

# Risk factors for postpartum sepsis: A nested case control study

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## Research article

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# Abstract

**Background:** Majority (99%) of maternal deaths occur in low and middle income countries. The three most important causes of maternal deaths in these regions are postpartum hemorrhage, pre-eclampsia and puerperal sepsis. There are several diagnostic criteria used to identify sepsis and one of the commonly used criterion is systematic inflammatory response syndrome (SIRS). However, these criteria require laboratory investigations which may not be feasible in resource constrained settings. Therefore, this study aimed to develop a model based on risk factors and clinical signs and symptoms that can identify sepsis early among postpartum women.

**Methods:** A case control study was nested in an ongoing cohort of 4000 postpartum women who delivered or were admitted in study hospital. According to standard criteria of SIRS, 100 women with sepsis (cases) and 498 women without sepsis (controls) were recruited from January to July 2017. Information related to socio-demographic status, antenatal care and maternal life styles were obtained via interview while pregnancy and delivery related information, comorbid and clinical sign and symptoms were retrieved from ongoing cohort. Multivariable logistic regression was performed and discriminative performance of the model was assessed using area under the curve (AUC) of the receiver operating characteristic (ROC).

**Results:** Multivariable analysis revealed that 1-4 antenatal visits (95% CI 0.01 - 0.62), 3 or more vaginal examinations (95% CI 1.21 - 3.65), home delivery (95% CI 1.72-50.02), preterm delivery, diabetes in pregnancy (95% CI 1.93-20.23), lower abdominal pain (95% CI 1.15 - 3.42)) vaginal discharge (95% CI 2.97-20.21), SpO<sub>2</sub> <93% (95% CI 4.80-37.10) and blood glucose were significantly associated with sepsis. AUC was 0.84 (95% C.I 0.80-0.89) which indicated that risk factors and clinical sign and symptoms based model has adequate ability to discriminate women with and without sepsis.

**Conclusion:** This study developed a non-invasive tool which can identify postpartum women with sepsis as accurately as SIRS criteria with good discriminative ability. Once validated, this tool has a potential to be scaled up for community use by frontline health care workers.

## Background

Pregnancy and childbirth related complications are a major public health concern worldwide. Approximately 830 women globally die every day from preventable causes related to pregnancy and childbirth and almost one third of these occur in South Asia (1). About 60% of maternal deaths occur during delivery and the immediate postpartum period (2). (1). In Pakistan, there is one death in every 40 minutes due to pregnancy or delivery complications (3). Pakistan Demographic Health Survey (PDHS 2006) reported sepsis as a third major cause of maternal mortality which contributes to 14% of maternal deaths in Pakistan (4, 5). According to International Consensus, sepsis is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” (6). Increasing severity of

infection correlates with increasing mortality, which is 16.7% for sepsis, 25–30% for severe sepsis and up to 40–70% for septic shock (7, 8) in the general population.

There are many associated distant, intermediate and proximal risk factors contributing to sepsis. Distant and intermediate factors are those which make women vulnerable or predispose them to develop sepsis. Our primary concern is proximal risk factors which can lead to sepsis within few hours and provide a window of opportunity to identify women at high risk of sepsis (9).

Previous studies on sepsis were focused on sepsis in the general population but limited studies have taken into account physiological changes of pregnancy and postpartum period. Catherine et al, in 2011, designed sepsis obstetric score (SOS) among pregnant and postpartum women in emergency department to identify risk of intensive care unit (ICU) admission. This scoring system took into account clinical parameters and laboratory investigations and reported sensitivity and specificity of 88.9% and 95.2% respectively (AUC ROC = 0.92) (10). The limitation of this obstetric score was that it involved immature neutrophils and serum lactate levels which are not feasible in low resource settings.

The progression of sepsis is lethal hence early identification may help reduce further complications. The aim of the study was to develop a model based on risk factors and clinical sign and symptoms that can enhance early identification of postpartum women with sepsis in low resource settings.

