Clinical And Laboratory Findings Of Late Onset Sepsis In Extremely Low Birth Weight Infants According To Causative Organisms

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Abstract

Background: Late onset sepsis (LOS) remains a significant source of morbidity and mortality in extremely low birth weight (ELBW) infants. Early and accurate diagnosis is very important but is difficult due to the similarities in clinical manifestation between the causative microorganisms. We tried to identify the differences between causative microorganisms in clinical and laboratory findings, when sepsis was suspected in ELBW infants.

Methods: A retrospective study was conducted on preterm infants born at less than 28 weeks of gestation with a birth weight of less than 1,000 g between January 2009 and December 2019. Clinical and laboratory findings of suspected LOS were assessed. We classified them into three groups according to blood culture results (gram-positive, gram-negative, and fungal groups) and compared them.

Results: A total of 107 patients were included after using the exclusion criteria, with 45 (31.5%) in the gram-positive group, 35 (17.5%) in the gram-negative group, and 27 (11.5%) in the fungal group. There were no significant differences in mean gestational age, birth weight, and neonatal morbidities, except for the age of onset, which was earlier in the fungal group than in the bacterial groups. White blood cell (WBC) counts were the highest in the gram-negative group and the lowest in the fungal group. The mean platelet counts were significantly lower in the fungal group ($137,000/mm^3$, $100,000/mm^3$, and $61,000/mm^3$ in the gram-positive, gram-negative, and fungal groups, respectively; $p < 0.001$). C-reactive protein (CRP) levels were significantly higher in the gram-negative group, while glucose was significantly higher in the fungal group.

Conclusion: In conclusion, we showed that there are some differences in laboratory findings, according to causative microorganisms, in the LOS of ELBW infants. WBC and CRP were increased in gram-negative infection, and thrombocytopenia and hyperglycemia were predominant in fungal infection. These data may be helpful for choosing empirical antibiotics when sepsis is suspected.

Introduction

Neonatal sepsis is classified as either early onset sepsis (EOS, ≤ 3 days after birth) or late onset sepsis (LOS, > 3 days after birth) [1, 2]. Advances in obstetric and neonatal care have decreased the incidence of neonatal sepsis, especially EOS [3]; however, the incidence of LOS has increased along with the improvement in the survival of premature infants [4].

Extreme prematurity is one of the greatest risk factors for LOS. Among 9575 infants born between 22 and 28 weeks of gestation, 36% developed LOS [5]. There are multiple factors that put extremely low birth weight (ELBW) infants at particularly high risk, such as prolonged hospitalization, central venous catheters and parenteral nutrition, endotracheal intubation and mechanical ventilation, and lack of enteral feeding [6]. Due to the high risk of nosocomial infection and the associated morbidity in extremely preterm infants, these patients are frequently exposed to broad-spectrum antibiotics [7]. Epidemiological data on neonates show that the predominant pathogens causing LOS are coagulase negative

staphylococci (CoNS), followed by gram-negative bacteria, and fungi. Because CoNS is usually resistant to a number of commonly used antibiotics, neonatologists usually add vancomycin to the empirical combination when treating suspected LOS in extremely low birth infants [7]. However, early and accurate diagnosis of LOS is challenging because the presenting signs and symptoms are subtle and nonspecific [8]. In addition, invasive bacterial and fungal infections are all similar in clinical manifestation [9].

In order to diagnose LOS early and choose the right empirical antibiotics while avoiding broad-spectrum antibiotics or vancomycin, we tried to identify the differences between causative microorganisms using clinical findings and routine laboratory findings, when sepsis was suspected in ELBW infants.

Materials And Methods

Materials

A retrospective study was conducted on preterm infants born at less than 28 weeks of gestation with a birth weight of less than 1,000 g between January 2009 and December 2019 at Pusan National University Yangsan Hospital.

Neonates with suspected sepsis were defined as having one or more of the following signs: apnea, acutely ill appearance, decreased activity, fever (>37.8°C), lethargy, irritability, gastrointestinal dysfunction with milk intolerance, hypotension, and sudden increased respiratory support.

Patients were included if they required laboratory tests, including blood culture, under suspicion of sepsis during the hospital stay. For the purpose of our investigation, negative blood cultures and episodes of polymicrobial sepsis were excluded, and in infants with multiple episodes of LOS, only the first episode was included.

