	3.8

Table 7 highlights some of the major survival and evasion tactics of depicted pathogens. While emerging antibiotic resistance is a major combat tool of pathogens, less considered are the various evasion and escape mechanisms that inhibit phagocytosis and killing. The specimen found in sample blood cultures use the following survival mechanisms [8-15].

Table 7: Bacteria Cultivated from Blood Cultures, Main Mechanisms of Immune Evasion

CPS- capsular polysaccharide, LPS- lipopolysaccharide, NLRP3- NOD-, LRR- and pyrin domain-containing protein 3, AIM2- absent in melanoma 2, ROS- reactive oxygen species, CAMP-pore forming toxin, MRSA - methicillin resistant staphylococcus aureus, SCIN - staphylococcal complement inhibitor, PVL -Panton Valentine Leucocidin, NET -neutrophil extracellular trap, AIPs - autoinducible peptides, SLO -streptolysin O, SLS -streptolysin S, CEF- streptococcal evasion factor, ActA - actin assembly inducing protein

	pathogen	evasion of engulfment				
1	Klebsiella pneumoniae (8)	CPS	alters LPS	facultative IC	inhibits NLRP3, AIM2	siderophores
2	Cutibacterium acne	biofilms	low inflammation	fac IC, inh. fagosome maturation	inhibits ROS	CAMP
3	MRSA (9)	Capsule Biofilm spA	SCIN	Enzyme degradation		PVL
4	Enterococcus faecium (10)	biofilm	gelatinase	Steal mode	Survives IC	On dry surfaces For months
5	Clostridium perfringens	Alpha toxin Neu killing	Perfringolysin, phagocyte killing	Survives in macrophages	Uses NETS to spread	
6	MSSA (14)	spA	SCIN		Inhibits ROS	
7	Staphylococcus hominis (12)	biofilm	Medical devices in immune compromised	Protective skin commensal	AIPs	
8	Streptococcus pyogenes(11)	SLO,SLS	M protein	fH binding proteins CEF	NET DNAse	Degrades IgGs
^9	Streptococcus dysgalaciate	Biofilsms, pili	M protein	Antigenic variation	Net escape via DNAse	
10	Listeria monocoytogenes (13)	Ndeac of PDG	Listeriolysin O	ActA	Survives IC	
11	Streptococcus dysgalactiare					
12	MSSA					
13	Enterobacter cobei(15)	Robust biofilms	Adaptability and resistance	Gen. adaptability, horizontal gene transfer	Survives IC	

Table 8: Comparison of Septic and Non-Septic Patients

	nonseptic	septic	p welch	se nonseptic	se septic
FA %	95.6	77.15	0.0015	1.46	4.48
CRP mg/l	74.58	222.1	0.0004	17.48	25
age	60.67	68.05	0.29		
mortality	44	30	0.47		
SI %	29.36	16.97	0.0036	2.3	3.1
Leu x10*9/l	12.7	20.6	0.033	1.53	3.16
PCT ug/l	0.77	20.05	0.008	0.43	6.13
CI	6.3	7+/-0.5	0.5	0.83	0.65
SOFA	10.5	11.8+/-2.9	0.38	0.97	1.1

Many bacteria hide using biofilm formation, coating with sturdy capsular polysaccharide, staphylococcal protein A that binds to the Fc region of bacteria, disabling phagocyte recognition. Toxins that trigger death of leukocytes, streptolysin 0 and S (SLO, SLS), staphylococcal pore- forming leukocidins, clostridial alpha toxin, and perfringolysin, etc. Complement is targeted on several levels, by gelatinase degrading C3 and iC3b, staphylococcal complement inhibitor (SCIN) that degrades C3 convertases, streptococcal complement evasion factor (CEF) inhibiting C3b and C5a etc. The steal mode in E. faecium refers to in vitro susceptibility to vancomycin while in vivo E. faecium can revert to resistant phenotype. Staphylococcus hominis auto inducible peptides (AIPs) inhibit quorum sensing.

Obligate intracellulars use different mechanisms, Listeria monocytogenes (LM) alters its surface peptidoglycan using deacetylation to avoid engulfment, but most importantly once intracellular, it hijacks the host's apparatus to avoid killing and to enhance spreading, via ActA to use the hosts cytoskeleton for spreading, blocks macrophage apoptosis, using listeriolysin and phospholipases breaks the wall of phagosomes, escapes to the cytosol to secure survival. Our patient with LM bloodstream infection had outstandingly high ROS activity, indicating intensive intracellular processes in place to fight the intracellular pathogen.