## Methods

A nested case control study was conducted at Jinnah Postgraduate Medical Center (JPMC) from January to May 2017 to determine risk factors and clinical sign and symptoms for identification of sepsis among postpartum women. JPMC is one of the largest public health facility in Karachi which serves a large catchment area within and outside Karachi, representing a diverse patient population. This study was nested in a large cohort of 4000 women of age 15-49 years who delivered or presented within 42 days of delivery to JPMC (from October 2016 to May 2017) with suspected sepsis and postpartum hemorrhage (PPH). The aim of the cohort was to develop and internally validate a predictive model to identify women who may have 'severe maternal outcome' following childbirth. This cohort collected information on demographics, obstetric history which were obtained through a pre tested questionnaire. Blood pressure, blood oxygen saturation level (SpO<sub>2</sub>) and blood glucose level were objectively measured with validated point of care devices. Other vital signs such as temperature and laboratory parameters such as hemoglobin, renal laboratory investigations etc. were collected through medical records. Women were followed up till discharge and assessed for outcomes including shock, organ dysfunction, prolonged hospital admission and death.

Out of 4000 postpartum women from the cohort 100 cases and 498 controls with ratio of 1:5 were identified from January 2017 to May 2017 via purposive sampling (Figure 1).

The sample size calculation for this nested case-control study was performed using Open EPI version 3.1. Minimum sample size of 100 cases and 498 controls was required in order to achieve 80% power, with an

anticipated prevalence of risk factors among the controls ranging from 4% to 59%, an anticipated odds ratio of 2 and a level of significance of 5%. Sepsis was defined as women who fulfilled two of four criteria according to SIRS criteria. These included heart rate >90beats/ minute, respiratory rate >20 breaths/minutes, temperature >38.0 Celsius and white blood cell counts >12000/mm<sup>3</sup> and <4000/mm<sup>3</sup> (11). Postpartum women with any autoimmune diseases, unable to provide informed consent in Urdu and those who had missing information or incomplete follow up from cohort were excluded from the study. Before administering any questionnaire, study was explained to the patients and written informed consent was obtained. All participants were above 18 years of age so no parental consent was required.

For nested case control study there were two sources of information. Socio-demographic status, antenatal care and tobacco use information was obtained through direct interview from the enrolled women. Information regarding comorbid such as hypertension, diabetes, current pregnancy and delivery details and clinical sign and symptoms were obtained from the primary cohort.

Means and standard deviation were estimated for normally distributed continuous data and proportions for the categorical variables. WAMI (Water, assets, maternal education and household income) scoring system was used for formulating socioeconomic status based on monthly income, education and household assets (11). (Table 1). Odds ratio (OR) with 95% confidence interval (CI) were computed using binary logistic regression analysis. Model calibration was assessed by Hosmer lemeshow test and model accuracy was assessed by receiver operating curve (ROC) by plotting sensitivity against 1- specificity for different cut offs of parameters. All statistical analysis was performed using STATA version 12.

## Results

We recruited 100 cases and 498 controls from the large cohort. (Figure 1). Mean age of the cases was 27.1 +/- 5.10 and of controls was 26.6 +/-5.02. Majority of women in cases (40%) and controls (39%) belonged to middle tertile of socioeconomic status. Cases had higher proportion of more than 3 vaginal examinations (46%) and cesarean deliveries (39%) as compared to controls (36% and 30% respectively). Preterm delivery was present in 20% of women with sepsis as compared to 11% in controls.

Proportions of women reporting lower abdominal pain, vaginal discharge and dyspnea were more common among cases as compared to controls (56%, 14% and 7% respectively). Approximately one-fifth (19%) of cases were found to have significantly low oxygen saturation of <93% as compared to controls (1.81%) (p value=0.001). Mean blood glucose among cases was 96.5 +/- 15.6 mg/dl while it was 110.9 +/- 34.0 mg/dl in controls. **(Table 1)**

In this study women of receiving 1-4 antenatal visits were 75% less likely in women with sepsis versus women without sepsis (aOR 0.25, 95% CI0.01-0.62). Increased number of vaginal examinations was 2 times higher among cases as compared to controls (aOR 2.10; 95% CI= 1.21-3.65). Home delivery was approximately 9 times more likely in cases as compared to controls (95% CI=1.72-50.02).

