A Dynamic Approach for Early Risk Prediction of Gram-Negative Bloodstream Infection and Systemic Inflammatory Response Syndrome in Febrile Pediatric Hemato-Oncology Patients

José Antonio Villegas Rubio (javillegas10@hotmail.com)
Central University Hospital of Asturias: Hospital Universitario Central de Asturias
https://orcid.org/0000-0001-9377-7529
Pilar Palomo Moraleda
Central University Hospital of Asturias: Hospital Universitario Central de Asturias
Ana de Lucio Delgado
Central University Hospital of Asturias: Hospital Universitario Central de Asturias
Gonzalo Solís Sánchez
Central University Hospital of Asturias: Hospital Universitario Central de Asturias
Belén Prieto García
Central University Hospital of Asturias: Hospital Universitario Central de Asturias
Corsino Rey Galán
Central University Hospital of Asturias: Hospital Universitario Central de Asturias

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Abstract

The aim of this paper was to evaluate the usefulness of C-Reactive Protein (CRP), Procalcitonin (PCT) and Interleukine 6 (IL6) biomarkers in predicting the existence of Gram negative bloodstream infections (Gr-BSI) or the development of Systemic Inflammatory Response Syndrome (SIRS) during the first 24 hours of fever in pediatric cancer patients.

The present study included a total of 103 consecutive fever episodes in 44 hemato-oncological pediatric patients, from whom samples for biomarkers CRP, PCT and IL6 were taken upon initial evaluation and then between 12 and 24 hours after.

An IL6 value at the first evaluation (IL6-1) higher than 164 pg/ml and an increase in CRP higher than 291% between the first and subsequent samples (CRP-2vs1) showed a statistically significant OR of 26.03 and 19.62, respectively, in multivariate analysis.

***Conclusion**:* IL6-1 and CRP-2vs1 showed a strong, independent correlation with Gr-BSI and SIRS episodes and, therefore, could be used as reliable predictors of these kinds of severe episodes. The approach taken in our study, using biomarker variations over time as a variable, has shown itself to be an improvement in the predictive model.

What Is Known

- In recent years, several studies have tried to establish models for predicting severe infection in pediatric cancer patients with contradictory results.
- Most of these analyze clinical and analytical parameters at different points within the first days of fever, trying to determine the risk of infection at those moments.

What is new:

- IL6-1 and CRP-2vs1 showed a strong, independent correlation with Gr-BSI and SIRS episodes.
- An approach taking into account the dynamics of the infective process could provide more information than analysis at different static points.

Introduction

In recent decades there has been a significant improvement in survival rates among pediatric cancer patients, reaching nearly 85%, or even higher for some kinds of tumors like lymphoma or low-risk lymphoblastic leukemia, for which a survival rate of greater than 90% has been achieved [1, 2]. Much of this improvement has occurred thanks to an increase in the intensity of treatment, which frequently induces severe immunosuppression, leading to the appearance of infection. According to different reports, the risk of bloodstream infection (BSI) in febrile neutropenic patients is 25-70% [3, 4, 5] although

infections are quite common in non-neutropenic patients as well, with overall BSI rates reported at nearly 15%. [6, 7].

When signs of infection appear in a cancer patient, especially fever, it would be very useful to have indicators that allow us to discriminate between mild conditions and those that could potentially be severe. Among all the possible infectious conditions, there are two which are especially life-threatening: gram-negative bloodstream infection (Gr-BSI) and those episodes in which a systemic inflammatory response syndrome (SIRS) develops. Henceforth, we will refer to these as high-risk episodes (HRE).

In recent years, several studies have tried to establish models for predicting infection in pediatric cancer patients with diverse and sometimes contradictory results [5, 8–12]. This situation makes it difficult to reach an agreement in stratifying the risk of infection in these patients [13–14]. This lack of consensus leads to variations in management, and thus safety, use of resources and patient quality of life among different institutions [12, 15, 16]. These studies are based on the analysis of clinical and analytical parameters to find indicators that allow us to distinguish the potential severity of a febrile condition. Most of them analyze these parameters at different points during the onset of fever, trying to establish the risk of infection at those moments [5, 8, 9, 10, 11, 12, 17, 18, 19, 20].

The principal objective of this study is to evaluate the usefulness of biomarkers C-Reactive Protein (CRP), Procalcitonin (PCT) and Interleukine 6 (IL6) in predicting of existence of Gr-BSI and / or development of SIRS (High risk episodes) during the first 24 hours of fever in pediatric cancer patients.

