

Measurement of Monocyte CD86 Expression as Prognostic markers of Post Inflammatory Immunodeficiency in Critically Ill Patients

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Abstract: Post inflammatory immunodeficiency frequently becomes life threatening since patients are predisposed to nosocomial infection. MHC-II molecules are essential for the activation of CD4+ cells and therefore for the initiation of any adaptive immune response and enhancement of the innate immunity. Aim Of The Work: The aim of this work is to study the prognostic effect of the level of monocyte CD86 expression as an indicative of post inflammatory immunodeficiency states in critically ill patients. Also to study the relation of the level of monocyte CD86 to patient outcome. Study Design: This is a prospective non randomized control trial conducted in Critical Care Department, Faculty of medicine Cairo University, Egypt. Inclusion criteria: Twenty critically ill patients who were admitted to critical care department. Exclusion criteria was age more than 80 years, Age less than 18 years, Disseminated malignancy and Co-morbid severe organ dysfunction. All patients subjected to: 1. History taken, 2. Complete detailed clinical examination, 3. vital signs 4. Complete blood count (CBC), Liver profile, Coagulation profile & Daily arterial blood gases. 5. Measurement of monocyte expressive co-stimulatory factor CD86 using systematic flow cytometry analysis technique starting from day 1 to day 4. Results: Out of the twenty patients 7 survivors and 13 non survivors. Age of the survivor group ranged from 30-60 years, non survivors age ranged from 35 to 70 years. Five out of 14 males (35.7%) were survivors as compared to 2/6 females (33.3%). There were statistically significant difference between both groups as regards higher mean of arterial blood pressure and central venous pressure in survivors, and a highly significant difference was encountered as regard higher hear rate, temperature and respiratory rate in non survivors. A highly statistically significant difference was encountered also as regards total leucocytic count, serum glutamic pyruvate transaminase, serum glutamic oxaloacetic transaminase, serum creatinine, prothrombin time and international normalized ratio which was higher in non survivors (P<0.001). Of the 7 surviving patients, only 30% showed positive blood culture; while in non survivors 70% of pts showed positive blood C/S and there was no statistically significant difference (P: 0.089). Positive sputum culture was encountered in 43% of the 7 surviving patients, and it was +ve in 70% of non survivors with borderline significance statistically (P: 0.05). In day 1 CD86 monocytes expression by mean fluorescent ratio showed statistically significant higher level in non survivors, in day 2 there were no statistically significant difference. In day 3 CD86 monocytes expression was higher in survivors and in day 4 both CD86 were statistically significant higher in the survivor group. Survivors vs non survivors mean fluorescent (4+2 vs 7+2.5) (4+2.4 vs 5+2.2, 6.3+2.1 vs 4.2+1.5 & 7+2.5 vs 3.5+1.6) with P value 0.01, 0.4, 0.0 & 0.001 respectively). The trend of CD86 expression change over the 4 days is presented as CD86 mean showed an increasing pattern in survivors. Conclusion: Semiquantitative measurement of CD86 level expressed by mean fluorescent ratio is a good and valid prognostic test of mortality in post inflammatory immuno deficiency patients.

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1. Introduction

Major surgery, poly trauma, burns, stroke and pancreatitis are often accompanied by a massive activation of the immune system called systemic inflammatory response syndrome (1).

Due to counter regulatory mechanisms such as endocrine, paracrine or autocrine actions along with intracellular alterations this hyperinflammation is followed by a temporary immunodeficiency called compensatory anti-inflamantory response syndrome. In its most severe form it is also referred to as immune paralysis state (2).

Post inflammatory immunodeficiency frequently becomes life threatening since patients are predisposed to contract nosocomial infection. However, these infections are difficult to identify since they are scarcely associated with any clinical signs. Moreover, these infections can not be fought by the enfeebled immune system of such patients and may evolve into sepsis. It is therefore not surprising that sepsis and resultant multiple organs failure are the most common causes of death in intensive care units (ICUs) (2). In fact, in the United States alone more than 20.000 patients die of sepsis each year (3).