Preterm delivery was 3.15 times (95% CI= 1.58-6.25) higher among women with sepsis as compared to those without sepsis. Cases were also more likely to be diabetic (aOR 6.62 (95% CI= 1.93-20.23)) than controls. The odds of lower abdominal pain and vaginal discharge was high among cases as compared to controls (aOR1.99 (95% CI= 1.15-3.42); (aOR7.77 (95% CI= 2.97-20.21). The odds of low oxygen saturation <93% was 13 times high in septic cases as compare to controls (aOR=13.0; 95% CI=4.80-37.10). **Table 2.**

AUC, area under the receiver operating characteristic curve was 0.84 with 95% confidence interval 0.80-0.89 which represented adequate performance.

At optimal cut off of 0.069, the proposed model has 82% sensitivity and 64.8% specificity. As sepsis is a lethal condition and involves severe consequences, it required an optimal cutoff that has less chance to miss any women with sepsis.

## Discussion

This study used to develop a model based on risk factors and clinical sign and symptoms of sepsis among postpartum women. Internationally validated SIRS criteria were used as the gold standard for identification of women with sepsis. Previous studies identified sepsis among obstetric population based on sophisticated laboratory investigation.

Clinical and community settings both are different in terms of practice, feasibility and resource availability. As a result, models that are developed in hospital setting may have high sensitivity and specificity but needs to be adapted accordingly to make it feasible, available and applicable for community setting. The model proposed in the current study used risk factors, clinical sign and symptoms and only random blood sugar test instead of any advanced laboratory investigation. This would enable lay health workers in timely identification of postpartum sepsis in woman and help in early referral to tertiary care facility for management. One of the studies conducted at King Edward Hospital Lahore also provide evidence for using Score for Neonatal Acute Physiology II (SNAP II) for prediction of mortality among neonates with sepsis. The study assessed diagnostic accuracy of SNAP II tool which includes lowest mean arterial pressure, worst PaO<sub>2</sub>/FiO<sub>2</sub> ratio, lowest temperature, lowest serum, urine output less than 1 ml/Kg/hr and presence of seizures. Based on mentioned indicators severity of illness categorized into mild (1–20), moderate (21–40) and severe (> 40). SNAP II helps to identify neonates who were at high risk of mortality. (12).

Previous literature highlights that hemorrhage, lacerations, multiple vaginal examination, mode of delivery are major contributors to sepsis that may develop within few hours of giving birth (13, 14). This study also reinforced the risk factors mentioned in previous studies and antenatal care is one of them. Antenatal Care (ANC) helps women to promote healthy home practices, health seeking behaviors and identifies complications related to pregnancy (15, 16). Women are more likely to give birth with a skilled birth attendant if they have had at least one ANC visit (17). This study also depicts that not seeking antenatal care put women at a higher risk to develop sepsis. The results of this study are similar to that

reported by Joseph et al who identified that the odds of maternal deaths was 3.6 (95% CI, 1.8-7.0) times higher among those who had received no antenatal care visit (18).

Multiple vaginal examinations is a contributor to infectious morbidities associated with prolonged labor. Kenyan study reported that women who had vaginal examination from 2–4 times and > 5 times were 2.28 and 3.8 times at higher risk of developing sepsis as compared to those women who have vaginal examination < 2 times (19). These findings are coherent with our study as more than four hourly vaginal examinations could potentially increase the risk of sepsis due to the prolonged state of an open cervix which impairs normal mechanical barrier to infections (20).