Considering the fact that infections, especially the most serious ones, evolve very fast, we believe that variations in these parameters in first few hours could be a good clinical tool and could be included when analyzing infectious risk. An approach which takes into account the dynamics of the infectious process could provide more information than an analysis at different static points. To the best of our knowledge, there are no studies using this type of parameters for infectious risk analysis in pediatric hemato-oncology patients.

Material And Methods

We conducted a prospective, observational study in the Pediatric Hemato-Oncolgy Unit of a tertiary university hospital from August 2015 to January 2019.

Patients

A total of 103 consecutive episodes of fever in 44 hemato-oncological pediatric patients (aged < 18 years old) were prospectively recorded at the first clinical evaluation for a febrile episode. All of these patients were receiving antineoplastic treatment or inmunosuppresion after allogeneic stem cell transplantation (Allo-SCT). For this study, an individual patient may have had more than one febrile episode.

This study was approved by the Institutional Ethics Committee. Written informed consent was signed by the patients' parents or guardians and by children over the age of 16.

Methodology

According to our institutional protocol, hemato-oncologic patients with fever should be treated by medical staff within the first four hours of onset. After an initial clinical evaluation, samples for blood count, biomarkers (CRP, PCT and IL6) as well as microbiological samples (central and peripheral blood, urine and nasopharyngeal tract) were taken. All patients received intravenous empirical broad spectrum antibiotic therapy following our institutional protocol based on recommendations from the Infectious Diseases Society of America [21]. Posterior changes in antibiotic therapy were carried out according to clinical criteria. Subsequent samples were taken within 12 to 24 hours later to analyze biomarkers, as well as new blood samples for cultures, if fever was still present.

Definitions:

Fever was defined as a single axillary temperature ≥ 38.3°C for more than one hour or two episodes of fever ≥ 38°C within a 12 hour period.

Severe neutropenia was defined as an absolute neutrophil count ≤ 500/mm3.

Gr-BSI was defined as one or more blood cultures positive for a Gram-negative bacterial pathogen either in central or peripheral blood samples.

SIRS was defined according to the criteria defined by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005 [22].

Henceforth in this article, Gr-BSI and SIRS episodes will be called as high-risk episodes (HRE).

Samples and their resultant variables obtained in the first evaluation and those of the later 12-24 hour evaluation will be labeled with the number 1 and 2, respectively (for example CRP-1 or PCT-2). Resultant variables obtained from the calculation of the percentage of variation between moment 1 and 2 following the formula (Value-2 - Value-1) / Value 1 * 100, will be labeled as 2vs1 (example CRP-2vs1).

Statistical Analysis

A descriptive analysis was carried out providing distributions of relative frequencies and absolute values for qualitative variables and measures of position and dispersion for the quantitative ones. The median of the three biomarkers upon the first evaluation and the 12-24h evaluation, as well as median of the variation calculated between these two moments were compared by using non-parametric Wilcoxon test for independent samples, after checking the non-normal distribution of the sample. Optimal cut-off points for these biomarkers were calculated according to the Youden index, which simultaneously maximizes Sensitivity (Se) and Specificity (Sp). Cut-off points, Se, Sp, positive predictive value (PPV), negative predictive value (NPV), area value under the ROC curve (AUC) and the significance of the test were also provided.

Finally, taking into account the optimal cut-off points previously calculated, univariate and then multivariate logistic regression models were constructed to determine indicators associated with HRE, providing an odds ratio (OR) along with their 95% confidence intervals and significance of the Wald test. Goodness-of-fit is assessed through the likelihood-ratio test, AUC and Nagelkerke's coefficient R2. The statistical significance level used was 0.05.

Statistical analysis was carried out with the support received from the Statistical Consulting Unit of the Scientific-Technical Services of the University of Oviedo and R Program (R Development Core Team) version 3.6.3 was used for this purpose [23–26].

Results

Study population

We analyzed 103 febrile episodes in 44 hemato-oncological pediatric patients (29 females). Demographics are shown in Table 1. The mean age at the moment of the febrile event was 7.7 years. Acute Leukemia/ Non-Hodgkin´s Lymphoma were the most frequent diagnoses (52.3%). In 62.1% of the episodes, patients were in complete or partial remission, In 50.5% they presented severe neutropenia, and in 34% they were receiving G-CSF at the beginning of the febrile episode.

Table 1
Demographic and clinical characteristics of patients and episodes.

