Post-operative serum procalcitonin vs C reactive Protein as a marker of post-operative infectious complications in pancreatic surgery – A systemic review and meta-analysis.

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Keywords: Meta-analysis; Procalcitonin; pancreatic surgery; pancreaticoduodenectomy; Infectious complications.

Conflict of interests: none

Funding disclosure: none.

Word count: 3420

Abbreviations: C-Reactive Protein (CRP), Procalcitonin (PCT)

Abstract:

Aim of Study:

Aim of this meta-analysis was to compare diagnostic accuracy of C reactive Protein and Procalcitonin between postoperative day 3 to 5 in predicting infectious complications post pancreatic surgery.

Methods:

Systemic literature search was performed using MEDLINE, EMBASE and SCOPUS to identify studies evaluating the diagnostic accuracy of Procalcitonin (PCT) and C-Reactive Protein (CRP) as a predictor for detecting infectious complications between postoperative days (POD) 3 to 5 following pancreatic surgery. A meta-analysis was performed using random effect model and pooled predictive parameters. Geometric means were calculated for PCT cut offs. The work has been reported in line with PRISMA guidelines.

Results:

After applying inclusion and exclusion criteria 15 studies consisting of 2212 patients were included in the final analysis according to PRISMA guidelines. Pooled sensitivity, specificity ,Area under curve and diagnostic odds ratio (DOR)for day 3 C-reactive protein was respectively 62%,67% 0.772 and 6.54.Pooled sensitivity, specificity , Area under curve and diagnostic odds ratio (DOR)for day 3 procalcitonin was respectively 74%,79%,0.8453 and 11.03. Sensitivity, specificity, Area under curve, and Diagnostic odds ratio for day 4 C-reactive protein was respectively 60%,68%, 0.8022 and 11.90. Pooled Sensitivity, specificity and Diagnostic odds ratio of post-operative day 5 procalcitonin level in predicting infectious complications were respectively 83%,70% and 12.9. Pooled Sensitivity, specificity, AUROC and diagnostic odds ratio were respectively 50%,70%, 0.777 and 10.19.

Conclusion:

Post-operative procalcitonin is better marker to predict post-operative infectious complications after pancreatic surgeries and post-operative day 3 procalcitonin has highest diagnostic accuracy.

Introduction:

Pancreatic surgeries (Pancreaticoduodenectomy/ distal pancreatectomy) are the main treatments for various benign and malignant disease of pancreas, duodenum, and ampullary region. [1]. Pancreatic surgeries are still associated with very high morbidity and mortality. [2]. Majority of complications following pancreatic surgeries are infectious complications including pancreatic leaks and fistula. [3]. These complications can affect outcomes and also increase cost for pancreatic surgeries. [4].

C reactive protein (CRP) and procalcitonin are suggested as inflammatory markers for diagnosing infective complications following colorectal and abdominal surgeries. [5-10].

CRP is not considered as a specific marker for infection, as it can rise in any inflammatory condition. [11].

Procalcitonin is now emerging as a useful and specific marker for sepsis and guide to antibiotic treatment. [12]. It is suggested as a useful marker in predicting infectious complications for colorectal surgeries. [5].

However, there is still limited literature comparing effectiveness of C- Reactive Protein and Procalcitonin (PCT) as a marker of infectious complications post pancreatic surgeries and very few studies to show which is better marker to diagnose infectious complications.

Pancreatic surgeries are highly morbid surgeries where early diagnosis of complications can help to reduce mortality.

AIM of the study:

Aim of this meta-analysis was to compare diagnostic accuracy of C reactive Protein and Procalcitonin between postoperative day 3 to 5 in predicting infectious complications post pancreatic surgery.

Materials and Methods:

Data collection:

Medline (PubMed), Embase and Scopus were searched with key words like “procalcitonin”, “C reactive Protein”, “pancreatic surgery”, “pancreaticoduodenectomy”, “distal pancreatectomy”, “post- operative complications”, “infective complication”, “pancreatic leak”, “pancreatic fistula”, “anastomotic leak”. Studies after Year 2005 (last 15 years) were searched. Anastomotic leak and pancreatic fistula were considered as infectious complications and were included in search strategy. The work has been reported in line with PRISMA (Preferred Reporting Items for Systemic Reviews) and MOOSE (Meta-analysis of observational studies in epidemiology) guidelines. [13,14]

Definition of post-operative infectious complications:

Infectious complications were defined as any complications like intraabdominal abscess, pancreatic leak, pancreatic fistula, wound complications, urinary tract infection, post-operative pneumonia or adult respiratory distress syndrome. Only clinically significant

pancreatic fistula (ISGPS grade b/c) was considered as an infectious complication. [15] Screening was done by two reviewers (BV and HP) independently at the title, abstract, and full text stages. Any disagreements were discussed between the reviewers before a final decision was made.

Study selection:

Inclusion criteria:

- Randomized control trials
- Observational cohort study
- Studies which included post-operative procalcitonin or C-reactive protein level between postoperative day 3 to 5.
- Studies where subject underwent pancreaticoduodenectomy or distal pancreatectomy
- Studies which included patients with age 18 and above.
- Studies which evaluated post-operative complications.

Exclusion criteria:

- Studies where full text articles could not be obtained.
- Studies which included only post-operative day 1,2 or pre-operative procalcitonin or C-reactive protein level.

Data extraction:

Information on study characteristics including patient population, study duration, follow-up period, index test, and reference standard were extracted from each study. The primary outcome, i.e., diagnostic performance of PCT or CRP to detect infectious complications reported as sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) at POD 3 and 5, was collected. As anastomotic leakage or pancreatic fistula were considered a subset of infectious complications and expected to account for most cases of infectious

complications in pancreatic surgery, it was used as the surrogate outcome of interest during data extraction in studies which did not specifically report infectious complications.

Raw data from the articles were used to construct 2*2 tables (true positive, false positive, true negative, and false negative). When unavailable, the tables were constructed using the sensitivity and specificity values provided. For each study, the sensitivity and specificity values mentioned in the article were verified by the reconstruction of the 2*2 contingency table using the data specified in the article.

Risk of bias assessment:

The revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool developed by the Cochrane Collaboration was used to assess for the risk of bias and applicability of each study. [16].

The tool consists of four key domains, i.e., patient selection, index test, reference standard, and patient flow through the study and timing of tests. Two reviewers (BV and HP) assessed the study quality independently. In case of disagreement, the judgment was discussed among themselves before a final decision. publication bias was assessed with the Deeks test. [17].

Statistical analysis:

The statistical analysis was performed according to the Preferred Report Items for Systematic Reviews and Meta- analysis (PRISMA) statement. [13]. The pooled prevalence of infectious complications with corresponding 95% confidence interval (95% CI) was calculated using random effect model. The pooled PCT and CRP cut-off value was derived using geometric mean of the reported PCT and CRP cut-off values. [17]. Using a random effect model, the pooled Se, Sp, LR+, LR−, and diagnostic odds ratios (DOR) with corresponding 95% CI were calculated. Symmetrical summary receiver operating characteristic (SROC) curves were

also generated. The area under the curve (AUC) and Q* index (the point on the SROC curve where Se and Sp were equal) were calculated, respectively.[18]. Heterogeneity was assessed using the Higgins I^2 test, with values of 25, 50, and 75% indicating low, moderate, and high degrees of heterogeneity, respectively. [19]. Meta-regression and subgroup analyses were attempted whenever feasible.