Immune Characteristics of Septic Patients

When we looked at our patients, where sepsis was diagnosed by clinical assessment of SIRS accompanied by positive pathogen source, data revealed the following differences, with significance considered 0.05 and below based on welch t test. The groups were comparable, because no substantial difference between nonseptic and septic patients respectively was in age(60.67 vs 68.05 years), SOFA (10.5 vs 11.8) and comorbidity indices(6.3 vs 7).Traditional SIRS/sepsis parameters such as leukocyte count(12.7 vs 20.6x10*9/l,p:0.033), CRP(74.58 vs 222.s mg/l,p:0.0004) , PCT(0.77 vs 20.05ug/l,p:0,008) were considerably higher in septic patients in the blood, and sepsis was reflected in a strongly significantly lower phagocytic (95.6 vs 77.15%,p:0,0015) and stimulatory activity(29.36 vs 16.97%,p:0,0036) (Figure 4,5 and Table 8). A number of theories and conclusions can be drawn from such results, including a possible immunosuppressive effect of CRP and PCT, but first and foremost these data endorse the need to further study and understand this finding. In this study 20 septic and 9 non-septic patients were involved, with relatively low and unequal sample sizes. In addition, a moderate negative correlation is described between CRP, PCT and phagocytic activity in septic patients. (Figure 6,7 and Table 9,10). Several studies examine the differential role of pCRP and mCRP in their effect on phagocytosis and ROS production, and the results appear conflicting or vastly dependent on circumstances. In chronic periodontitis model for example extracellular ROS production is decreased by CRP, in other systems CRP may enhance phagocytosis in a complement dependent manner in that blockade of C3 convertases inhibited mCRP mediated ROS production [16-18]. CRP participated in complement mediated phagocytosis of Str pneumoniae and zymosan, but not E. coli. CRP is known to bind to C1q and activate the classical complement pathway [19]. We had the opportunity to examine serum levels of C3 and C4 enabling baseline differentiation between classical (C3, C4) and alternative (C3 only) pathways, finding that the dynamics were very limited in direction of upregulated production or consumption, the majority of patients demonstrated with normal C3 and C4 serum levels (data not shown). Correlations do not grant associations, even though the elements of the system crosstalk. While PCT is extensively used to monitor sepsis dynamics, emergence and or discontinuation of ATB treatment, experimental evidence of PCT function during sepsis and beyond that is extremely sparse. PCT during sepsis is produced in a ubiquitous manner and from available data appears to contribute to the phagocytic and microbicide defect of septic neutrophils, to impede their migration, to trigger cytokine production and to associate with mortality in sepsis [20]. Human recombinant PCT had a strong antiphagocytic effect in vitro on whole blood derived polymorphonuclears reflected in inhibited microbicidal outcome [21].

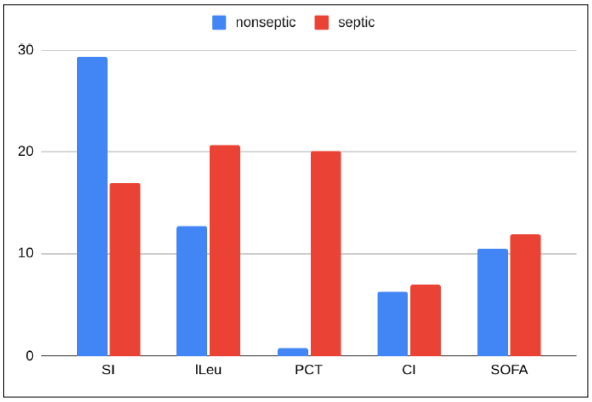


Figure 4: Comparison of SI-Stimulatory Index, Leukocyte Numbers, Procalcitonin Levels, Comorbidity Indexes and SOFA Score among Nonseptic and Septic Patients

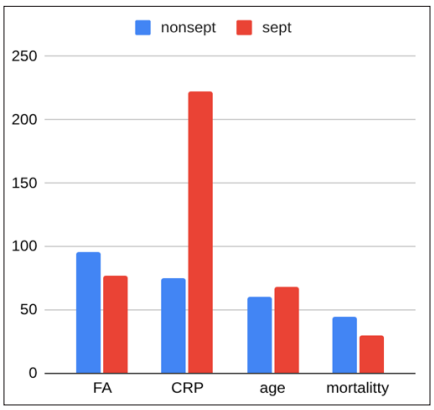


Figure 5: Comparison of Phagocytic Activity (Fa), CRP, Age And Mortality Among Non Septic and Septic Patients