	Patients (n=44)
Female, n (%)	29 (66%)
Mean (+/- standard deviation) in years at the first febril episode	7.7 (+/- 5.26)
Solid tumor/HL n (%)	21 (47.7%)
ALL/AML/NHL n (%)	23 (52.3%)
	Episodes (n=103)
Solid tumor/HL n (%)	56 (54.4%)
ALL/AML/NHL n (%)	47 (45.6%)
Disease status: Complete or Partial Remission n (%)	64 (62.1%)
Severe Neutropenia n (%)	52 (50.5%)
GCS-F: Yes, (%)	35 (34%)
Final diagnoses:	19 (18.5%)
HRE n (%)	84 (81.5)
Non-HRE n (%)	
ALL: acute lymphoblastic leukemia. AML: acute myeloblastic leukaemia. NHL:non-Hodgkin's lymphoma. HL: Hodgkin's lymphoma. GCS-F: granulocyte colony-stimulating factor.	

Clinical outcomes are shown in Table 1. Nineteen (18,5%) were classified as HRE (11 Gr-BSI, 4 SIRS and 4 with confluence of both). The most frequent Gram-negative bacteria was Escherichia coli, isolated in 6 episodes, followed by Enterobacter aglomerans in 4 episodes. No infection-related deaths occurred.

Biomarkers

The median and interquartile ranges of biomarkers variables (absolute value of CRP, PCT and IL6 at evaluations 1 and 2 and percentage of variation 2 vs 1) were compared between HRE and non-HRE groups (Table 2).

Table 2

Median and Interquartile range of biomarkers (absolutes values and variations) in HRE and non-HRE

	HRE	Non-HRE	p-value
CRP-1 (mg/dl)	2.3 (1.2 - 5.15)	3.15 (1.52 – 7.22)	0.451
CRP-2 (mg/dl)	11.1 (5.65 – 18.75)	6.55 (2.98 – 12.12)	0.017
CRP-2vs1 (%)	311.1 (77.66 - 618)	55.52 (8.10 – 154.7)	0.001
PCT-1 (ng/ml)	0.61 (0.34 – 3.71)	0.19 (0.13 – 0.35)	<0.001
PCT-2 (ng/ml)	5.89 (0.96 – 17.5)	0.28 (0.17 – 0.76)	<0.001
PCT-2 vs 1 (%)	290.2 (52.5 – 1077.3)	16.67 (-6.66 – 96.67)	<0.001
IL6-1 (pg/ml)	826 (249 – 4125.75)	76 (35.75 – 139.25)	<0.001
IL6-2 (pg/ml)	180 (29 - 341)	44.5 (23.5 – 86.75)	0.039
IL6-2 vs 1 (%)	-90.02 (-96.8 – 3.66)	-47.97 (-71.15 – 2.18)	0.109
HRE: High risk episode. CRP: C-Reactive Protein. PCT: Procalcitonin. IL6: Interleukine 6.			

Statistically significant differences between the median of biomarkers in HRE and non-HRE groups were found in CRP-2, CRP-2vs1, PCT-1, PCT-2, PCT-2vs1, IL6-1, and IL6-2.

Estimation of Optimal Cut-off point.

Table 3 shows the optimal cut-off point calculated according to the Youden index for biomarkers at evaluations 1 and 2, and percentage of variation 2vs1. Values higher than this point were associated with HRE.

Table 3
Optimal Cut-off points and Accuracy Indicators for CRP, PCT and IL6 to differentiate HRE from non-HRE.

	CRP-1	CRP-2	CRP-2vs1
AUC	0.438	0.667	0.785
(CI 95%)	(0.267-0.609)	(0.532-0.802)	(0.655-0.915)
Se (%)	13.33	94.74	60
Sp (%)	95.12	32.35	89.39
PPV (%)	33.33	28.13	56.25
NPV (%)	85.71	95.65	90.77
Cut-off point	14.4 mg/dl	3.5 mg/dl	291.37%
p-value	0.412	0.027	<0.001
	PCT-1	**PCT-2**	**PCT-2vs1**
AUC	0.805	0.836	0.812
(CI 95%)	(0.7-0.91)	(0.725-0.947)	(0.696-0.928)
Se (%)	81.25	78.95	68.75
Sp (%)	68.29	79.71	80.6
PPV (%)	33.33	51.72	45.83
NPV (%)	94.92	93.22	91.52
Cut-off point	0.32 ng/ml	0.94 ng/ml	113.64%
p-value	<0.001	<0,001	<0.001
	IL6-1	**IL6-2**	**IL6-2vs1**
AUC	0.89	0.665	0.361
(CI 95%)	(0.791-0.989)	(0.474-0.855)	(0.138-0.585)
Se (%)	92.86	64.71	21.43
Sp (%)	82.5	60.65	96,67
PPV (%)	48.15	47.82	60
NPV (%)	98.51	89.29	84.06

HRE: High risk episode. CRP: C-Reactive Protein. PCT: Procalcitonin. IL6: Interleukine 6. Se: Sensitivity.