The statistical analysis was performed using Meta-DiSc 1.4 (Hospital Ramon y Cajal and Universidad Complutense de Madrid, Madrid, Spain) and revman 5.4.

RESULTS:

Data extraction, Study characteristics and quality assessment:

"PUBMED", "SCOPUS", "EMBASE" database were searched using key words and search strategy described above. Initially 537 studies were screened. After exclusion of duplicates and unrelated studies 86 studies were thoroughly screened. After applying inclusion and exclusion criteria 15 studies consisting of 2212 patients were included in the final analysis according to PRISMA guidelines. [Figure 1]. [10,20-33]

6 studies included analysis of Post-operative day 3 procalcitonin analysis [20-25], 8 studies day 3 C-reactive Protein analysis. 5 studies Included analysis of CRP of day 4. 3 studies included day 3 CRP analysis and 2 studies included day 5 procalcitonin analysis.

Study containing procalcitonin analysis included 471 patients and study containing CRP included 1965 patients. The main characteristics of the included studies are summarized in Table 1. The results of the quality assessment using the QUADAS-2 are shown in Figure. 2. Flaw and timings were unclear in majority of studies.

DIAGNOSTIC ACCURACY ANALYSIS OF POST OPERATIVE DAY 3 C-REACTIVE PROTEIN AND PROCALCITONIN IN PREDICTING INFECTIOUS COMPLICATIONS POST PANCREATIC SURGERY. [FIGURE 3]

Six studies consisting of 465 patients evaluated post-operative day 3 procalcitonin as a marker of infectious complications and 8 studies consisting of 1745 patients evaluated role of post-operative day 3 C-reactive protein as a marker of post-operative infectious complications.

Pooled sensitivity, specificity , Area under curve and diagnostic odds ratio (DOR)for day 3 C-reactive protein was respectively 62%,67% 0.772 and 6.54. [Figure 3(a)].

Pooled sensitivity, specificity , Area under curve and diagnostic odds ratio (DOR)for day 3 procalcitonin was respectively 74%,79%,0.8453 and 11.03.[figure 3(b)].

DIAGNOSTIC ACCURACY ANALYSIS OF POST OPERATIVE DAY 4 C-REACTIVE PROTEIN [FIGURE 4]

Five studies consisting of 907 patients evaluated postoperative day 4 C-reactive protein as marker of infectious complications. Sensitivity, specificity, Area under curve, and Diagnostic odds ratio for day 4 C-reactive protein was respectively 60%,68%, 0.8022 and 11.90.

No studies evaluated day 4 PCT levels.

DIAGNOSTIC ACCURACY ANALYSIS OF POST OPERATIVE DAY 5 C-REACTIVE PROTEIN AND PROCALCITONIN IN PREDICTING INFECTIOUS COMPLICATIONS POST PANCREATIC SURGERY. [FIGURE 5]

Two studies consisting of 111 patients evaluated post-operative day 5 procalcitonin levels. Pooled Sensitivity, specificity and Diagnostic odds ratio of post-operative day 5 procalcitonin level in predicting infectious complications were respectively 83%,70% and 12.9. SROC could not be constructed as only 2 studies mentioned day 5 procalcitonin levels.

3 studies consisting of 578 patients evaluated post -operative day 5 C-reactive protein as a diagnostic marker for infectious complications after pancreatic surgery. Pooled Sensitivity, specificity, AUROC and diagnostic odds ratio were respectively 50%,70%, 0.777 and 10.19.

POSITIVE AND NEGATIVE LIKE HOOD RATIO. [SUPPLEMENT FIGURE 1 AND 2]

Pooled positive like hood ratios for post-operative day 3,4 and 5 C-reactive protein were respectively 2.29,2.53,2.62. Pooled Negative like hood ratios of day 3,4,5 CRP were 0.37,0.27,0.25.

Pooled positive like hood ratios for post-operative day 3 and 5 procalcitonin were respectively 3.17 and 2.91 . Pooled Negative like hood ratios of day 3 and. 5 Procalcitonin were 0.31 and 0.25.

C-reactive protein and Procalcitonin cut off.

Geometric mean PCT cut off for predicting infectious complications at day 3 was 0.80 with 95% C.I. 0.58-1.02. Geometric mean PCT cut off for predicting infectious complications at day 5 was 0.43 with 95% C.I. 0.20-0.65.

Geometric mean CRP cut off for predicting infectious complications at day 3 was 72.2 with 95% C.I. 2-142. Geometric mean CRP cut off for predicting infectious complications at day 4 was 25.3 with 95% C.I. 0-97. Geometric mean CRP cut off for predicting infectious complications at day 5 was 24.8 with 95% C.I. 0-104.

Deek test for publication bias was not significant. (p=0.456)

DISCUSSION:

In our meta-analysis we evaluated role of Post-operative C-reactive protein and Procalcitonin in predicting post-operative infectious complications. Tan et al. [5] and cousin et al. [34] had done similar meta-analysis showing use of PCT as a predictor for infectious complications following colorectal surgeries. However, to our knowledge this is the first diagnostic accuracy meta-analysis which simultaneously analysed role of .C-reactive protein (CRP) and procalcitonin (PCT).

Survival Sepsis Guidelines 2016.[35] suggests use of PCT as a marker for diagnosing sepsis as well as marker for de-escalation of antibiotics and its use in management of sepsis is gaining popularity now. We decided to use PCT levels at day 3 and day 5 as evidences suggests that PCT can be falsely elevated in first 2 post-operative days. [36,37,38].We found no study that reported day 4 PCT.

CRP is a known inflammatory marker, however CRP levels can rise in multiple inflammatory condition. We here evaluated day 3,4,5 CRP levels for the same reason as in initial post-operative days surgical stress itself can cause elevated CRP levels.

Highest pooled sensitivity , Diagnostic odds ratio, pooled area under curve for CRP in detecting infectious complications were highest on 4^{th} post-operative day which was respectively 60%, 11.90 and 0.8022. Highest pooled specificity was on 5^{th} post-operative day, which was 70%.

For procalcitonin pooled sensitivity, specificity, pooled area under curve was on post-operative day 3 which were respectively 74%,79%,0.8453 and 11.03. Pooled sensitivity, specificity and diagnostic odds ratios for day 5 procalcitonin were 83%,70% and 12.9. However only 2 studies evaluated post-operative day 5 procalcitonin levels so pooled area under curve could not be calculated. From above findings it seems that post-operative procalcitonin is more sensitive and specific than C-reactive protein in

predicting post-operative infectious complications after pancreatic surgeries. Post-operative day 3 procalcitonin is found to be more accurate marker of post-operative infectious complications after pancreatic surgery.

There were certain limitations of these analysis, first is that end point was not similar in every study. Some study evaluated infectious complications and majority evaluated pancreatic leak and fistula. We considered pancreatic fistula as an infectious complication. Heterogenicity was moderate to high in some analysis. Day 5 analysis included very small number of studies. Another limitation is majority of studies included pancreaticoduodenectomies only so to confirm these findings in distal pancreatectomies including laparoscopic distal pancreatectomies we need more data.