We also excluded all infants with other abnormalities including congenital malformation or chromosomal abnormalities and congenital infections such as cytomegalo virus.

We classified them into three groups according to the results of blood culture: the gram-positive, gram-negative, and fungal groups.

Methods

The data, including clinical characteristics and morbidities, were reviewed retrospectively.

The perinatal data were collected from the medical charts of the infants and included the parameters of gender, gestational age (GA), and birth weight (BW).

The following neonatal characteristics were reviewed: respiratory distress syndrome (RDS); patent ductus arteriosus (PDA; defined as needing either medical therapy with ibuprofen or surgical ligation); intraventricular hemorrhage (IVH; defined as grade ≥III); bronchopulmonary dysplasia (BPD; defined as

moderate and above); periventricular leukomalacia (PVL, defined as grade 2 and above); and retinopathy of prematurity (ROP, defined as stage 2 and above)

Statistical analysis

Values of all non-normally distributed variables are expressed as medians and interquartile ranges (IQR; 25%-75%). For comparing the categorical data of the groups, the chi-square test was used. A Kruskal-Wallis test and post-hoc analysis were performed for pairwise comparison of subgroups to verify differences across the patient groups. The statistical analyses were performed using MedCalc software (version 16.4.3; MedCalc, Mariakerke, Belgium) and RStudio (version 1.2b; RStudio, MA, USA). A P-value of <0.05 was considered significant. Receiver operating characteristics (ROC) and area under the curve were generated to determine the optimal cut-off value for each marker in detecting LOS, and to calculate sensitivity and specificity.

Results

During the study period, 455 preterm infants born at less than 28 weeks of gestation, with a BW of less than 1000 g, were admitted at our hospital. A total of 158 patients underwent laboratory tests for suspected sepsis. After applying the exclusion criteria, 107 patients were finally included, with 45 (31.5%) in the gram-positive group, 35 (17.5%) in the gram-negative group, and 27 (11.5%) in the fungal group. A detailed flowchart of the study population is shown in Fig. 1. The predominant organisms cultured in each group were *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Candida parapsillosis*, in each group, respectively. (Table 1)

Table 1. causative organisms asociated with LOS

type of microorganisms		Incidence
Gram positive bacteria		45
	Staphylococcus aureus	21
	Enterococcus faecium	7
	Coagulase-negative staph	6
	Staphylococcus capitis	6
	Group b streptococcus	2
	Other streptococcus	3
Gram negative bacteria		35
	Klebsiella pneumoiae	9
	Serratia marcescens	7
	Pseudomonas aeruginosa	6
	Enterobacter cloacae	3
	E. coli	3
	Klebsiella aerogenes	2
	Othe gram negative rods	5
Fungi		27
	Candida parapsilosis	24
	Candida albicans	3

LOS late onset sepsis

The demographic and clinical characteristics of the three groups are shown in Table 2. The mean GA was 25.5 (25.0-26.5) weeks, 25.4 (24.3−26.4) weeks, and 25.3 (24.3−26.2) weeks in the gram-positive, game-negative, and fungal groups, respectively. The mean BW was 790 (710−910) g, 790 (685−875) g, and 760 (685−835) g, in same sequence, respectively. There were no significant differences in mean GA and BW. No significant differences were observed between the three groups in terms of neonatal morbidities including RDS, PDA and BPD. However, the age of onset was lower in the fungal group than in the other bacterial groups (34, 31, and 21 days of life in the gram-positive, gram-negative, and fungal groups, respectively; $p = 0.001$).

Table 2. Comparison of demographic and clinical characteristics according to microorganisms