Sp: Specificity. PPV: Positive Predictive Value. NPV: Negative Predictive Value. AUC: Area value under the ROC curve.

	CRP-1	CRP-2	CRP-2vs1
Cut-off point	164 pg/ml	104 pg/ml	107.32%
p-value	<0.001	0.04	0.11
HRE: High risk episode. CRP: C-Reactive Protein. PCT: Procalcitonin. IL6: Interleukine 6. Se: Sensitivity.			
Sp: Specificity. PPV: Positive Predictive Value. NPV: Negative Predictive Value. AUC: Area value under the ROC curve.			

Statistically significant cut-off points that simultaneously maximize Sensitivity (Se) and Specificity (Sp) for absolute values were 3,5 mg/dl for CRP-2; 0,32 ng/ml for PCT-1; 0,94 ng/ml for PCT-2, 164 pg/ml for IL6-1 and 104 pg/ml for IL6-2. For 2vs1 variations, the optimal cut-off saw an increase of 291,37% and 113,64% for CRP-2vs1 and PCT-2vs1, respectively.

In figures 1, 2 and 3, we show ROC curves for biomarkers at evaluations 1 and 2, and for percentage of variation 2vs1, respectively. IL6 at evaluation 1 (IL6-1), with an AUC of 0.89, showed the best accuracy in discriminating HRE. This same accuracy was lost for IL6-2 and IL6-2vs1. PCT-2 (AUC=0.836) showed the best accuracy at evaluation 2. Regarding 2vs1 values PCT-2vs1 and PCR-2vs1 showed the best accuracy with AUC of 0.83 and 0.785, respectively.

Logistic regression models

Biomarker variables at evaluation 1 and 2 and their variations 2vs1 (only those that obtain cut-off points that significantly discriminate HRE) were studied as possible indicators.

Table 4 shows the odds ratio (OR), first univariate and then multivariate, together with a 95% confidence interval and p-value or significance of the Wald test.

Table 4
Cut-off values and odds ratio (95% confidence interval and p-value) in Univariate and Multivariate analysis for HRE diagnosis.

Variable	Cut-off point	Univariate OR	Multivariate OR
PCT-1	<0.32 ng/ml	-	-
	>0.32 ng/ml	6.67 (1.81-32.27, p=0.008)	-
IL6-1	< 164 pg/ml	-	-
	> 164 pg/ml	39.43 (6.88-750.81, p=0.001)	26.03 (3.68-556.47, p=0.006)
PCR-2	<3.5 mg/dl	-	-
	>3.5 mg/dl	5.56 (0.98-104.97, p=0.111)	-
PCT-2	<0.94 ng/ml	-	-
	>0.94 ng/ml	13.33 (3.48-66.82, p<0.001)	-
IL6-2	< 104 pg/ml	-	-
	> 104 pg/ml	6.40 (1.82-24.73, p=0.005)	-
PCR-2vs1	<291.37%	-	-
	>291.37%	31.50 (7.29-171.48, p<0.001)	19.62 (3.47-164.30, p=0.002)
PCT-2vs1	<113.64%	-	-
	>113.64%	4.67 (1.33-17.14, p=0.017)	-
CRP: C-Reactive Protein. PCT: Procalcitonin. IL6: Interleukine 6. OR: Odds ratio			

The likelihood ratio test was significant (p <0.001), an AUC of 0.918 and an explanatory power R2 of 62.7% were obtained.

Regarding these results, an IL6 value upon first evaluation (IL6-1) higher than 164 pg/ml and an increase of CRP-2vs1 greater than 291% are relevant in determining an increased risk of HRE that was 26.03 and 19.62 times greater, respectively. PCT-1, PCT-2 and PCT-2vs1 were statistically significant in univariate but not in multivariate analysis.

Discussion

The main objective of our study was to find indicators that allow us to make an early prediction of Gr-BSI or SIRS episodes, which we have called high-risk episodes (HRE). These two types of episodes were chosen as the outcome to be predicted due to the fact that they are two of the most serious infectious conditions that a pediatric cancer patient can present during treatment, the latter frequently being the consequence of the former.