However, to best of our knowledge this is the only meta-analysis in which an humble attempt is done to compare CRP and PCT as predictive markers for post0operative infectious complications after pancreatic surgeries.

In conclusion, it shows post-operative procalcitonin is better marker to predict post-operative infectious complications after pancreatic surgeries and post-operative day 3 procalcitonin has highest diagnostic accuracy.

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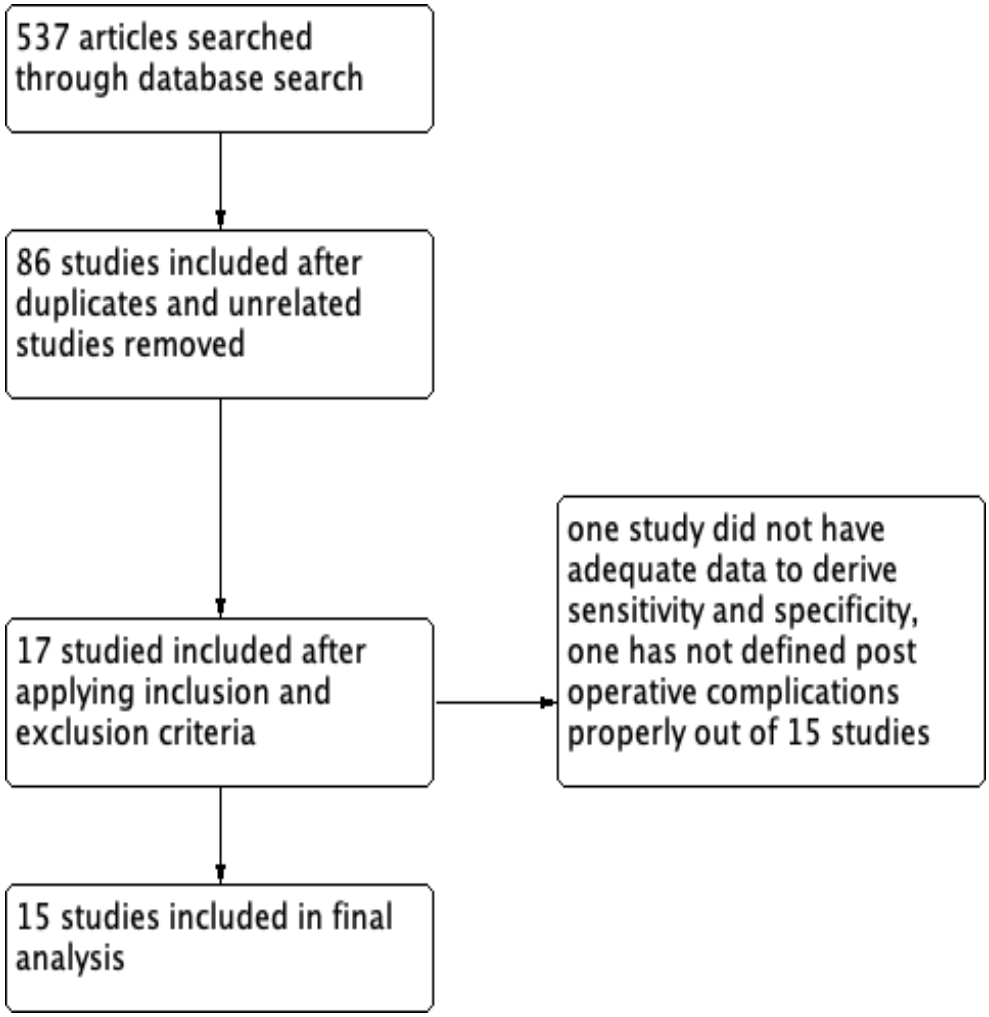


Figure 1: Prisma Flow diagram.

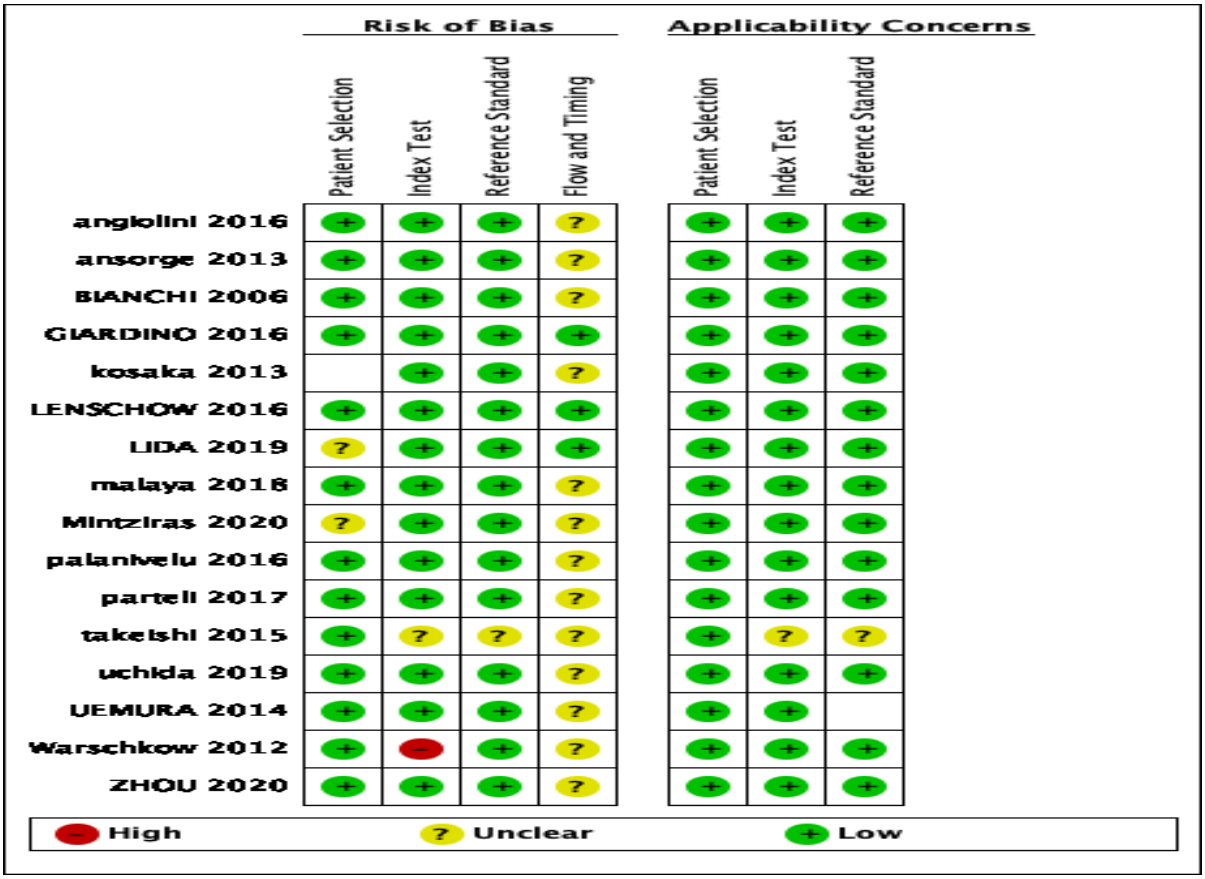
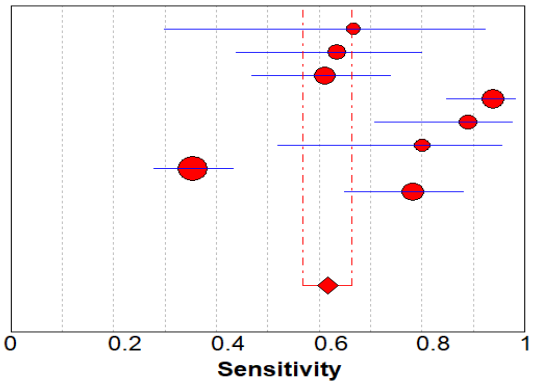