The mechanisms responsible for post inflammatory immuno deficiency are not clear, which is the reason why no causal therapy has been established to date (4). Most probably, monocytic cells play a key role in the development and maintenance of this state. This monocytic cells seem to be impaired in their antigen presentation and inflammatory capacity. In fact, blood monocytes show a strongly reduced expression of major histocompatibility complex class II (MHC-II) and produce only minor amounts of preinflammatory cytokines in response to bacterial lipopolysaccharides (LPs) (4). The magnitude of MHC-II reduction correlates with increased susceptibility to infection and subsequent mortality and is used for diagnosis of post inflammatory immunodeficiency (2).

MHC-II molecules are essential for the activation of CD4+ cells and therefore for the initiation of any adaptive immune response and enhancement of the innate immunity (5).

In fact, the engagement of the T-cell receptor (TCR) with MHC-II complexes with antigenic peptides delivers a stimulatory signal to CD4+ cells (6).

However, naïve CD4+ cells in particular need to receive a second signal set from Co-stimulatory molecule is blood antigen presenting cells from ICU patients is CD86 (2).

Aim of the Work

The aim of this work is to study the prognostic effect of the level of monocyte CD86 expression as an indicative of post inflammatory immunodeficiency states in critically ill patients.

Also to study the relation of the level of monocyte CD86 to patient outcome.

2. Patients and Methods

Study Design:

This is a prospective non randomized control trial was conducted in Critical Care Department, Faculty of Medicine Cairo University, Egypt, Which is a tertiary critical care centre that contains surgical, medical and coronary care units of total capacity 52 beds. Patients were managed by the ICU team, which were available 24 hours per day. The Ethics Committee of the Faculty of Medicine Cairo University Approved the study.

Inclusion criteria:

Twenty critically ill patients who were admitted to critical care department.

Exclusion criteria

Age more than 80 years, Age less than 18 years, Disseminated malignancy and Co-morbid severe organ dysfunction.

Data collection and classification:

1. History taken, 2. Complete detailed clinical examination was performed for all patients, 3. vital signs composed of arterial blood pressure, mean arterial blood pressure, heart rate, temperature, respiratory rate and central venous pressure, 4. Length of stay, 5. Investigation: Complete blood count (CBC), Liver profile, Coagulation profile & Daily arterial blood gases. 6. Measurement of monocyte expressive co-stimulatory factor CD86 using systematic flow cytometry analysis technique starting from day 1 to day 4. Flow cytometry uses the principles of light scattering, light excitation, and emission of fluorochrome molecules to generate specific multi-parameter data from particles and cells in the size range of 0.5 um to 40um diameter. Cells are hydro-dynamically focused in a sheath of PBS before intercepting an optimally focused light source. Lasers are most often used as a light source in flow cytometry.

As your cells or particles of interest intercept the light source they scatter light and fluorochromes are excited to a higher energy state. This energy is released as a photon of light with specific spectral properties unique to different fluorochromes for a listing of commonly used fluorescent dyes and their excitation and emission spectra.

One unique feature of flow cytometry is that it measures fluorescence per cell or particle. This contrasts with spectrophotometry in which the percent absorption and transmission of specific wave lengths of light is measured for a bulk volume of sample.

Scattered and emitted light from cells and particles are converted to electrical pulses by optical detectors. Collimated (parallel light waveforms) light is picked up by confocal lenses focused at the intersection point of cells and the light source. Light is sent to different detectors by using optical filters. For example a 525 nm band pass filter placed in the light path prior to the detector will only allow "green" light into the detector. The most common type of detector used in flow cytometry is the photomultiplier tube (PMT).

The electrical pulses originating from light detected by the PMTs are then processed by a series of linear and log amplifiers. Logarithmic amplifications most often used to measure fluorescence in cells. This type of amplification expand the scale for weak signals and compresses the scale for "strong" or specific fluorescence signals.

After the different signals or pulses are amplified they are processed by an Analog to Digital Converter (ADC) which in turn allows for events to be plotted on a graphical scale (one parameter, two parameter Histograms).