Home delivery was a significant contributor to postpartum sepsis (aOR = 9.0; 95% CI = 1.72–50.02) in this study. A study in Pakistan reported that the odds of puerperal infection was 2.7 (95% CI; 1.1–6.2) times among women who delivered in unhygienic conditions at homes as compared to deliveries conducted at health facilities (21). The report by State of World Children (2009) identifies that the regions with high maternal deaths have 60% of home deliveries where lack of practice of aseptic measures like hand washing, use of antiseptic materials and perinatal hygiene by unskilled birth attendants were key features for developing sepsis (22, 23). Similar to home delivery Preterm delivery was also reported to increase chance of sepsis by 2–3 folds (24, 25) which was also reported in this study.

Lower abdominal pain is a well-recognized non-specific symptom of puerperal sepsis. After delivery, invasion of bacteria may infect the uterus and cause pelvic inflammation which presents with lower abdominal pain (26, 27). In this study, women with sepsis reported lower abdominal pain and vaginal discharge more commonly as compared to women without sepsis. Moreover, the odds of foul smell vaginal discharge was 3.2 times higher among women with sepsis as compared to those without.

Blood glucose level and diabetes during pregnancy were significant risk factors for sepsis in this study. In sepsis, the activation of pro inflammatory indicators may lead to pathological changes that include hyperglycemia (28). Acosta et al explained that diabetic women had 47% greater adjusted odds of developing severe sepsis compared to septic women without diabetes (7). All these pathological changes also effect blood oxygen saturation. Pulse oximetry is a non-invasive method to determine oxygen level in the blood. In the adult population, SpO<sub>2</sub> (> 95%) has been shown to have 90% sensitivity to detect probability of having pulmonary embolism (29, 30). In SOS scoring, SpO<sub>2</sub> had a low discriminative ability in identifying sepsis (10). However, in this study, contribution of SpO<sub>2</sub> was high as evident by adjusted odds ratio of 13.0 (95% CI 4.80–37.10). One of the reasons for this discrepancy may be that for SOS scoring, missing values were considered as normal so subjects with missing SpO<sub>2</sub> values was considered as having oxygen saturation (> 95%) which ultimately make remarkable difference in results.

Strength of this study was representative sample. Study was conducted at a tertiary level public health facility such as JPMC where women belonged to a wide range of ethnicities and socio-demographic backgrounds. This makes our study generalizable to a wider population of postpartum women. Secondly, we have used calibrated instruments for collecting information on clinical signs to reduce bias introduced by instruments. One limitation of this study was using standard SIRS criteria for identification of cases of

sepsis which itself has low sensitivity. Michael et al, found 52% (95% CI 46%– 58%) sensitivity of SIRS criteria for critical illness (31). Despite this limitation, we used this diagnostic criteria as others such as SOS criteria, SOFA require sensitive laboratory investigations which are not routinely done in our study setting.

## Conclusion

We developed a non-invasive tool which will help identify postpartum women with sepsis as accurately as SIRS with good discriminative ability. The model revealed that women with no antenatal care, having home and preterm deliveries along with symptoms like abdominal pain, vaginal discharge and having > 3 vaginal examinations during labor, diabetes with high blood glucose and SpO2 less than 93% were more prone to have sepsis. The model in this study showed adequate diagnostic accuracy with high sensitivity which helps in correctly identifying woman who actually has sepsis. Although this model requires further validation in community based settings to identify its applicability, it does not require highly skilled personnel for obtaining this data. This tool would be helpful in far to reach communities where front-line health workers can use it to identify high risk women and refer them to health facility for management of sepsis and its complications, hence improving maternal outcomes. Due to differences in resource availability in remote settings, there is a dire need to identify approaches which keep in mind the feasibility and adaptability of the model based on local needs.

## Declarations

### **Ethical consideration:**

This study received ethical approval from Ethics Review Committee of Aga Khan University Hospital, Karachi, Pakistan (4569-obs-ERC-16)) along with permission from Jinnah Postgraduate Medical Centre, Karachi, Pakistan (47237).

### **Consent for publication:**

As in this study human population involved we took permission from each individual for their information to be published in journal by keeping their names confidential.

### **Data Availability:**

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

### **Competing Interest:**

The authors declare that they have no competing interests

### **Funding Source:**

This study was funded by University of British Columbia. There is no role of funding agency in the design of the study, collection, analysis, and interpretation of data and in manuscript writing.