Figure 2: Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study

STUDY ID	STUDY DESIGN	BIOMARKER STUDIED. CRP/PCT	PRIMARY END POINT OF STUDY	TOTAL NUMBER OF PARTICIPANTS	INFECTIOUS COMPLICATIONS	DAY 3P CT CUT OFF	DAY 5 PCT CUT OFF	DAY 3 CRP CUT OFF	DAY 4 CRP CUT OFF	DAY 5 CRP CUT OFF
BIANCHI 2006	PROSPECTIVE COHORT	PCT	INFECTIOUS COMPLICATIONS	31	24	0.5	0.5	NA	NA	NA
GIARDINO 2016	PROSPECTIVE COHORT	PCT	INFLAMMATORY COMPLICATIONS	84	58	0.34	0.24	NA	NA	NA
LENSCHOW 2016	RETROSPECTIVE COHORT	PCT	INFECTIOUS COMPLICATIONS	40	28	NA	NA	NA	NA	NA
LIDA 2019	RETROSPECTIVE COHORT	PCT	INFECTIOUS COMPLICATIONS	77	34	1.8	NA	NA	NA	NA
ZHOU 2020	RETROSPECTIVE COHORT	PCT	PANCREATIC FISTULA	67	19	1.27	0.66	NA	NA	NA
MINITTZIRAS 2020	RETROSPECTIVE COHORT	CRP and PCT	PANCREATIC FISTULA	188	30	0.80	NA	203	NA	NA
MALAYA	RETROSPE	CRP	PANCREAT	117	9	NA	NA	22.	NA	19

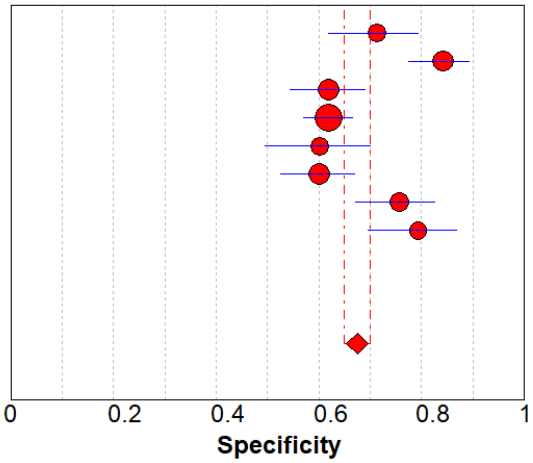
2018	CTIVE COHORT		IC FISTULA					5		
PALANIVELU 2016	PROSPECTIVE COHORT	CRP	PANCREATIC FISTULA	230	54	NA	NA	204	134	NA
PARTELI 2017	RETROSPECTIVE COHORT	CRP	PANCREATIC FISTULA	463	64	NA	NA	185	NA	NA
TAKEISHI 2015	RETROSPECTIVE COHORT	CRP	PANCREATIC FISTULA	120	27	NA	NA	NA	NA	NA
UEMURA 2014	PROSPECTIVE COHORT	CRP	PANCREATIC FISTULA	200	15	NA	NA	14.5	15.6	NA
WARSCHKOW 2012	RETROSPECTIVE COHORT	CRP	INFLAMMATORY COMPLICATIONS	280	153	NA	NA	237	184	161
ANGIOLINI 2016	PROSPECTIVE COHORT	CRP	INFECTIOUS COMPLICATIONS (SURGICAL SITE AND ORGAN SPACE)	251	115	NA	NA	17.27	14.72	NA
KOSAKA 2013	RETROSPECTIVE COHORT	CRP	PANCREATIC FISTULA	100	32	NA	NA	NA	9.3	NA
UCHIDA 2019	RETROSPECTIVE COHORT	CRP	PANCREATIC COLLECTION	211	83	NA	NA	NA	NA	5

Table 1: Study characteristics



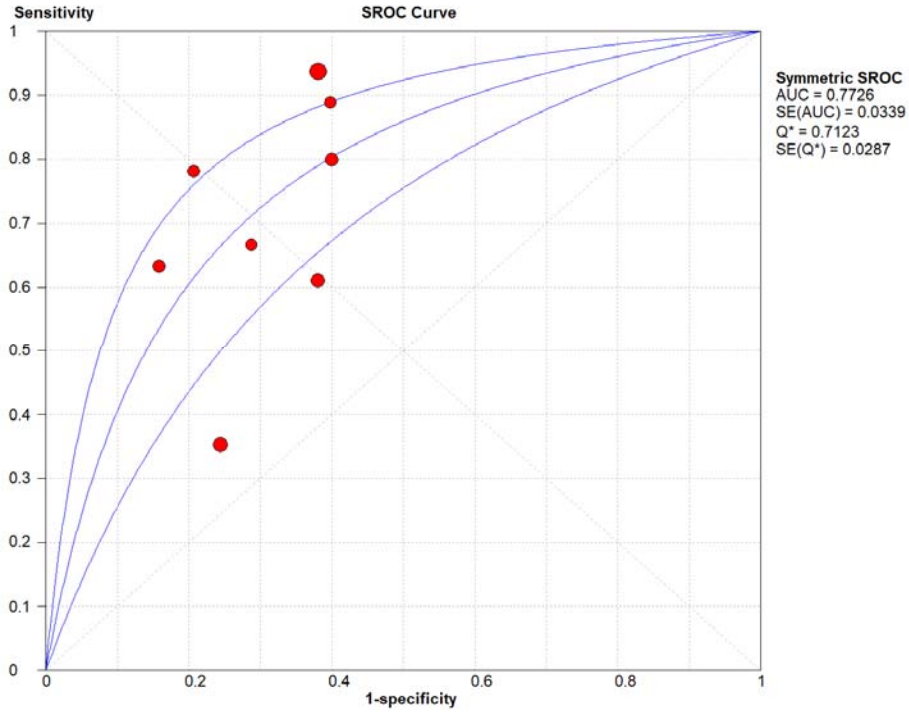
	Sensitivity (95% CI)	
MALAYA 2018	0.67	(0.30 - 0.93
MINTZIRAS 2020	0.63	(0.44 - 0.80
PALANIVELU 2016	0.61	(0.47 - 0.74
PARTELI 2017	0.94	(0.85 - 0.98
TAKESHI 2015	0.89	(0.71 - 0.98
UEMURA 2014	0.80	(0.52 - 0.96
WARSCHOW 2012	0.35	(0.28 - 0.43
ANGIOLINI 2016	0.78	(0.65 - 0.88