Flow cytometry analysis of a single cell suspension yields multiparameter data corresponding to Forward Light scatter (FLS), 90° Light Scatter (90 LS), and FL1-FL4. By the Beckman-Coulter XL instruments are bench-top, flow cytometer, analyzers.

This information allows researches to identify and characterize various subpopulations of cells. The process of separating cells using flow cytometry multiparameter data, is referred to as sorting.

Outcome and mortality: According to outcome and mortality patients were classified into 2 groups: Survivors, Non survivors

Data Analysis:

All data were collected prospectively, Categorical data were displayed as absolute and relative frequencies. Continuous data were reported as mean values \pm standard deviation (SD), or as median and range according to presence or not of a normal data distribution. Comparisons were performed with an unpaired student's t test for continuous, normally distributed data, and with a Mann Whitney U test, or Wilcoxon rank sum test for continuous non normally distributed data. Comparisons between categorical variables were

performed with Chi square X2 test. Yates correction equation, or Fisher exact test was used instead of any frequency was <5 . A two sided probability value <0.05 was considered as significant. Professional statistical Package for Social Science version 15 (SPSS Incorporation, Chicago, IL, USA) computer software was used for data analysis.

Receiver operator curve (ROC) was used to estimate the cut-off value for the different predictor and assessment of these predictors was madder using the area under curve (AUC) and for each cut off sensitivity and specificity was calculated.

3. Results

Demographic data of critically ill patients classified into survivors and non survivors:

Age: The age of the survivor group ranged from 30-60 years with a mean of 45 ± 12 , and a median of 44 years, non survivors age ranged from 35 to 70 years with a mean of 52.4 ± 13 and a median of 53 years.

Gender: Five out of 14 males (35.7%) were survivors as compared to 2/6 females (33.3%). There was no statistically difference between both groups as regards gender.

Table (1): Hemodynamics and vital signs in 7 survivors and 13 non survivors critically ill patients

Parameter	MAP	CVP	HR	Temp	RR
Survivors					
Mean \pm SD	84 \pm 6	7 \pm 3.6	92.4 \pm 13	37 \pm 0.5	22.9 \pm 4.6
Range	75-92	1-12	76-109	36.6-38	17-30
Non survivors					
Mean \pm SD	74 \pm 11.3	2.9 \pm 2.9	128.5 \pm 10	38.5 \pm 0.6	34.3 \pm 5.0
Range	55-90	0-8	112-151	37.8-40	25-43
	0.04	0.02	0.02	0.041	0.03

MAP: Mean arterial blood pressure **CVP:** Central venous pressure **HR:** Heart rate **Temp:** temperature **RR:** Respiratory rate

Statistically significant difference between both groups was encountered as regards mean arterial blood pressure and central venous pressure, and a

highly significant difference was encountered as regard hear rate, temperature and respiratory rate.

Table (2): Laboratory parameters in 7 survivors and 13 non survivors critically ill patients

Parameter	Hb%	TLC	PLT	S.Alb	SGPT	SGOT	S. Creatinine	PT	INR
Survivors									
Mean \pm SD	11.4 \pm 1.7	12.8 \pm 3.1	254.3 \pm 93.5	3.6 \pm 0.4	30 \pm 13	42.4 \pm 6.6	0.9 \pm 0.3	13.5 \pm 0.9	1.2 \pm 0.1
Range	9-14.2	8.7-18.1	119-412	2.8-4.4	10-50	36-52	0.6-1.2	12.2-14.8	1.1-1.3
Non survivors									
Mean \pm SD	9.7 \pm 1.4	26.1 \pm 5.1	93.1 \pm 71	2.9 \pm 0.1	158 \pm 68	193 \pm 82	2.4 \pm 0.4	17 \pm 1.7	1.7 \pm 0.3
Range	6.9-11.2	16.1-33	21-245	2.2-3.6	63-245	79-324	1.9-3	14.4-20	1.3-2.2

Hb%: hemoglobin percentage, TLC: Total leucocytic count, PLT: Platelet count, S. Alb. Serum albumin, SGPT: serum glutamic pyruvate transaminase; SGOT: Serum glutamic oxaloacetic transaminase; S. Creatinine: serum creatinine, PT: Prothrombin time; INR: International normalized ratio.