Among the possible indicators, analytical biomarkers are of special interest. An ideal biomarker for use in febrile oncologic patients should be able to predict, identify, and thus stratify risk in febrile patients early in their clinical course. In addition, the biomarker should be able to provide robust discrimination of all parameters between mild and serious infections [11].

Many studies have tried to determine the best predictive biomarkers of infection in cancer with contradictory results in many cases [5, 8–12]. This fact may be due to differences in the cut-off points used, type of episodes to be predicted, and use of only univariate rather than both uni- and multivariate models.

In our study, in addition to the static values of biomarkers, we added their kinetics in the first 24 hours in order to try to approximate our predictive model to the changing reality that this type of infectious disease entails. We have not found in the literature any publication that has used these types of variables in pediatric oncology patients.

Among the biomarkers analyzed, those that proved to be good predictors of HRE in the multivariate analysis were an IL6-1 value greater than 164 pg / ml (OR = 26.03) and a CRP-2vs1 value greater than 291% (OR = 19.62).

IL6-1, the best predictor according to our study, had high sensitivity (92.8%), specificity (82.5%), positive predictive value (56.1%) and negative predictive value (98.1%) with an AUC of 0.89 (0,791-0,989). IL6-2 and IL6-2vs1 did not prove to be good predictors, although IL6-2 did have statistical significance in univariate analysis.

This finding concurs with other studies that show that IL6 is useful as an infection marker in initial moments of fever, especially in detecting patients with a low risk of presenting an HRE given its high negative predictive value [18, 20]. On the other hand, there are others studies where its utility has not been demonstrated [11]. It is worth pointing out that the IL6 value loses its accuracy within 12 to 24 hours from the beginning of antibiotic treatment due its rapid decrement. This is shown by the fact that median IL6-2vs1 is a negative value.

Regarding CRP, neither the CRP-1 nor CRP-2 values showed statistical significance in predicting HRE in the multivariate analysis. However, CRP-2vs1 was clearly significant in the multivariate analysis. The increase of 291% present between CRP-1 and CRP-2 implied a risk of HRE that was 19.62 times greater than in the absence of this increase. This may be due to the fact that elevated CRP values can occur in these patients due to other types of less serious and slower-evolving infections, as well as non-infectious causes such as mucositis or the oncological disease itself. In these cases, even if the absolute values were high, they would not vary much in a period as short as 12 to 24 hours, as could happen in the HRE. In this case, we can observe that the dynamic approach to the infectious phenomenon provides more information than the assessment of static parameters.

Regarding PCT, neither the absolute values nor the variations in biomarkers showed statistical significance in predicting HRE in the multivariate analysis. In the initial analysis, cut-off points of 0.32 ng/ml for PTC-1, 0.94 ng/ml for PCT-2, and an 113% increase between PCT-1 and PCT-2 appeared to show a good capacity for discriminating HRE with AUC of 0.8, 0.83 and 0.81 respectively and remained significant in the univariate analysis. However, this statistical significance was not maintained in the multivariate analysis, so PCT could not be considered to be a good independent predictor if IL6 and CRP are available within the first 24 hours from the fever onset. This fact is also shown in a study with a large sample size and multivariate analysis carried out by Santolaya et. al., in which the predictive value of CRP, PCT and IL8 for severe sepsis was analyzed [10]. In this study, the authors concluded that the use of PCT does not provide a significant benefit in the early detection of severe sepsis compared to CRP and IL8. Similarly, in our study, PCT does not appear to provide a significant benefit in the early detection of Gr-BSI or SIRS when IL6 and CRP are used. Conversely, this lack of usefulness of PCT seems discordant with the results from another study carried out by Mian et. al., which concluded that CRP and PCT were useful in risk stratification of febrile neutropenia episodes in pediatric oncology patients [11]. This study had a slightly smaller sample size than our study and a multivariate analysis was carried out. Comparative analysis between studies must be performed cautiously as populations, statistical analysis and outcomes are different.

In clinical practice according to our results, if we only had one biomarker available in the laboratory, PCT would be the elecction because it had good diagnostic accuracy during the first 24 hours. IL6 had the best performance in the first hours from the fever onset and CRP-2vs1 after 12-24 hours. Therefore, if we have IL6 and CRP available, PCT did not add any value to IL6 and CRP combination.