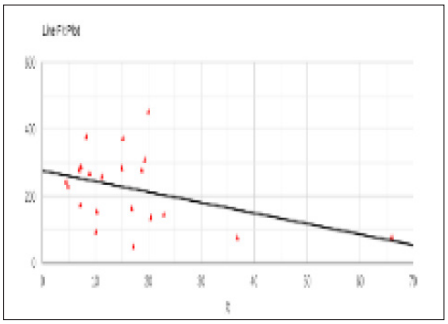


Figure 6: Pearson Correlation, FA/CRP of Septic Patients, y axis: Phagocytic Activity, x - axis: CRP Level

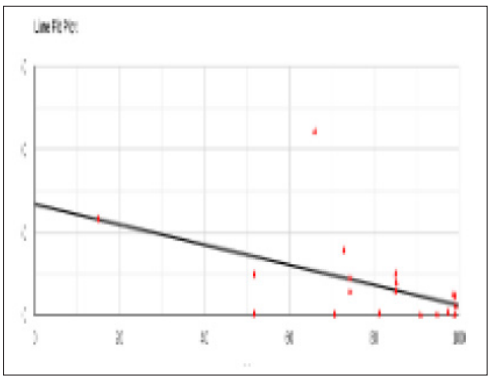


Figure 7: Pearson Correlation FA/PCT, y axis: Procalcitonin, x -axis: Phagocytic Activity of Septic Patients

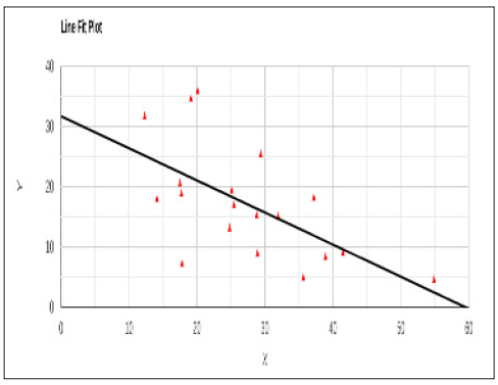


Figure 8: Strong Negative Correlation Between Leukocyte Numbers and Stimulatory Activity X axis - Stimulatory Index, y axis- Leukocytes

Table 9

	FA/CRP	FA/PCT
Pearson correlation coefficient	-0.431	-0.48
P value	0.05	0.03

Table 10

	Leukocytes/FA	Leukocytes/SI
Pearson correlation coefficient	-0,26	-0,6
P value	0,36	0,005

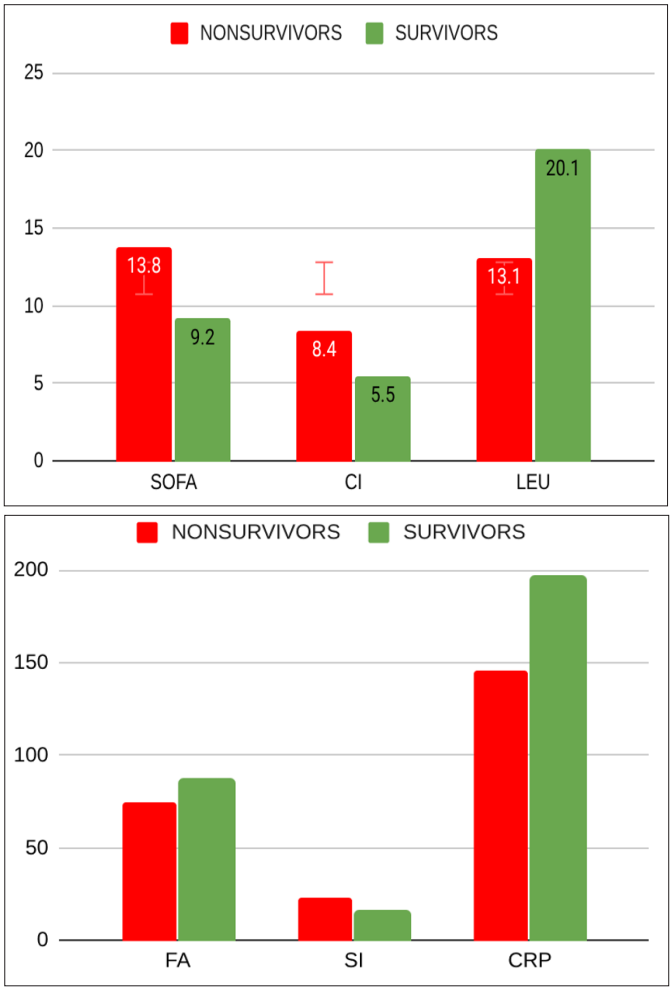


Figure 9a, 9b: Comparison of Survivors to Non Survivors in SOFA /absolute number/, CI/absolute numbers/, Leu(x10*9/l) in their Respective Values, FA (%), SI (%), CRP (mg/l)