A highly statistically significant difference was encountered as regards total leucocytic count, serum glutamic pyruvate transaminase, serum glutamic oxaloacetic transaminase, serum creatinine,

prothrombin time and international normalized ratio ($P<0.001$) and a statistically significant difference was encountered as regards serum albumin and

platelet count ($P < 0.05$) and statistically insignificant difference as regards Hb% ($P > 0.05$) (Table 2).

A highly statistically significant difference was encountered between both groups as regards the pH

and pCO_2 and a statistically significant difference as regards HCO_3 and a non significant difference as regards PO_2 and oxygen saturation (Figure 1).

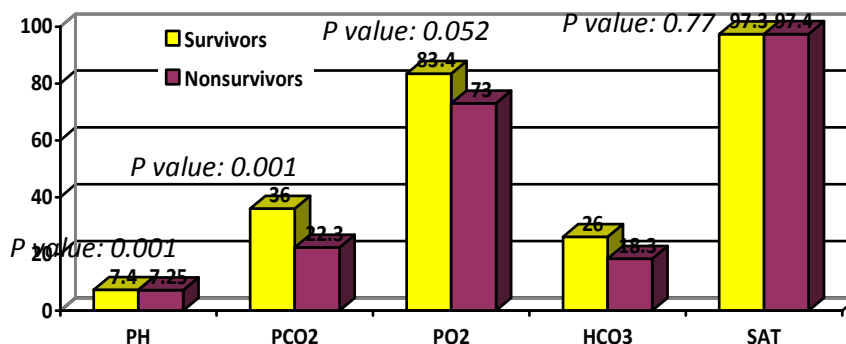


Figure (1): Arterial blood gases in 7 survivors and 13 non survivors critically ill patients

Of the 7 surviving patients, only 30% showed positive blood culture; while in non survivors 70% of pts showed positive blood C/S and there was no statistically significant difference ($P: 0.089$).

Positive sputum culture was encountered in 43% of the 7 surviving patients, and it was +ve in 70% of non survivors with borderlines significance statistically ($P: 0.05$).

Positive urine culture was encountered in 43% of the 7 surviving patients, and in 70% of non survivors and again in there were borderline statistically significant relationship ($P: 0.054$).

Table (3): CD86 level by Relative intensity in both groups

Parameter	Survivors	Non survivors	P value
CD86 level by relative intensity	16.25±3.5	5.4±2.7	0.004

Table (4): Monocyte CD86 mean fluorescent ratio and relative intensity in 7 survivors and 13 non survivors critically ill patients at different time results

Parameter	Outcome		P value
	Non Survivors	Survivors	
Day 1			
MFR	7±2.5*	4±2*	0.01
RI	15±6.3*	7±4.2*	0.001
Day 2			
MFR	5±2.2*	4±2.4*	0.4
RI	10±3.4*	9±5*	0.53
Day 3			
MFR	4.2±1.5*	6.3±2.1*	0.0
RI	6.4±3*	4±12.3*	0.001
Day 4			
MFR	3.5±1.6*	7±2.5*	0.001
RI	5.4±2.7*	3.5±16.25*	0.0001

There were statistically significant higher level of CD86 level by relative intensity in survivors compared to non survivors ($P: 0.0004$). When we compare the 7 survivors with the 13 non survivors as regards CD86 mean fluorescent (MFR) and relative intensity (RI) which were calculated by dividing mean fluorescent channel by number of he monocytes (% expression) as semi quantitative evaluation for the CD86 number of member.

In day 1 CD86 monocytes showed MFR with statistically significantly higher values in non survivors, RI showed the same statistically significant difference.

In day two there were no statistically significant difference between both groups for any of the CD86 parameters.