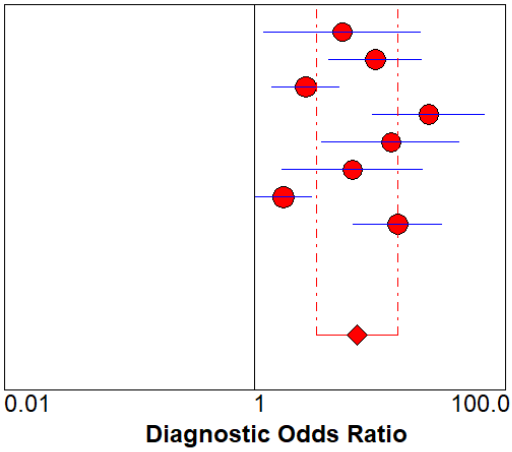
Pooled Sensitivity = 0.62 (0.57 to 0.66)
Chi-square = 98.63; df = 7 (p = 0.0000)
Inconsistency (I-square) = 92.9 %



	Specificity (95% CI)	
MALAYA 2018	0.71	(0.62 - 0.80
MINTZIRAS 2020	0.84	(0.78 - 0.89
PALANIVELU 2016	0.62	(0.54 - 0.69
PARTELI 2017	0.62	(0.57 - 0.67
TAKESHI 2015	0.60	(0.50 - 0.70
UEMURA 2014	0.60	(0.53 - 0.67
WARSCHOW 2012	0.76	(0.67 - 0.83
ANGIOLINI 2016	0.79	(0.70 - 0.87

Pooled Specificity = 0.67 (0.65 to 0.70)
Chi-square = 48.55; df = 7 (p = 0.0000)
Inconsistency (I-square) = 85.6 %

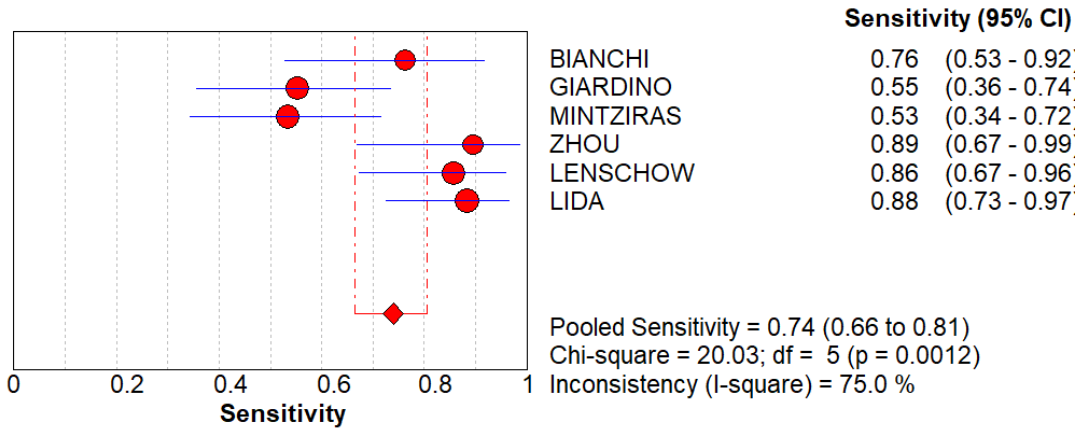


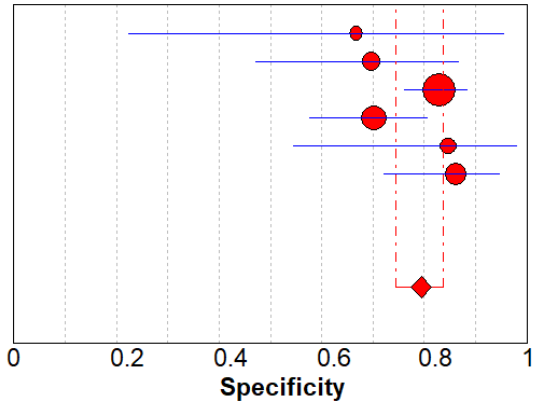


	Diagnostic OR (95% C
MALAYA 2018	4.97 (1.17 - 21.12)
MINTZIRAS 2020	9.19 (3.90 - 21.64)
PALANIVELU 2016	2.56 (1.37 - 4.78)
PARTELI 2017	24.38 (8.68 - 68.42
TAKESHI 2015	12.11 (3.40 - 43.12
UEMURA 2014	6.00 (1.64 - 21.99)
WARSCHOW 2012	1.69 (1.00 - 2.85)
ANGIOLINI 2016	13.77 (6.09 - 31.10

Random Effects Model
Pooled Diagnostic Odds Ratio = 6.54 (3.10 to 13.8
Cochran-Q = 39.91; df = 7 (p = 0.0000)
Inconsistency (I-square) = 82.5 %
Tau-squared = 0.9025

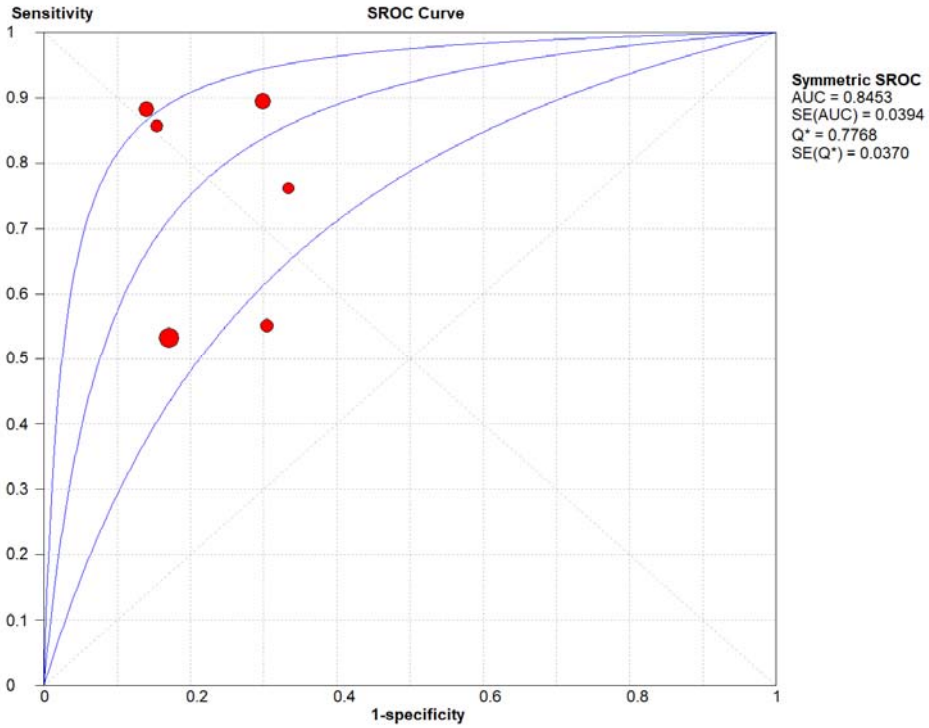
Figure 3(a) sensitivity, specificity and SROC curve ,Diagnostic odds ratio of day 3 CRP as a predictor