Effect of Leukocytosis on Phagocytic Activity and Stimulatory Index of Blood Leukocytes

When patients were grouped based on high leukocyte count above 12x10*9g/l singularly, there was no correlation between phagocytic activity and leukocyte numbers, while SI /Leu negative correlation was strong indicating that leukocytosis was not accompanied by fortified stimulatory activity (pcc: -0.6, p:0.005). (Figure 8). In every instance of correlation, association is not proven until investigated in a targeted, causative manner and leukocytosis is a ubiquitous reaction to stress, such as bleeding, ischaemia, strain, inflammation and infection.

High IL-6 levels in individual patients did not culminate in enhanced stimulatory activity of phagocytes, nor increased CRP levels correlated with such activity, suggesting that contributors beyond the measured parameters play a decisive role in whether enhanced activity and stimulation occurs, such as age, other cytokines, Fc receptor priming, or pattern recognition receptors, bacterial load and opsonisation. Due to age and comorbid state immune involution is expected, and we compared our indices in relation to age and comorbidity index on individual and group level finding highly significant correlation between age and comorbidity indices (Table 4).

Comparison of Survivors to Nonsurvivors

The overall hospital mortality rate of the studied patients was 36.1%. Higher phagocytic activity was found among patients who survived as opposed to those who subdued to their condition during hospitalisation (85.6% vs 74.9%), the difference did not reach statistical significance. (p=0.16). The average stimulatory index was lower among survivors, significance using the Welch t test was marginal. The SOFA (9.2 vs 13.8, p:0.05) and comorbidity index scores (5.5 vs 8.4, p:0.04) were strongly significantly higher in nonsurvivor, providing major determinants of coping ability with the severe acute illness in light of comorbidities. Interestingly, leukocyte numbers were higher in survivors (13.1 vs 20.1x10*9g/l, p:0.0027), (Figure 9a, b and Table 11a, b).

Table 11a: Comparison of Nonsurvivors (Nonsurv) to Survivors(surv)

Using welch t test, significance considered below 0.05

	NONSURV	SURV	P welch
SOFA	13.8+/-3.5	9.2+/-4.2	0.05
CI	5.5+/-2.5	8.4+/-1.4	0.004
LEUx10*9 /l	13.1+/-8.4	20.1+/-9.6	0.0027

Table 11b

	NONSURV	SURV	P welch
FA % (80-100%)	74.9+/-25.5	86.6+/-12.1	0.16
SI %(30-100%)	23+/-16	15.4+/-8.2	0.16
CRP (mg/l)	145.4+/-40.9	196.7+/-25.4	0.23

Reflections on IL-6 Levels

Extremely high levels of IL-6 in septic patients did not lead to enhanced phagocytic and stimulatory activity, but were predictors of mortality. Statistical analysis due to small sample size could not be realized. Extremely high serum IL- 6 levels in blood, signaling a cytokine storm like phenotype are strong predictors of mortality and morbidity [22,23]. This phenotype in fulminant sepsis and septic shock is frequently accompanied by hepatic SIRS. This study does not provide data on the above statement, which is drawn from clinical experience. Data from the scientific literature demonstrated that very high IL-6 can paradoxically decrease neutrophil extravasation to affected tissues via inhibiting ICAM-1 and VE cadherin, a dose and pathogen dependent effect [24]. Whether neutrophil persistence in blood is a purposeful property to enhance clearance of bloodstream pathogens or a move to limit inflammation remains to be understood. While IL-6 is produced upon triggers from a wide range of stimuli, including ROS its effect on neutrophils is not multipotential [25]. IL-6 increases egress of neutrophils from the bone marrow. In an experimental model of acute pancreatitis, IL-6 led to increased “homing” by upregulated CXCL1 expression on pancreatic acinar cells [26]. Besides IL-6, interferon gamma is fundamental to regulate neutrophil influx

and apoptosis [27]. Interferon gamma production is inducible in NK, NKT, Th1, CD8 cells and is also produced upon antigen presentation in ILC1's, macrophages and dendritic cells to a lesser extent, and is downregulated by IL-4 and IL-10. The issue being the time needed for the immune response maturation to the point of sufficient interferon gamma production. IL-6R activation induces NET (neutrophil extracellular trap) formation via PAD4(peptidyl arginine deiminase-4), as demonstrated on tocilizumab treated STEMI patients [28,29]. In H1N1 infected human lungs IL-6 had no effect on mROS production, but protected neutrophils from ROS induced cell death [30].