### **Author's Contribution:**

SB was involved in study designing, execution of study, supervision of data collection, data cleaning, data analysis and writing manuscript, SS was involved in study designing, data analysis, interpretation and critical analysis of manuscript. RQ has contributed as clinical expert personnel related to maternal and child health and has given final approval of the version to be published, ZH made significant intellectual support for execution of study and presentation of data. IA took very considerable efforts in sample size calculation, data analysis and critically analyzing the statistical part of manuscript. BP and PVD participated in proposing thesis conception, data analysis and manuscript editing. All authors read and approved the final manuscript.

## **Abbreviations**

SIRS: systematic inflammatory response syndrome

AUC: Area under the curve

ROC: Receiver operating characteristics

PDHS: **Pakistan Demographic Health Survey**

**SOS: Sepsis Obstetric Score**

ICU: intensive care unit

JPMC: Jinnah Postgraduate Medical Center

PPH: postpartum hemorrhage

AOR: adjusted odds ratio

CI: Confidence Interval

PPV: Positive Predictive value

NPV: Negative Predictive Value

LHW: lady health workers

ANC: Antenatal Care

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Tables

Table 1: Descriptive of variables

Baseline characteristics of the study participants			
Variables	Cases n=100 n (16.7%) Mean±SD	Controls n=498 n (83.27%) Mean±SD	
Socio-demographic Information:			
Maternal age	27.1±5.10	26.6±5.02	
Socioeconomic status			
Low tertile	35 (35.00)	163	(32.30)
Middle tertile	39 (39.00)	198	(40.00)
High tertile	26 (26.00)	137	(27.70)
Pregnancy and delivery Information:			
Booking status			
No	21 (21)	73	(14.66)
Yes	79 (79)	425	(85.36)
Antenatal care visits			
0 times	14 (14)	47	(9.44)
1-4 times	21 (21)	223	(44.76)
>4 times	65 (65)	228	(45.70)
Antenatal care provider			
None	14 (14)	47	(9.44)
Skilled Birth attendant	84 (84)	445	(89.36)
Unskilled birth attendant	2 (2)	6	(1.26)
Parity			
0	1 (1)	3	(0.60)
1-4	84 (84)	431	(86.55)
≥5	15 (15)	64	(12.85)
Mode of delivery			
Spontaneous vaginal delivery	58 (58)	293	(58.84)
Assisted delivery	3 (3)	24	(4.82)
Caesarean delivery	39 (39)	181	(36.3)
Prolonged labor			
≤12 hours	84 (84)	428	(85.92)
>12 hours	16 (16)	70	(14.10)
Rupture of membrane			
≤ 24hours	97 (97)	478	(95.98)
>24hours	3 (3)	20	(4.0)
Number of vaginal examination			
1-3 times	54 (54)	348	(69.86)
>3 times	46 (46)	150	(30.10)
Place of delivery			
Health facility	94 (94)	494	(99.2)
Home	6 (6)	4	(0.80)
Preterm			
No	80 (80)	443	(88.9)
Yes	20 (20)	55	(11.01)
Diabetes in pregnancy			
No	90 (90)	488	(97.9)
Yes	10 (10)	10	(2.01)
Clinical Sign and Symptoms:			

Upper abdominal pain		
No	94 (94)	472 (94.7)
Yes	6 (6)	26 (5.21)
Lower abdominal pain		
No	44 (44)	303 (60.84)
Yes	56 (56)	195 (39.12)
Vaginal discharge		
No	86 (86)	481 (96.55)
Yes	14 (14)	17 (3.41)
Dyspnea		
No	93 (93)	471 (94.50)
Yes	7 (7)	27 (5.42)
Spo2		
≥ 93%	81 (81)	488 (98.10)
<93%	19 (19)	9 (1.81)
Blood glucose	96.5±15.6	110.8±34.00
Systolic blood pressure	110.1±12.2	116.1±13.45
Diastolic blood pressure	74.9±9.9	74.6±10.30