	Gram positive (N=45)	Gram negative (N=35)	Fungal (N=27)	P value
Gestational age	25.5 (25.0-26.5)	25.4 (24.5-26.4)	25.3(24.3-26.2)	0.365
Birth weight	780 (695 – 900)	790 (710 – 910)	760 (685 – 835)	0.580
Male gender, n	27 (60%)	19 (54 %)	16 (59 %)	0.865
Inborn	41 (91 %)	28 (80%)	21 (78 %)	0.234
Onset (age,d)	34 (26-61)	31 (19-59)	21 (11-31)	0.001*
RDS	45 (100.0)	35 (100.0)	27 (100.0)	NA
PDA	16 (35.6)	19 (54.3)	14 (51.9)	0.191
IVH	6 (13.3)	6 (17.1)	9 (33.0)	0.066
BPD	42 (93.3)	28 (80.0)	23 (85.2)	0.205
ROP	7 (15.6)	4 (11.4)	0 (0.0)	0.105
PVL	4 (8.9)	2 (5.7)	1 (3.7)	0.670
Mean (range) for gestationa age and birth weight				
RDS Respiratory distress syndrome; PDA Patent ductus arteriosus; IVH Intraventricular hemorrhage; BPD Bronchopulmonary dysplasia; ROP Retinopathy of prematurity; PVL Periventricular leukomalasia				

White blood cell (WBC) counts were the highest in the gram-negative group and the lowest in the fungal group, while remaining normal in the gram-positive group. The mean platelet counts were significantly lower in fungal group (137,000/mm^3, 100,000/mm^3, and 61,000/mm^3 in the gram-positive, gram-negative, and fungal groups, respectively; p < 0.001). C-reactive protein (CRP) levels were significantly higher in the gram-negative group (2.2 mg/L, 6.8 mg/L, and 1.13 mg/L, respectively, in each group (p < 0.001)). Glucose levels were significantly higher in the fungal group, while the other two groups showed normal ranges (133 mg/dl, 130 mg/dl, and 253 mg/dl in the gram-positive, gram-negative, and fungal groups, respectively). (Table 3)

Table 3. Comparison of main laboratory findings according to microorganisms

	Gram positive	Gram negative	Fungal	P value
WBC	11440 [7220 − 18740]	16880 [9005-26005]	9080 [5585-13325]	0.034*
Hb	10.9 [9.7 − 11.9]	10.6 [9.0 − 12.4]	10.9 [9.8 − 12.0]	0.889
PLT	137,000[83,000-225,000]	100,000[48,000-185,500]	61,000[32,000-70,000]	< 0.001*
CRP	2.2 [1.6 − 4.6]	6.8 [4.7 − 11.6]	1.13 [0.4 − 3.3]	< 0.001*
Glucose	133 [99 − 155]	130 [102 − 167]	253 [219 − 288]	< 0.001*
ph	7.34 [7.27 − 7.37]	7.29 [7.21 − 7.38]	7.28 [7.18 − 7.34]	0.191
Mean [range]				
WBC Whole blood count; Hb Hemoglobin; PLT Platelet; CRP C reactive protein				

The optimal cut-off values for CRP, platelets, and glucose were identified by drawing ROC curves. For gram-negative infection, the cut-off value for the CRP was found to be 4.4 mg/dL, with sensitivity and specificity of 77.8% and 82.95%, respectively. The optimal cut-off value for platelet counts was 90,500/µl, with 63.7% sensitivity and 100.0% specificity. The optimal cut-off value for glucose level was 180.5 mg/dl, with 90.1% sensitivity and 97.05% specificity, for diagnosing fungal infections. (Fig. 2)

Discussion

The clinical presentation of LOS in ELBW infants is subtle, and as invasive bacterial and fungal infections are similar, this may cause diagnostic delay [9]. In this present study, we were unable to identify differences in clinical findings between microorganisms except in the age of onset, which was the lowest in the fungal group. At birth, most infants are uncolonized or have low colony counts of yeast. In the absence of antifungal prophylaxis, up to 60% of ELBW infants become colonized in the first 2 ~ 3 weeks after birth [10]. Clerihew et al. described a median age at diagnosis of 14 days, using 94 cases of invasive fungal infection in ELBW infants [11]. According to our study, the mean age of onset was 21 days after birth. These results are consistent with the fungal colonization timings mentioned above. Therefore, it is speculated that the fungal infection may occur as soon as colonization occurs in ELBW infants with compromised immunity, but the exact etiology needs to be investigated.

Although blood culture results are important for diagnosing neonatal sepsis, its unavailability within the 2 ~ 3 days of incubation and low culture rate make early diagnosis difficult. For the rapid identification of microorganisms causing sepsis, novel laboratory methods, such as cytokine and molecular analyses, have been developed; however, it is unlikely that these methods will be useful in the near future because they are not very cost effective [12, 13]. So far, reliable laboratory diagnosis has not been achieved.