Activated and Regulatory T Cell Phenotypes (Figure 10)

Upon examining the level of activation and regulation in blood CD3 T cells, defined by DR+, or CD3+CD25+CD127^{low}, there was a moderate positive correlation present between CRP level and the proportion of regulator T cells. (pcc:0.6, p:0.03, Figure 11a). There are several reports on CRP's ability to increase regulatory T cell numbers, indirectly by inhibiting dendritic cell maturation [30]. CRP primarily recognizes apoptotic cells for clearance, in this situation inflammation is not a desirable attribute. The levels of CD4+CD25+CD127^{low} Tregs negatively predicted organ failure in acute pancreatitis patients [31]. Importantly, CD3+DR+ cell numbers positively correlated with leukocyte stimulatory activity (pcc:0.61, p:0.02, Figure 11b). These activated lymphocytes via cytokine release (IL-12, IFNg, ILl-17) enhance neutrophil and macrophage phagocytic activity. A significant negative correlation was present between SOFA score and Treg numbers (pcc: -0.59, p:0.03, Figure11c), indicating that a stronger inflammation is associated with low regulatory T cells and indirectly with mortality. A sustained enhanced T cell activation has been shown to predict survival in sepsis [32-35].

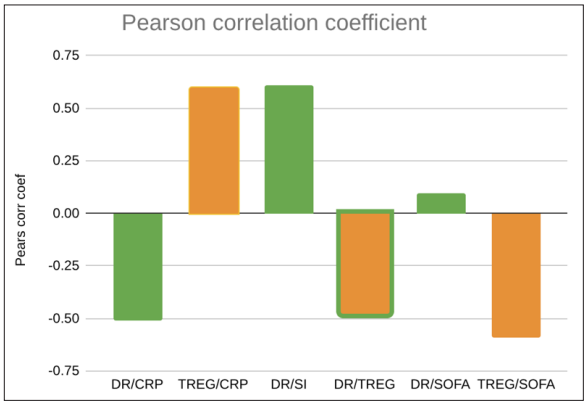
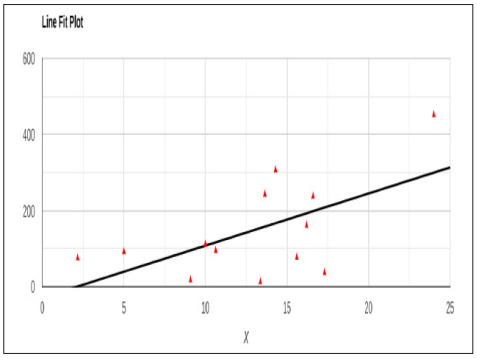
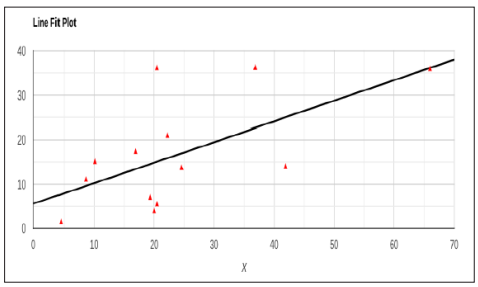


Figure 10: Regulatory (CD3+CD25+CD127^{low}) and Activated T cells (CD3+DR+) in Blood, Mutual Moderate Correlations Above Pearson Correlation Coefficient 0.5 and above or -0.5 and Below





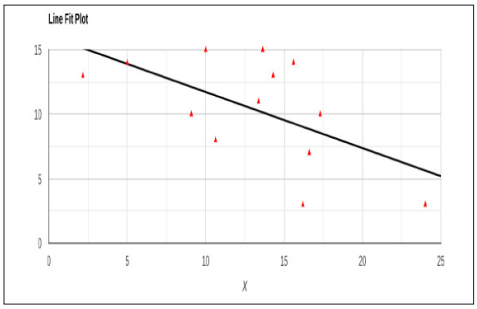


Figure 11: A, B, C:

A- Treg/CRP: x axis - regulatory T cells % of total CD3+ T cells, y axis - CRP levels mg/l

B- DR/SI: x axis - regulatory T cells % of total CD3 +T cells, y axis- DR+ cells % of total CD3+T cells

C-SOFA-/Treg: x axis - regulatory T, % of total CD3+ T cells, SOFA- y axis

Discussion

The immune phenotype in blood is of special focus always, and particularly when the disease complexity and severity grants ICU admission. Blood is the environment, representing another level of defense, particularly protecting against dissemination and providing clearance.