Study Limitations

This study presents several limitations that must be taken into consideration:

First, it was a single-center study with a small number of subjects and heterogenous diagnosis, all of which could potentially introduce bias. Results of single-center studies are less easily generalized. Second, we have performed an observational study that does not allow any conclusion to be drawn concerning therapeutic interventions. Third, biomarkers levels were analyzed within the first 24 hours from the onset of fever, but follow-up measurements were not available. The evolution of biomarker levels during the first days would have higher accuracy. However, an early severity prediction is more useful in clinical practice in improving patient outcomes.

Conclusions

Biomarkers with appropriately utilized critical cut-off thresholds may be an important clinical tool for early prediction of infection. In our study IL6-1 >164 ng/ml and PCR-2vs1> 291% showed a strong and independent correlation with HREs in multivariate analysis and therefore could be used as a reliable predictor of this kind of severe episode. We would like to highlight the approach of our study using

biomarker variations over time as a variable and that, in the case of CRP, we have provided an improvement in predictive models.

List Of Abbreviations

ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic Stem cell transplantation
AML	Acute myeloblastic leukaemia
AUC	Area under the ROC curve
BSI	Bloodstream infection
CRP	C-Reactive Protein
G-CSF	Granulocityc stimulator factor
Gr-BSI	Gram negative bloodstream infections
HL	Hodgkin's lymphoma.
HRE	High-risk episodes
IL6	Interleukine 6
NH	Non-Hodgkin's lymphoma.
NPV	Negative predictive value
PCT	Procalcitonin
PPV	Positive predictive value
Se	Sensitivity
SIRS	Systemic Inflammatory Response Syndrome
Sp	Specificity

Declarations

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Code availability: Not applicable

Authors´ contributions

JAVR was responsible for study design, methodology, data collection, statistical analysis and writing of the manuscript first draft.

PPM and ALD were responsible for study design and data collection.

CRG was responsible for study design, data interpretation and manuscript oversight.

BPG participated in laboratory sample management and data interpretation.

GSS collaborated in statistical analysis.

All the authors reviewed and approved the final manuscript.

Ethics approval: This study was approved by the Institutional Ethics Committee.

Consent to participate: Written informed consent was signed by the patients' parents or guardians and by children over the age of 16.

Consent to publish: Consent to publish has been received from all participants in the study.