**Table: 2 Model based on risk factors and clinical signs and symptoms**

Variables	Unadjusted OR (95% confidence interval)	Adjusted OR (95% confidence interval)
<b>Pregnancy and Delivery Information:</b>		
Antenatal visits None (reference)	----	----
1-4	0.31 (0.14 - 0.66)	0.25 (0.01 - 0.62)
>4 visits	0.95 (0.49 - 1.84)	0.82 (0.38 - 1.78)
Number of vaginal examination 0-3 times (reference)	----	----
>3times	2.97 (1.27-3.06)	2.10 (1.21 - 3.65)
Place of delivery Health facility (reference)	---	----
Home delivery	7.88 (2.18 - 28.4)	9.29 (1.72 - 50.02)
Preterm Yes	2.01 (1.14 - 3.54)	3.15 (1.58 - 6.25)
Diabetes in pregnancy Yes	5.42 (2.19-3.42)	6.22 (1.93 - 20.03)
Lower abdominal pain Yes	2.53 (1.63 - 3.93)	1.99 (1.15 - 3.42)
Vaginal discharge Yes	9.10 (2.18 - 19.65)	7.77 (2.97 - 20.21)
SpO2 <93%	12.7 (5.56- 29.08)	13.0 (4.80 - 37.10)
Blood glucose	0.98 (0.97 - 0.99)	1.01 (1.00- 1.02)

**Table 3: Optimal cut offs based on probability with sensitivity and specificity:**

Method	Optimal Cutoff of probability	Sensitivity%	Specificity%	*PPV	*NPV
High sensitivity and low specificity	0.069	82% (73.0-88.6)	64.8% (60.4-65.9)	31.9% (28.7-35.2)	94.7% (92.1-96.4)
Similar sensitivity and specificity	0.086	76.3% (66.3-83.9)	74.0% (71.4-79.6)	38.7% (34.3-43.3)	94.0% (91.7-95.7)
High specificity and low sensitivity	0.106	70.0% (62.1-80.5)	80.7% (77.1-84.2)	43% (37.8-48.6)	93.5% (91.2-95.1)