	Specificity (95% CI)
BIANCHI	0.67 (0.22 - 0.96)
GIARDINO	0.70 (0.47 - 0.87)
MINTZIRAS	0.83 (0.76 - 0.88)
ZHOU	0.70 (0.58 - 0.81)
LENSCHOW	0.85 (0.55 - 0.98)
LIDA	0.86 (0.72 - 0.95)

Pooled Specificity = 0.79 (0.74 to 0.84)
Chi-square = 7.70; df = 5 (p = 0.1733)
Inconsistency (I-square) = 35.1 %



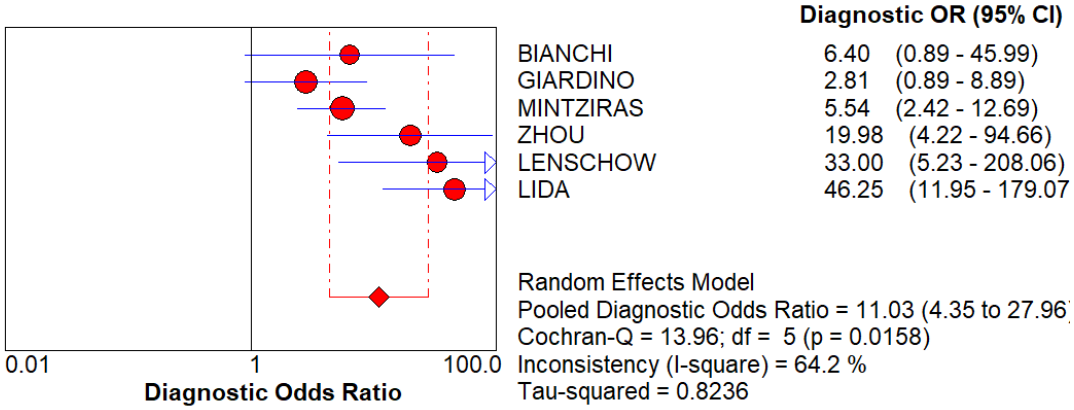
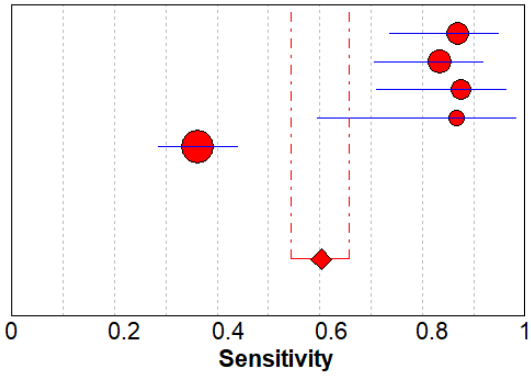
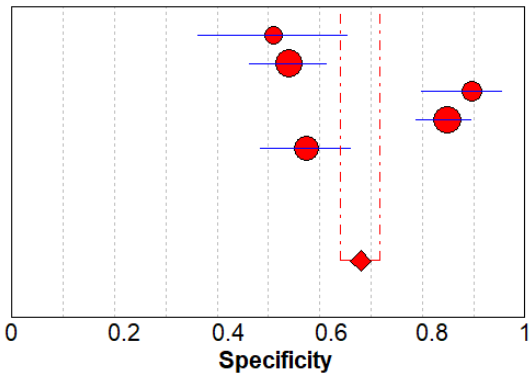


Figure 3 (b) Sensitivity, specificity, SROC curve and Diagnostic ODDS ratio of day 3 Procalcitonin.



	Sensitivity (95% CI)	
ANGIOLINI 2016	0.87	(0.74 - 0.95)
PALANIVELU 2016	0.83	(0.71 - 0.92)
KOSAKA 2013	0.88	(0.71 - 0.96)
UEMURA 2014	0.87	(0.60 - 0.98)
WARSCHOW 2012	0.36	(0.29 - 0.44)

Pooled Sensitivity = 0.60 (0.55 to 0.66)
Chi-square = 82.88; df = 4 (p = 0.0000)
Inconsistency (I-square) = 95.2 %



	Specificity (95% CI)	
ANGIOLINI 2016	0.51	(0.36 - 0.66)
PALANIVELU 2016	0.54	(0.46 - 0.62)
KOSAKA 2013	0.90	(0.80 - 0.96)
UEMURA 2014	0.85	(0.79 - 0.90)
WARSCHOW 2012	0.57	(0.48 - 0.66)

Pooled Specificity = 0.68 (0.64 to 0.72)
Chi-square = 72.78; df = 4 (p = 0.0000)
Inconsistency (I-square) = 94.5 %

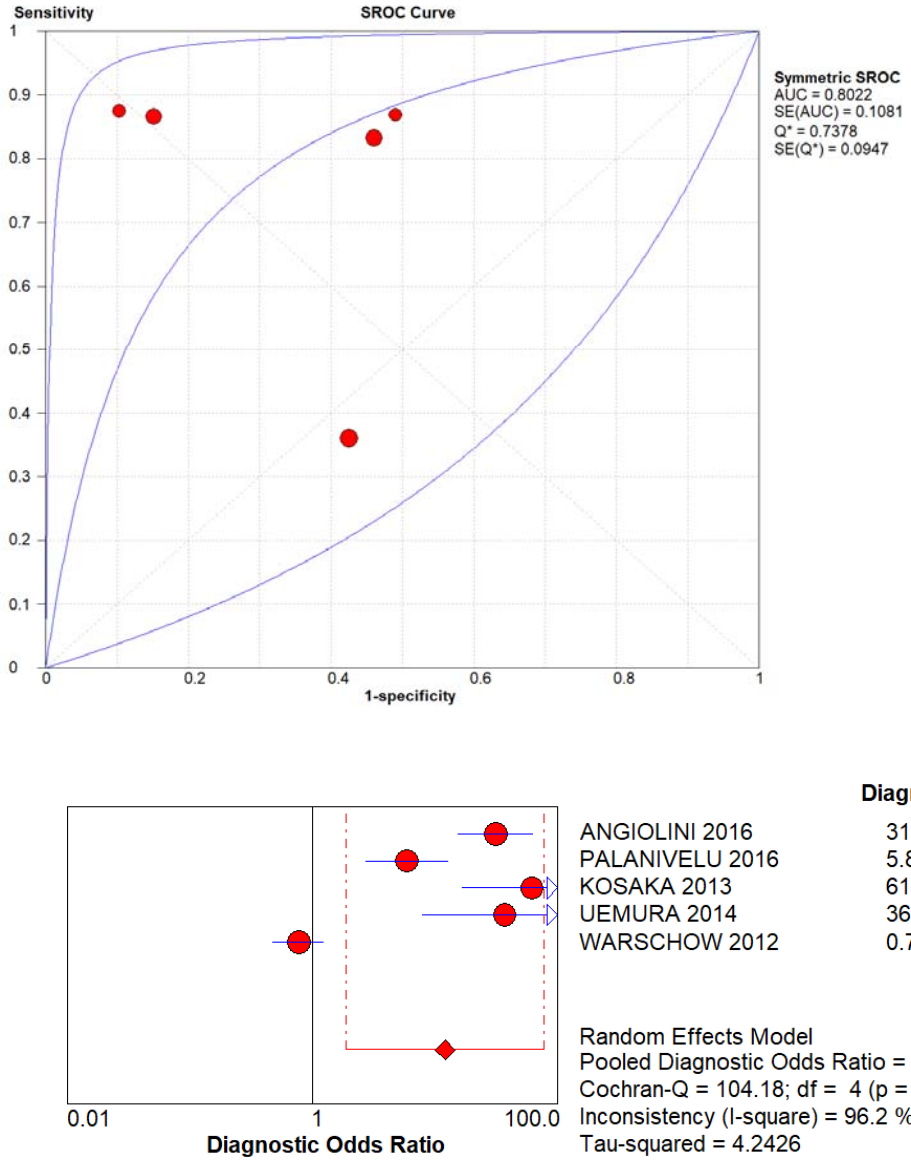
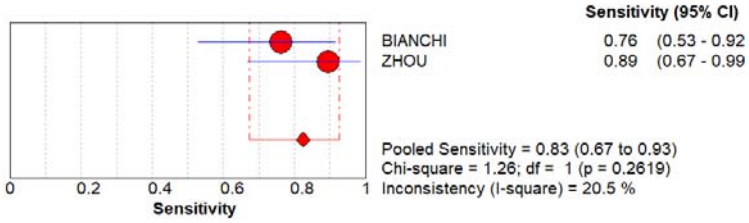
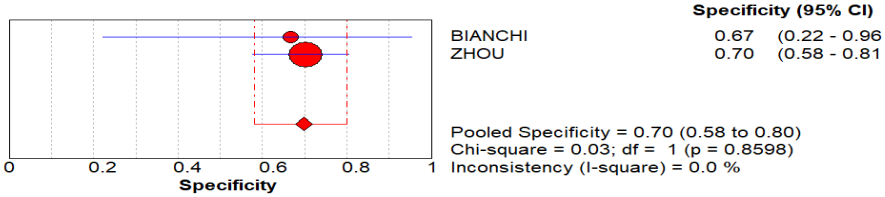