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Figures

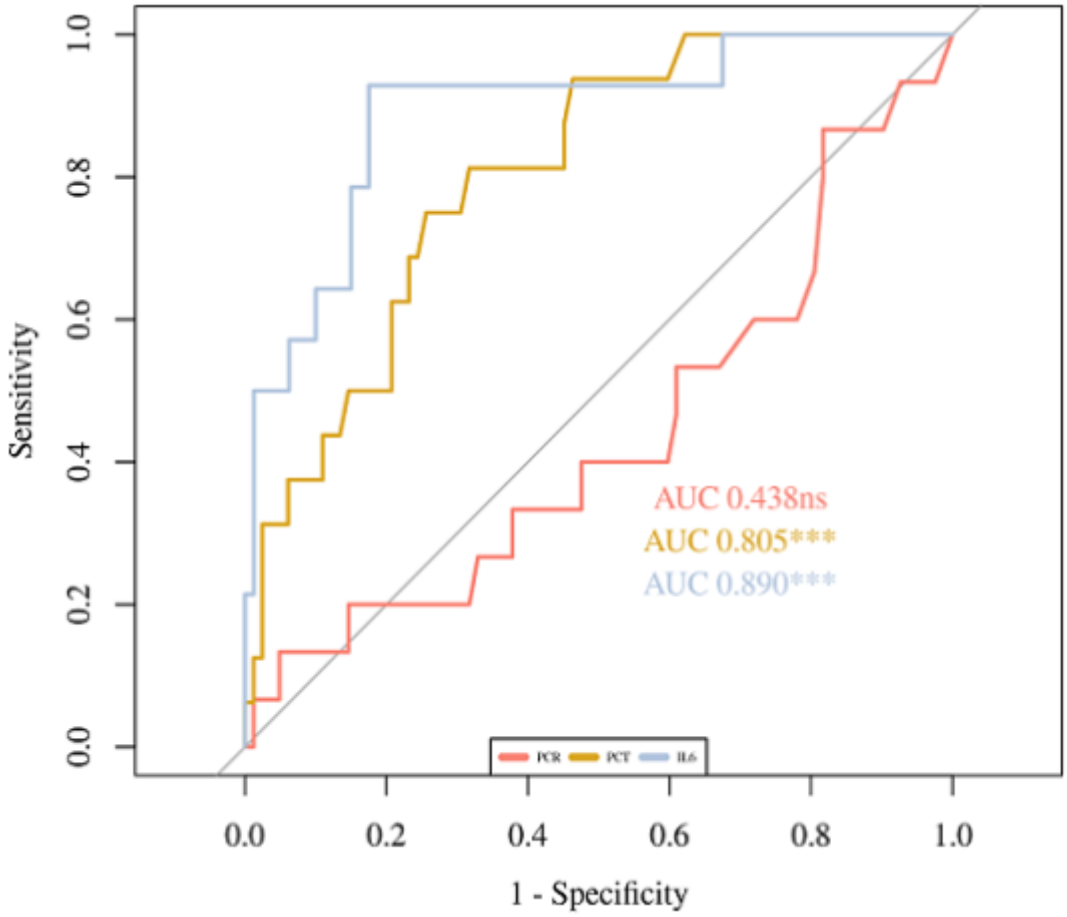

Figure 1

ROC Curves of CRP-1, PCT-1 and IL6-1

ns: non significance, * p<0.05, ** p<0.01, *** p<0.001

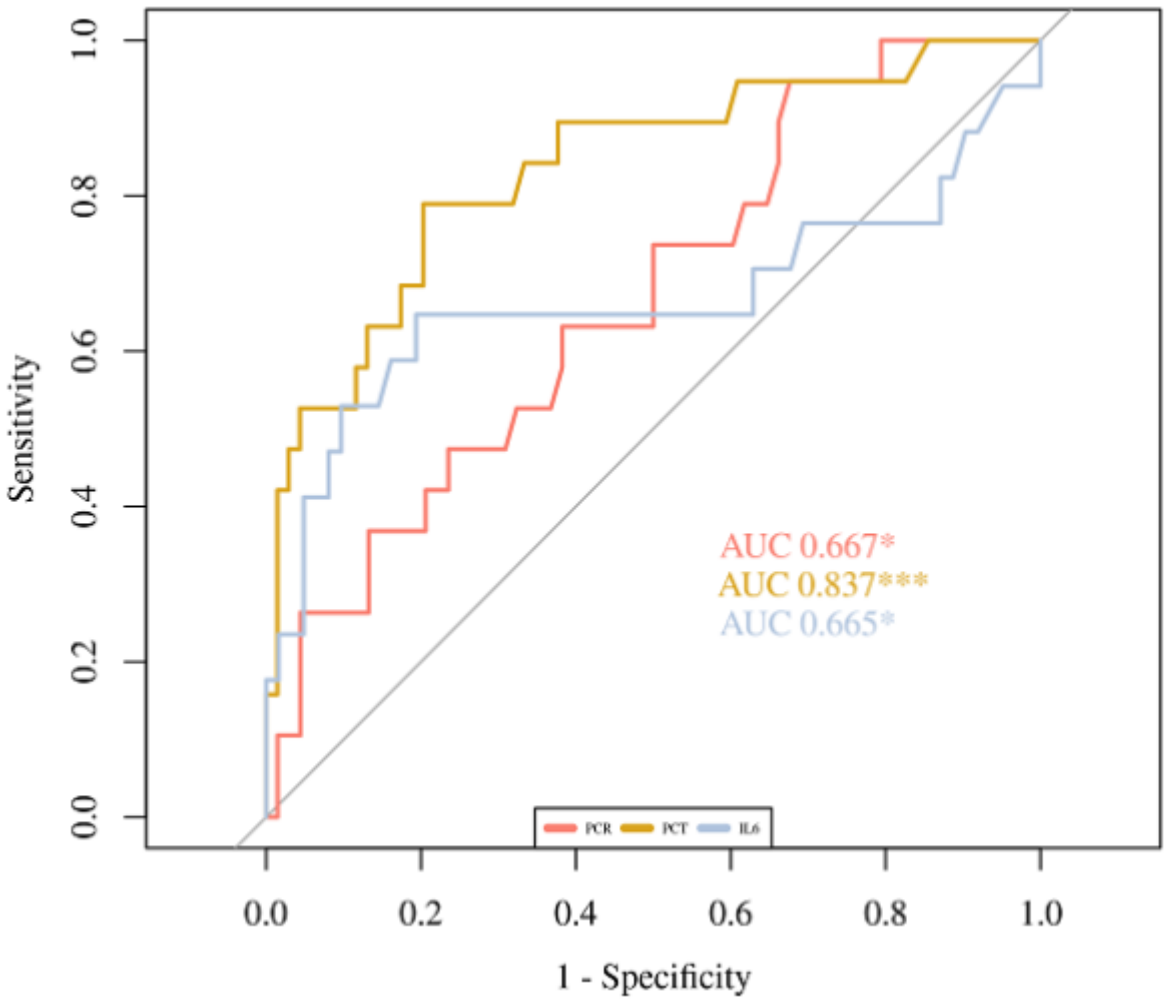