\*Positive predictive value    \*Negative predictive value

## Figures

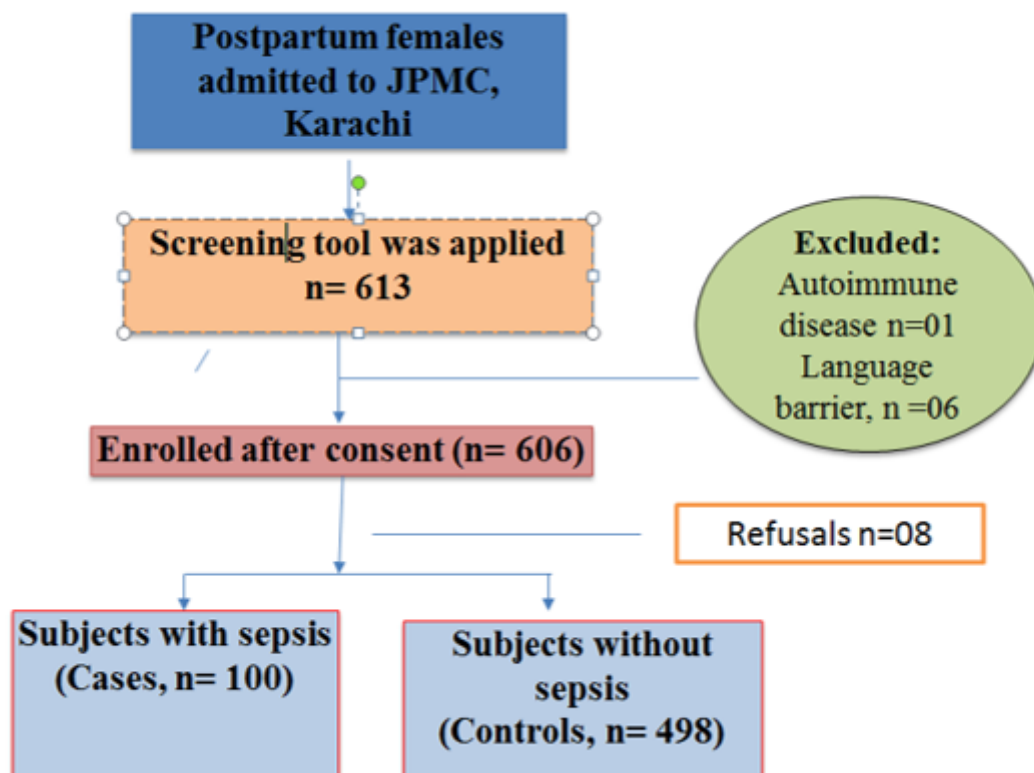


Figure 1

Figure 2 was not provided by the authors.

Figure 2

N/A

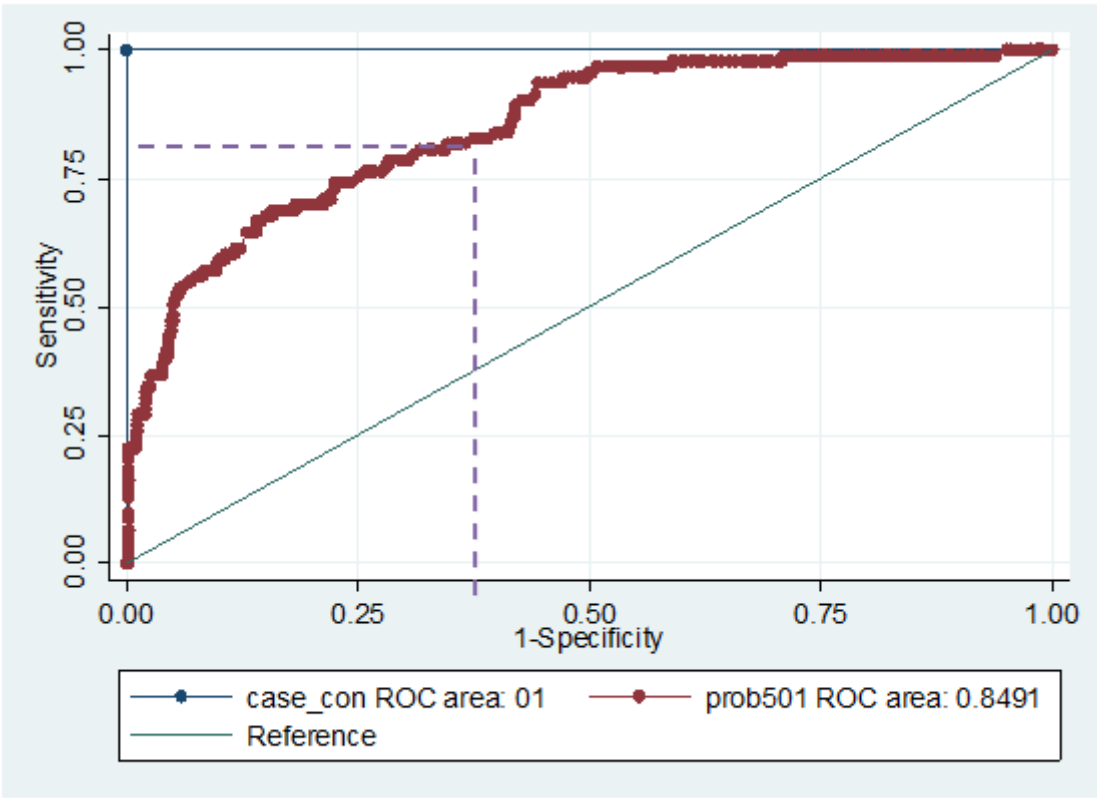


Figure 3

Receiver-operating characteristic curve for the clinical probability AUC= 0.84 (95% CI=0.80-0.89)