In day 3 CD86 monocytes parameters were higher in survivors. The difference was statically significant for mean fluorescence ration ($P: 0.02$) and for relative intensity ($P: 0.001$).

In day 4 both CD86 MFR and RI were statistically significant higher in the survivor group (P value: 0.001 and 0.0001, respectively).

The trend of CD86 expression change over the 4 days is presented as CD86 mean fluorescent ratio which showed an increasing pattern in survivors and a decreasing pattern in non survivors. The same trend was encountered with CD86 relative intensity.

Table (5): Comparison of change in CD86 level between 7 survivors and 13 non-survivors critically ill patients

Parameter	Survivors	Non survivors	P value
CD86	Increasing	7	0.001
	Decreasing	0	
		13	

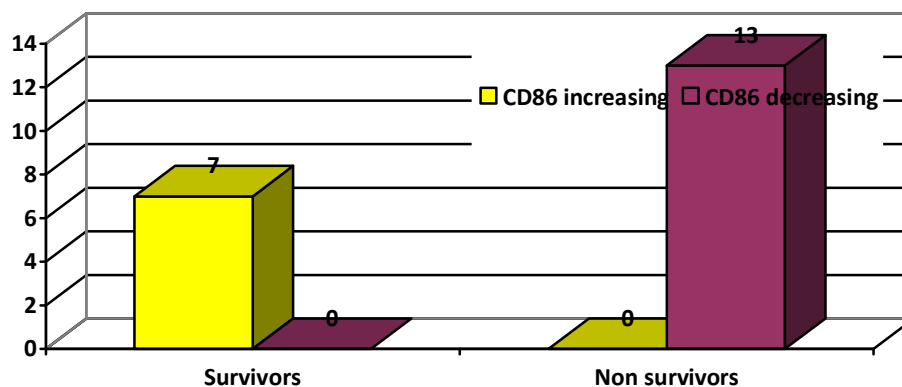


Figure (2): Comparison of change in CD86 level between 7 survivors and 13 nonsurvivors critically ill patients

ROC curves were used for parameters that showed statistical significance to determine a cut-off that can best discriminate between survivors and non survivors by using mean fluorescence ratio and relative intensity of CD86 monocytes.

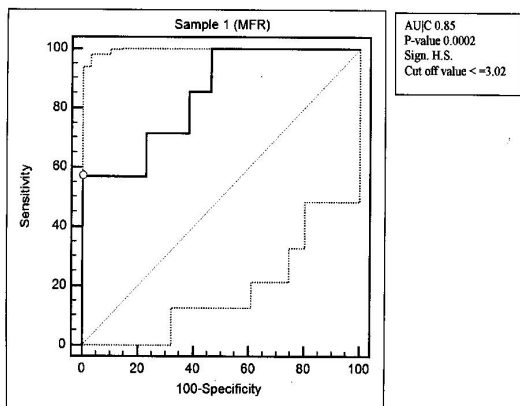


Figure (3): ROC curve of mean fluorescence ratio of CD 86 level in 7 survivors and 13 non survivors critically ill patients (day one).

Figure (3) shows that the best discriminative cut off for the mean CD86 fluorescent ratio in day 1 was 3.02 with a sensitivity of 57%, a specificity of 100%, a total accuracy of 85%, a positive predictive value of 100% and a negative predictive value of 81.2%. 5/7 survivors showed values < 3.02 as compared to 13/13 non survivors showed levels >3.02. The difference is statistically highly significant (P: 0.002).

In day 3 the best discriminative cut off for the mean CD86 fluorescent ratio was 6 with a sensitivity of 42.86%, a specificity of 100%, a total accuracy of 70%, a positive predictive value of 100% and a negative predictive value of 76.5%. Seven survivors showed values >6 while 10/13 non survivors showed

levels <6 the difference was found to be statistically significant (P: 0.01), Figure (4).