The complete blood cell (CBC) count is a rapid, inexpensive, and widely available diagnostic test [14, 15]. However, the diagnostic accuracy of the CBC count is not well-defined in neonatal sepsis and the usefulness of the CBC count have reported conflicting results in preterm infants, especially in very low BW

(VLBW) infants [16, 17]. Hornik et al. studied the diagnostic accuracy of CBC count in LOS in a large multicenter population and reported CBC parameters associated with LOS, including a total WBC count of < 5000/mm^3 and an immature neutrophil/total neutrophil (I/T) ratio of > 0.10 [18]. According to some studies on the pathogenesis of organisms responsible for LOS, elevated I/T ratios were significantly more common in gram-negative infections than in gram-positive ones [19, 20]. Dogan et al. analyzed red-cell distribution width (RDW) during a LOS episode and its association with the type of growing microorganism [21]. According that study, RDW levels increased in preterm infants with LOS, which was especially evident in gram-negative infections. Unfortunately, we did not check I/T ratio and RDW levels in this study. Nevertheless, we found that higher WBC counts were associated with gram-negative LOS in ELBW infants. However, CBC count varies significantly with day of life and GA and are affected by non-infectious comorbidities. More specifically, VLBW infants are known to develop physiologic late onset neutropenia, which does not correlate with sepsis. Therefore, we have to cautiously interpret the WBC count during diagnosis of LOS in preterm infants.

Thrombocytopenia has been used as an early but nonspecific marker for sepsis [22]. Several studies have shown quantitative differences in the platelet response to infection with the three major categories of organisms causing sepsis in the VLBW infants. Daniel et al. reported that thrombocytopenia at the time of blood culture was a risk factor for candidemia [23, 24]. In our study, mean platelet count was 54,000/mm^3 in the Candida group, which was significantly lower than those of the other two bacterial groups. This result was similar to previously published results. According to Benjamin et al., fungal sepsis is associated with a greater degree of thrombocytopenia than CoNS sepsis [25]. Although the mechanisms for this result have not yet been identified, it is known that administration of platelet activating factor is protective in a mouse model of *C. albicans* sepsis, suggesting that platelet activation plays a role in the host defense against fungal pathogens [26, 27]. On the other hand, Scheifele et al. demonstrated evidence of a relationship between gram-negative infections and thrombocytopenia [28]. Further work is needed to understand the basis for the effects of different species of microorganisms.

The most extensively studied laboratory marker for determining the diagnosis of neonatal sepsis has been CRP [29]. The increased survival of extremely premature infants has brought the diagnostic validity of the method to the point of great scientific controversy. Some clinicians suggest that CRP is an inappropriate method in extremely premature infants as they are incapable of sufficiently increasing CRP levels following a septic event. One possible explanation for this is that an extremely immature liver cannot respond to septic stimuli as those in more mature premature and full term infants [30, 31].

On the other hand, in a study of 123 ELBW infants with a mean GA of 27 weeks and mean BW of 1000 g, Wagle et al. concluded that infants with gram-negative sepsis are capable of mounting significant CRP responses similar to those of full term infants [32].

In addition, Dritsakou et al. found that gram-negative microorganisms were associated with higher CRP levels in ELBW infants [33]. On the contrary, some studies found that CRP could not serve to disclose CoNS infection. Previous studies have suggested that CoNS are associated with lower levels of

inflammation than other bacteria [34–36]. These studies showed that CoNS, involving *S. epidermidis*, does not cause local inflammatory reactions or immunoglobulin G responses in animal models [36].

The results of our study are consistent with those of the abovementioned studies to some extent. According to our study, CRP increased in the gram-negative group, whereas CRP in the gram-positive group did not increase as much. However, in our study, the majority of the gram-positive group had *S. aureus* involvement, and not CoNS. CoNS are a common skin commensal and the most frequent organism associated with nosocomial infection in ELBW infants. However, recent studies have suggested that CoNS infection has decreased with central intravascular line care protocols and the reduction of the use and duration of central lines, which is consistent with our result [37, 38]. Therefore, we do not know exactly why the gram-positive group showed lower CRP level than the gram-negative group.