FIGURE. 4: sensitivity, specificity, SROC and DOR of day 4 C-reactive protein.





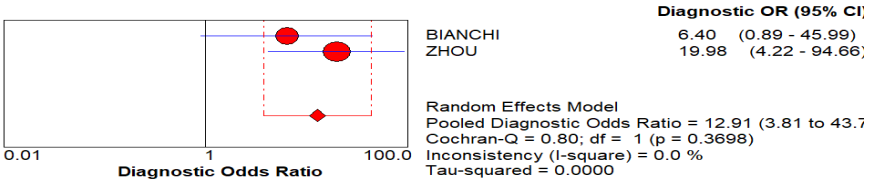
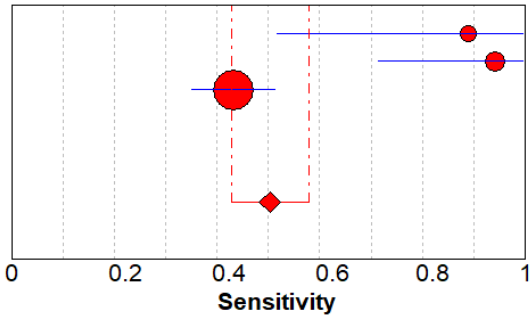
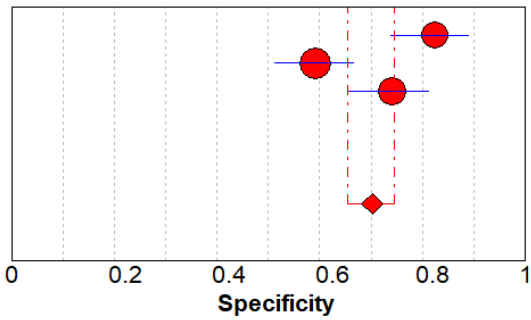


Figure 5(a) Sensitivity, Specificity and Diagnostic Odds ratio of post-operative day 5 Procalcitonin.



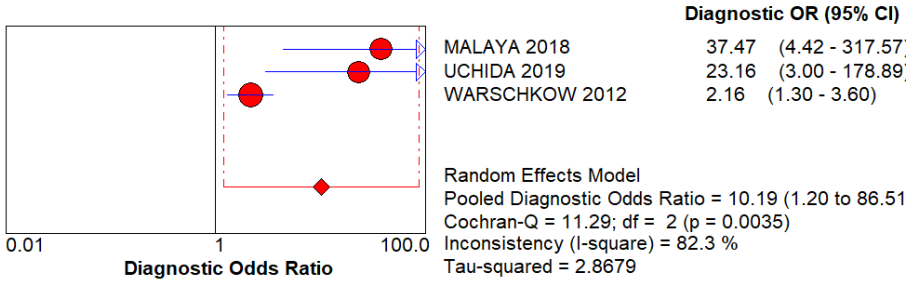
	Sensitivity (95% CI)
MALAYA 2018	0.89 (0.52 - 1.00)
UCHIDA 2019	0.94 (0.71 - 1.00)
WARSCHKOW 2012	0.43 (0.35 - 0.51)

Pooled Sensitivity = 0.50 (0.43 to 0.58)
Chi-square = 25.04; df = 2 (p = 0.0000)
Inconsistency (I-square) = 92.0 %



	Specificity (95% CI)
MALAYA 2018	0.82 (0.74 - 0.89)
UCHIDA 2019	0.59 (0.51 - 0.67)
WARSCHKOW 2012	0.74 (0.65 - 0.81)

Pooled Specificity = 0.70 (0.65 to 0.75)
Chi-square = 18.46; df = 2 (p = 0.0001)
Inconsistency (I-square) = 89.2 %