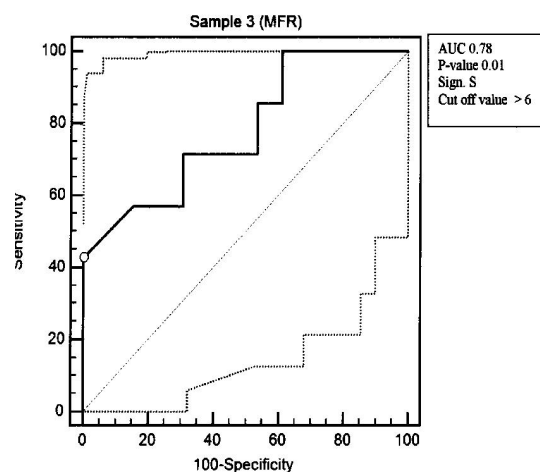


Figure (4): ROC curve of mean fluorescence ratio of CD86 level in survivors and non survivors (day three)

While in day 4 we found that the best discriminative cut off for the mean CD86 fluorescent ratio was 5.6 with a sensitivity of 71.43%, a specificity of 100%, a total accuracy of 90%, a positive predictive value of 100% and a negative predictive value of 86.7%. Seven/7 survivors showed values >5.6 while 8/13 non survivors showed levels <5.6. The difference is statistically highly significant (P: 0.0001), Figure (5).

When we studied ROC curve for relative intensity we found that the best discriminative cut off for the CD86 relative intensity in day 1 was 8 with a sensitivity of 85.71%, a specificity of 100%, a total accuracy of 95%, a positive predictive value of 100% and a negative predictive value of 92.9%. Six/7 survivors showed values <8 while 13/13 non

survivors showed levels >8 . The difference is statistically highly significant ($P: 0.0001$), (Figure 6).

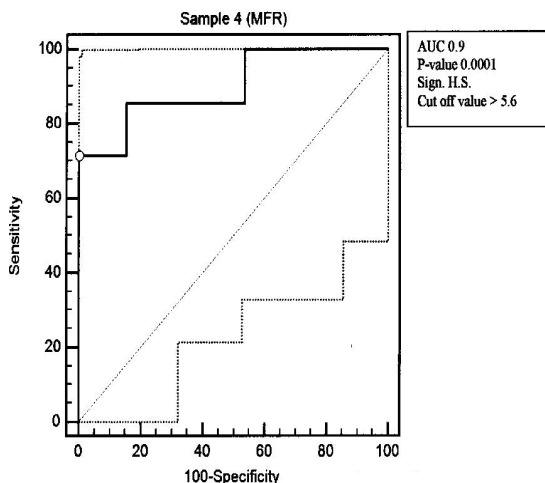


Figure (5): ROC curve of mean fluorescence ratio of CD86 level in survivors & non survivors (day four)

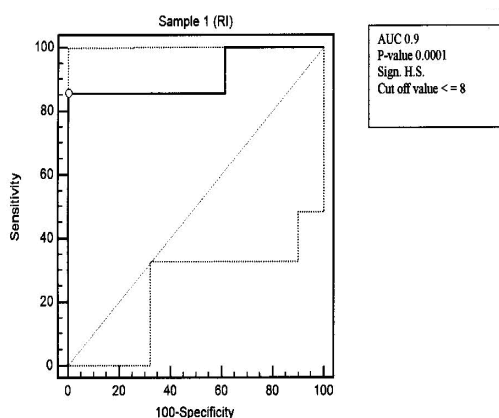


Figure (6): ROC curve of relative intensity of CD86 level in survivors & non survivors (day one).

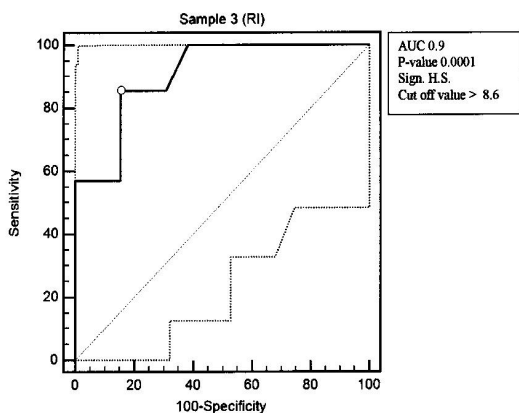


Figure (7): ROC curve of relative intensity of CD86 level in survivors & non survivors critically ill pts (day three).