Figure 2

ROC Curves of CRP-2, PCT-2 and IL6-2

ns: non significance, * p<0.05, ** p<0.01, *** p<0.001

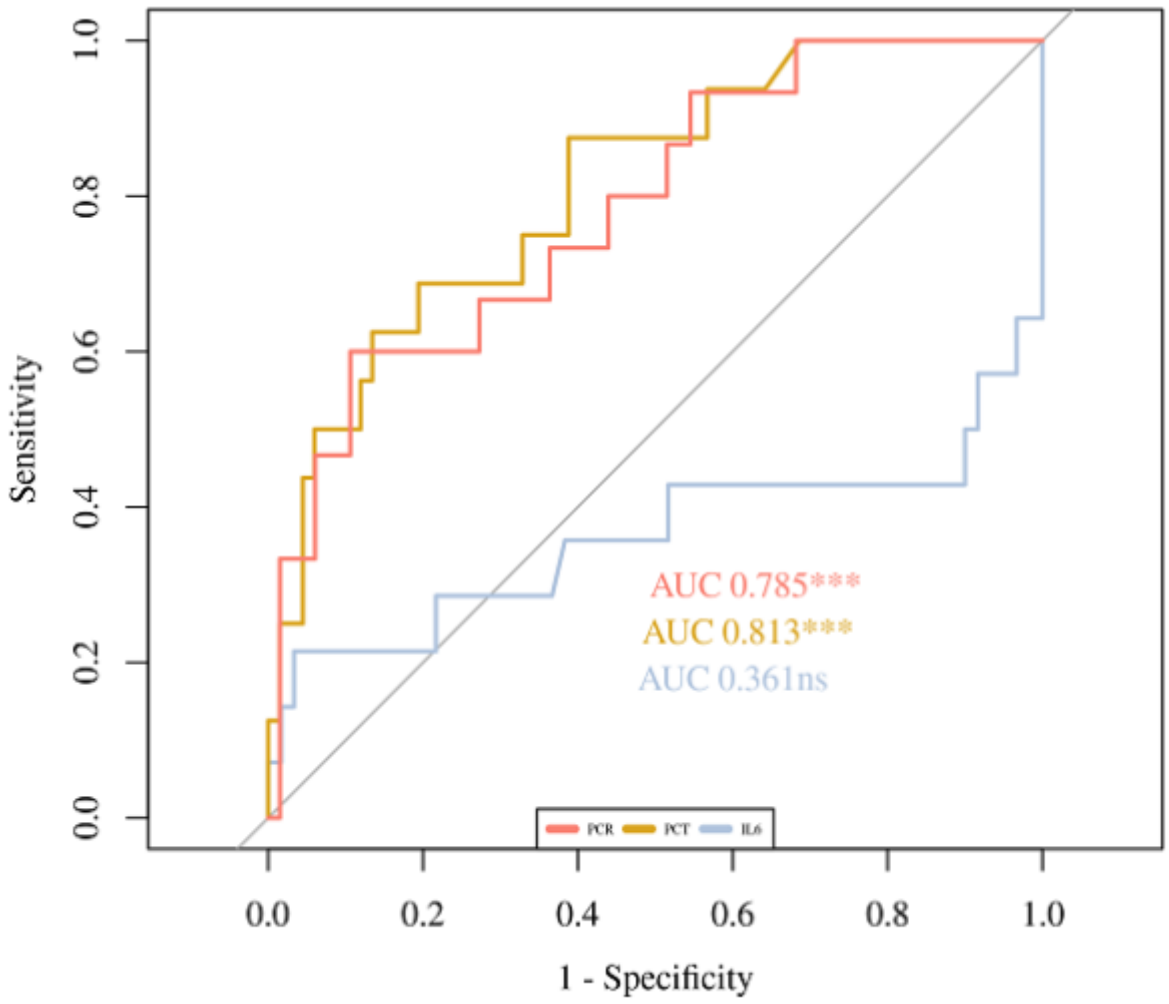

Figure 3

ROC Curves of CRP-2vs1, PCT-2vs1 and IL6-2vs1

ns non significance, * p<0.05, ** p<0.01, *** p<0.001