It has been recognized that hyperglycemia may be an important early sign in neonatal sepsis [39, 40]. It is known that inadequate hepatic and diminished pancreatic insulin secretory responsiveness increase the risk of hyperglycemia in stressful episodes, such as sepsis, in preterm infants [41]. Interestingly, blood glucose was higher in the fungal group than in the other two bacterial groups in our study. This result is consistent with another study by Manzoni et al, which revealed that hyperglycemia is more frequent in fungal LOS sepsis than in bacterial LOS sepsis in preterm infants [40, 42]. They suggested that hyperglycemia could be a possible surrogate marker predictor of invasive fungal infection in preterm infants. However, Levit et al. reported that sepsis-related death was associated with hypoglycemia in VLBW infants and that there was no specific correlation between glucose disturbances and the type of pathogen [43]. We do not know exactly why the Candida group showed higher glucose level than the bacterial groups in our study. Further studies are needed to know this association.

This study has several limitations, including its retrospective design and small number of patients. Furthermore, we only included blood culture-proven sepsis and the first LOS episode. Unfortunately, culture-negative sepsis is common in neonates. Therefore, we were unable to retrieve the complete information for all cases of LOS in ELBW infants.

In conclusion, we have shown that there are some differences in laboratory findings according to causative microorganisms in LOS of ELBW infants. WBC and CRP were increased in gram-negative infection, and thrombocytopenia and hyperglycemia were predominant in fungal infection. These data may be helpful to choose empirical antibiotics when sepsis is suspected.

Abbreviations

ELBW: Extremely low birth weight; LOS: Late onset sepsis; WBC: Whole blood count; CRP: C reactive protein; EOS: Early onset sepsis; CoNS: Coagulase negative staphylococcus; GA: Gestational age; BW: Birth weight; RDS: Respiratory distress syndrome; PDA: Patent ductus arteriousus; IVH: Intraventricular hemorrhage; VLBW; Very low birth weight; BPD: Bronchopulmonary dysplasia; PVL: Periventricular leukomalacia; ROC: Receiver operating characteristics; CBC: Complete blood cell; RDW: Red-cell distribution width; I/T: Immature neutrophil/total neutrophil

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (2101-002-098). The requirement for informed consent was waived by the IRB of Pusan National University Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None of the authors have any conflicts of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' contributions

SY was the major investigator and supervisor for data analysis and review all drafts of the article. KH participated and was largely involved with data analysis and interpretation of the data and drafted the article. NR, YM, and MH performed data collection. All authors contributed to the drafting of the article and revised. All authors read and approved the final draft.