While in day 3 we found that the best discriminative cut off for the CD86 relative intensity was 8.6 with a sensitivity of 85.71%, a specificity of 84.62%, a total accuracy of 85%, a +ve predictive value of 75% & a negative predictive value of 91.7%. Seven/7 survivors showed values >8.6 while 13/13 non survivors showed levels <8.6 . The difference is statistically highly significant ($P: 0.0001$) (Figure 7).

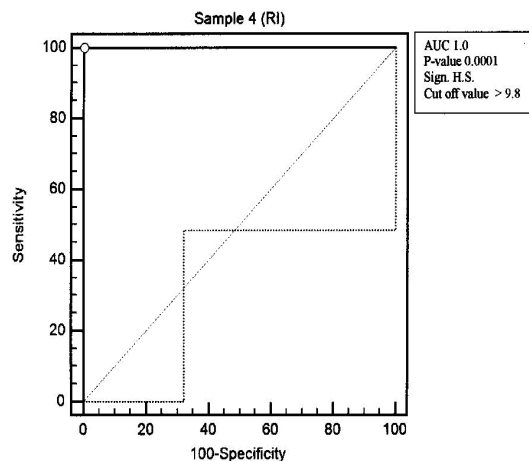


Figure (8): ROC curve of CD86 relative intensity level on monocytes in survivors & non survivors (day four).

As regards day four result we found that the best discriminative cut off for the CD86 relative intensity was 9.8 with a sensitivity of 100%, a specificity of 100%, a total accuracy of 100%, a positive predictive value of 100% and a negative predictive value of 100%. Seven/7 survivors showed values >9.8 while 13/13 non survivors showed levels <9.8 . The difference is statistically highly significant ($P: 0.0001$). (Figure 8).

4. Discussion

Comparing laboratory parameters between both groups in our study showed a remarkable affection in the non survivors group in comparison to the survivor group. This can be attributed to the ongoing sepsis and MODS and this matches with *Nolan et al. (7)* who studied laboratory parameters together with CD40 and CD80/86 and their role to regulate inflammation and mortality in polymicrobial sepsis.

When we have compared the hemodynamics and vital signs parameters between both groups survivors and non-survivors it showed maintained, mean arterial blood pressure in the surviving group, together with the central venous blood pressure, while in the non-surviving-group, patients was vasodilated with low central venous pressure

secondary to the ongoing inflammatory response and sepsis.

Heart rate was in the normal range in the survivor group while tachycardia was evident in the non-surviving group, expressing a highly significant statistical difference between both groups. This can be attributed to the continuous production of inflammatory mediators of sepsis.

Temperature parameter was normal in survivor group while in the non-surviving group fever was evident expressing a highly statistically significant statistical difference between both groups. This can be attributed to the ongoing inflammatory response and sepsis.

Respiratory rate was in the normal range in the non survivor group while in the non-survivor group, tachypnea was evident because of fever this leads to a highly statistically significant statistical difference in comparing both groups.

All hemodynamics and vital signs matches with *Plosone*, (8) who studied the differential role for CD 80 and CD 86 in the regulation together with concomitant hemodynamic variables during this study of the innate immune response in murine polymicrobial sepsis and concluded that down regulation of CD 80 and loss of constitutive CD 86 expression on monocytes are associated with higher severity of illness and inflammation confirming the previous findings.

Our study findings as regards haemodynamices variation was also concordant with *Ludger et al.*, (9) who studied the enhanced expression of CD 80 (B7-1), CD 86 (B7-2) and CD 40 and their ligands CD 28 and CD 154 in fulminant hepatic failure, and MODS. They found that CD 40 and CD 80/ CD 86 expression is upregulated before tissue damage and their increased expression leads to better prognosis while decreased expression leads to unfavorable outcome.