At the same time collateral, immune mediated damage and organ failures are of worry, such as C3 mediated glomerular dysfunction.

The present study provides indicators of immune disequilibrium during sepsis and raises important questions. The mechanisms and reasons of suboptimal phagocytic and stimulatory activity are yet to be deciphered. The ultimate question is how would a normal, supraoptimal or medicamentously enhanced phagocytic activity and stimulation influence morbidity, mortality, hospital stay and full recovery of septic patients. The available evidence indicated multiple layers of discoordination and dissonance in immune response during sepsis. In vivo studies, despite faithful representation of the clinical environment, they too carry the burden of complexity.

Positive blood cultures could have remained undetected, because pathogen release to blood from the original source is periodical, not always attainable to measurement. Fever is not as frequent in septic patients as expected from the phenotype, suggesting a decapitated immune response due to several factors, potentially impaired pyroptosis, pathogen evasion tactics, environmental toxins and immune senescence [36]. ROS are essential tools for intracellular killing of microbes by neutrophils. Mechanisms that downregulate ROS production induce a phenotype reminiscent of chronic granulomatous disease induced by defective NADPH oxidases and impaired ROS production with frequent, persistent, often staphylococcal infections and abscesses [37,38]. While oxygen is used for ROS production, fermentative glycolysis is used

by neutrophils for energy production. Itaconate is a mitochondrial metabolite that regulates oxidative stress and glycolysis. Itaconate, while protective in limiting overt inflammations, may paradoxically during its overproduction skew the balance toward impaired ROS production and defective glycolysis and promote staphylococcal survival and biofilm formation [39,40]. Overt leukocyte ROS contributes to SIRS and tissue damage. ROS is accidentally produced during ischemia and reperfusion injury (IRI). During experimental TBI (traumatic brain injury), microglia react with overt ROS, modification of which leads to lesser neurodegeneration in mice [41,42]. Experimentally tumor selective Oxphos inhibitors are tested to strangulate cancer cells [45]. ROS has important physiological housekeeping functions, antibacterial role, but its aberrant and uncontrolled production during mitochondrial damage (IRI), inefficient clearance by antioxidants or prolonged upregulation leads to damage [43,44]. CRP carries important scavenging function in that matter. It is crucial to realize that ROS may be the byproduct of dysfunctional mitochondrial oxidative phosphorylation, excessive ROS leads to mitochondrial dysfunction and DNA damage, T cell exhaustion, during infections however has targeted bactericidal role and physiological levels are important for T cell maturation. Cooling applied during cardioplegia and post cpr decreases metabolic rate and ROS production [46]. Neutrophils demonstrate antibacterial and antiviral activity besides intracellular ROS mediated killing, also by creating NETs. These structures may be NOX dependent or independent, extracellular or intracellular webs, not necessarily associated with cell death, containing chromatin, DNA and antimicrobial peptides are designed to prevent bacteria from spreading using slightly different mechanisms of NET formations, based on triggering ligand, such as TLR4, C5a, ICs, UV light [47,48].

Despite relative simplicity, custom immunoglobulin level monitoring is seldom arranged in septic patients. A significant proportion of our patients presented with low IgG and IgM numbers. Immunoglobulin administration is not recommended by experts, articulated in Surviving Sepsis guidelines [49]. Large dose IgG, used as scavenger and suppressant of autoantibody production in selected autoimmune conditions, such as Guillain Barre syndrome, blunts intrinsic immunoglobulin production [50]. Moreover, affinity towards specific given pathogens may be low due to the production of immunoglobulin preparations from randomly pooled healthy donors [51]. Septic patients with low immunoglobulin M and G levels may benefit from low dose immunoglobulin substitution, providing an additional layer of protection. The lesson from sepsis research supports the notion that the immune response is somewhat chaotic, dissonant and lacks efficient coordination inevitably leading to organ pathology, tissue damage and energy exhaustion [52-54].

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