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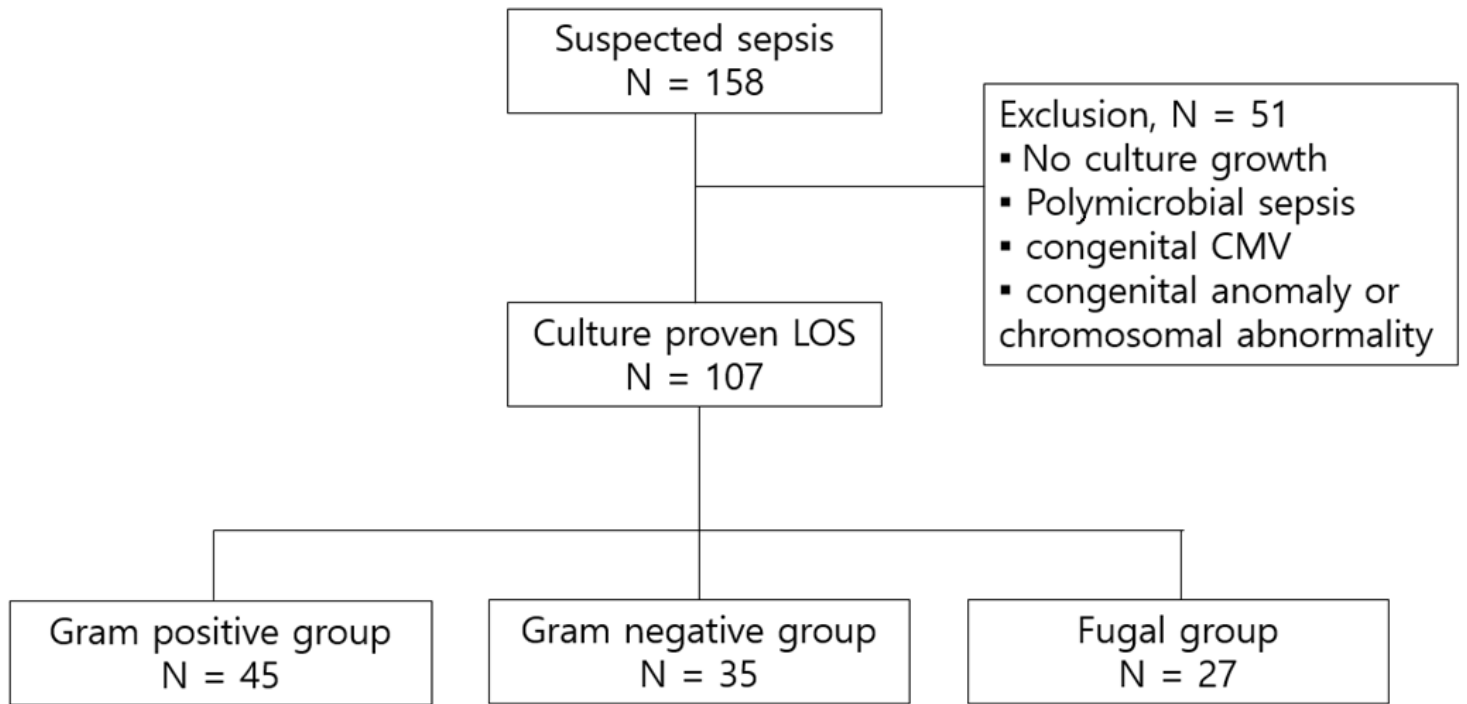
Figures

Figure 1
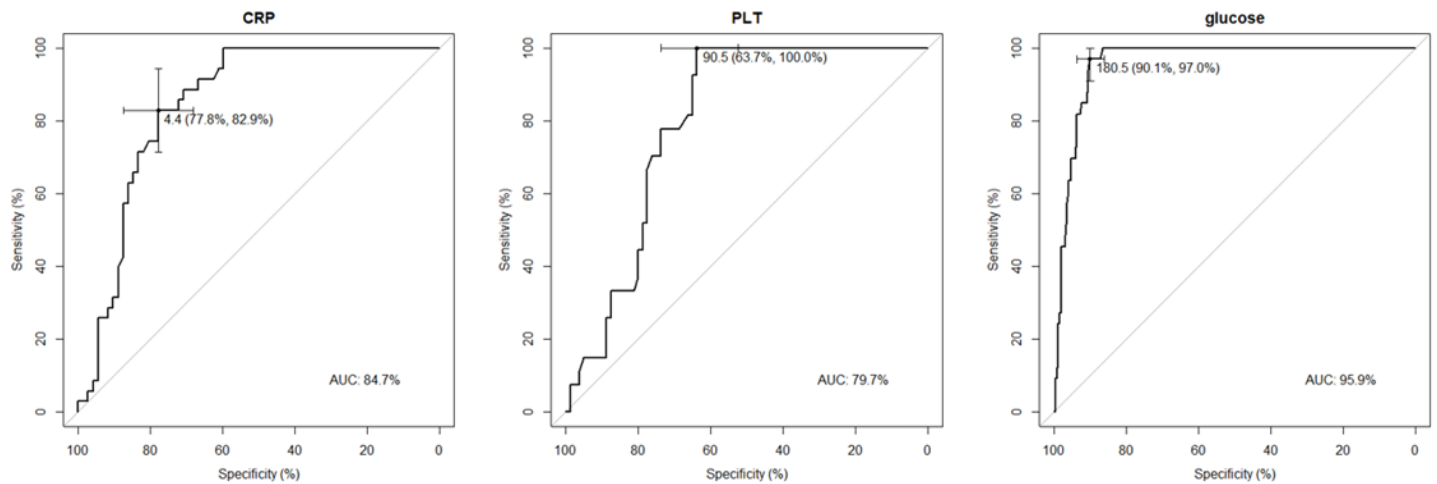
Study selection flowchart

Figure 2

Receiver operating characteristics curves calculated for cut-off value of CRP, PLT and gulcose