Arterial Blood gases parameters also showed an important role in the course of both groups with a highly statistical significant difference as regards pH and PCO₂. This is in concordance with *Newton et al.* (10).

Blood culture positivity was studied in both groups in relation to CD 86 level showing that although there was 30% of the survivors with positive blood culture they survived because of the high level of CD 86 while in the non-surviving group there was 70% of the patients with positive blood culture leading to their death because of the low level of CD 86 (*Nolan et al.*) (7).

The major findings of the present study were that reduced expression of CD 86 presented by MFR, and RI of expression of CD86 on blood monocytes, for four consecutive days is associated with unfavorable prognosis and this made us consider

monocyte CD 86 expression as a helpful prognostic variable and enables us to postulate that reduced monocyte CD 86 expression contributes to worsened post inflammatory immunodeficiency in critically ill patients. The first study to match with our study on CD86 expression was by *Kerstin et al.* (2); they found reduced monocytes with: long term (>3 days); had a long term reduction of CD 86 together with an unfavorable prognosis. Such patients often had infections and stayed on average three times as long in the ICU because of diminished monocyte CD 86 expression. More important, most of the patients who died in the ICU or within a month-after their stay due to multiple organ failure secondary to infection had at least a 3-day reduction of CD 86 level during their stay.

Based on these findings *Kerstin et al.*, (2) recommended that ICU patients with low CD86 expression on monocytes will be considered extremely vulnerable to infection.

This emphasizes the role of CD 86 in evaluating the prognosis of systemic inflammatory response syndrome and septic patients, it is in agreement with *Nolan et al.* who stressed on the importance of assaying the co-stimulatory molecules especially CD 86 as a biomarker for outcome in septic patients.

From these results, we have concluded that relative intensity and mean fluorescence ratio for CD 86 level from day one, day three and day four can be used as a prognostic marker in post inflammatory immunodeficiency patients and septic patients, as day one results are as highly statistically significant as day three and day four in relative intensity, while in mean fluorescence ratio showed a highly significant statistical p-value in day one and day four and significant statistical difference in day three. Accordingly to CD86 evaluation may be performed from day one and two giving early prediction of the outcome.

We can use either mean fluorescence ratio or relative intensity from day one, as their results in day one are equivalent with day three and day four. This is a new finding in prediction of the outcome in septic patients using CD86 MFR or relative intensity in day one and two this is an earlier prediction than that reported by *Kerstin et al.* (2) demonstrated that the reduction of CD 86 expression on blood monocytes for at least three consecutive days have an unfavourable prognosis but in our study we can use either MFR or relation intensity as prognostic semiquantitative method from day one in prediction of outcome.

However, it is worth mentioning that CD86 mean florescent ratio and relative intensity in day one were actually higher in the non survivor group.

The finding sounds paradoxical; a higher CD86 expression should reflect a better function of the monocytes as antigen presenting cells. Apparently, this was a trial from the immune system to mount up a reaction that could not face the overwhelming infection and ended up by failure. Consequently CD86 was down-regulated from day 2 with failure to control infection and ultimate death. On the other hand the survivor group mounted up their response gradually starting with CD86 levels lower in day one than the non survivors but the immune system could escalate its response with increasing CD86 levels from day 2 on.

Though the paradoxical results on day one are statistically significant and showed good predictive values, yet it may be better to include at least day 1 and 2 in our predictive model to judge according to the trend rather than the absolute values of CD86 expression.

Conclusion:

Post inflammatory immunodeficiency frequency become life threatening.

Monocytic cells play a key role in the development and maintenance of post inflammatory immunodeficiency, CD86 is an important co stimulatory molecule on monocytic cells.

Semiquantitative measurement of CD86 level expressed by relative intensity is a good and valid prognostic test in post inflammatory immunodeficiency patients.

Relative intensity of CD86 level has a higher sensitivity and specificity together with mean fluorescence ratio in predicting the mortality of post inflammatory; in immunodeficiency patients. It can be used on day one and two in order to determine the trend of expression.

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