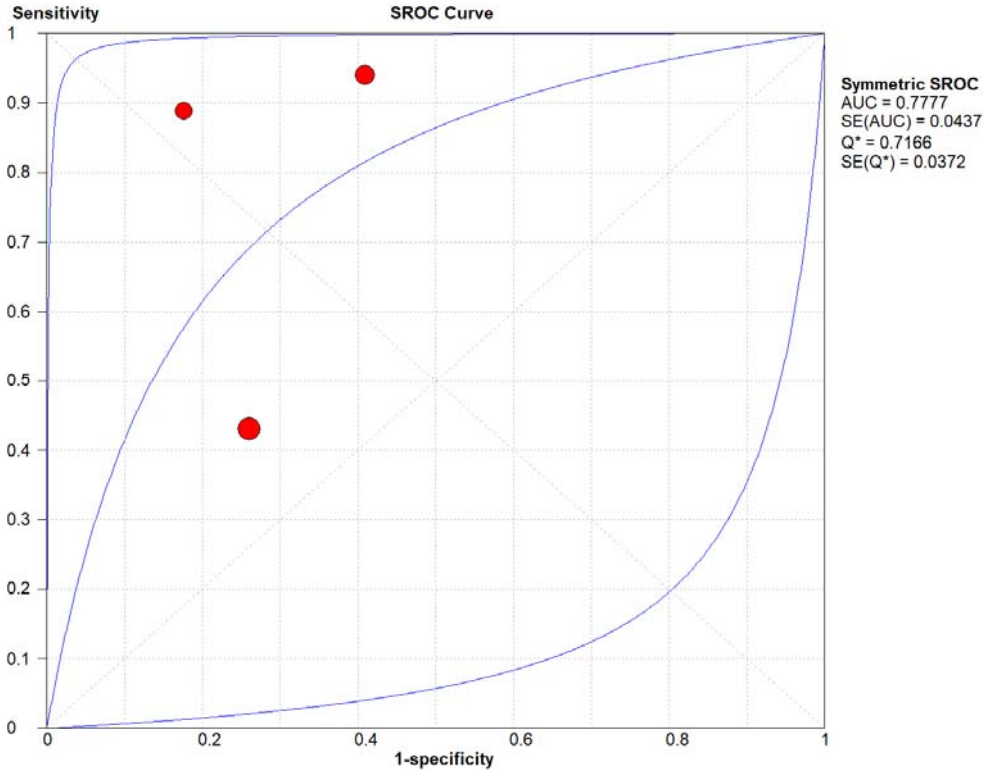
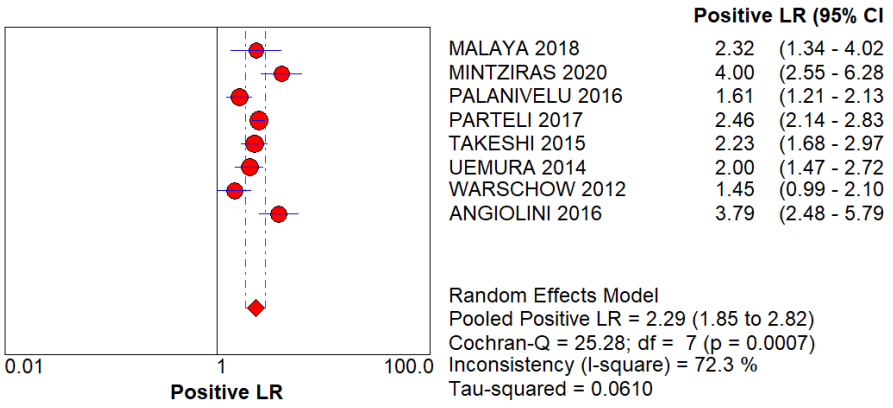
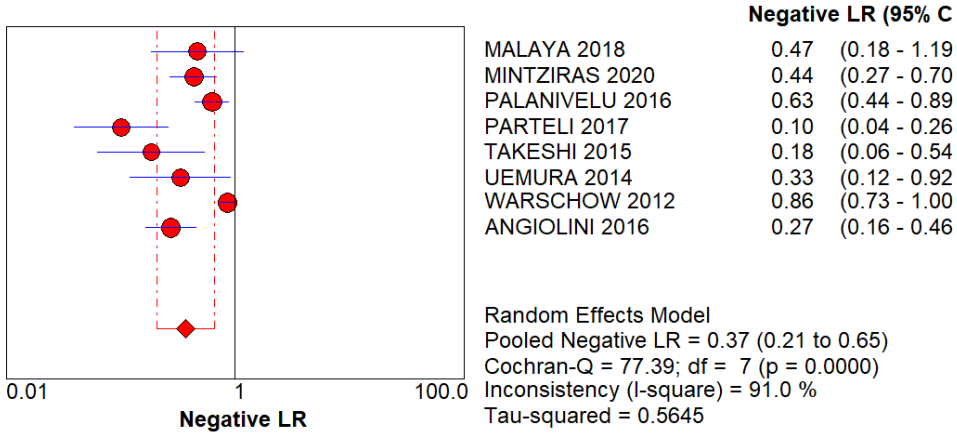


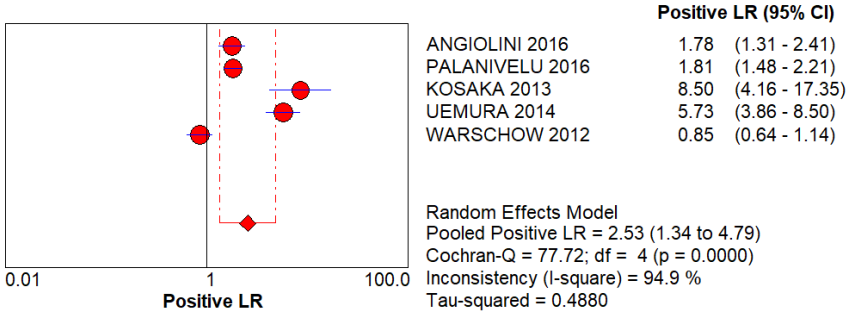
Figure 5 (b) Sensitivity, Specificity, DOR and SROC of post-operative day 5 C reactive protein.



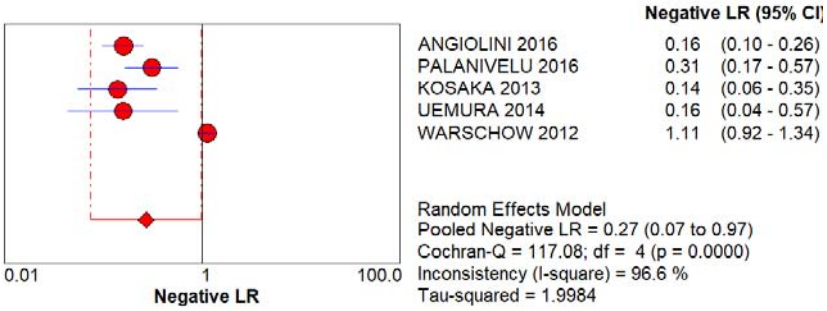
Positive like hood ratio day 3 CRP



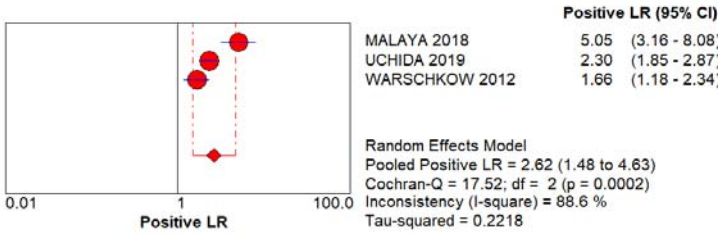
Negative likehood ratio day 3 CRP



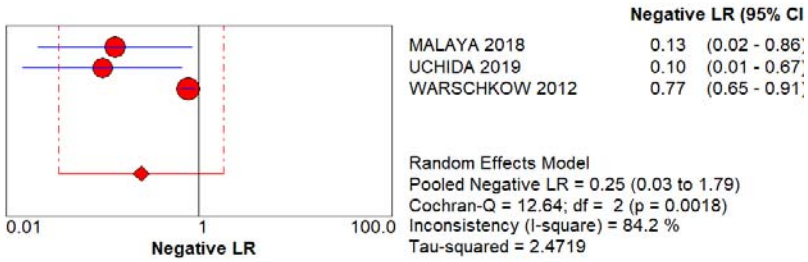
Positive like hood ratio day 4 CRP



Negative like hook ratio day 4 CRP.

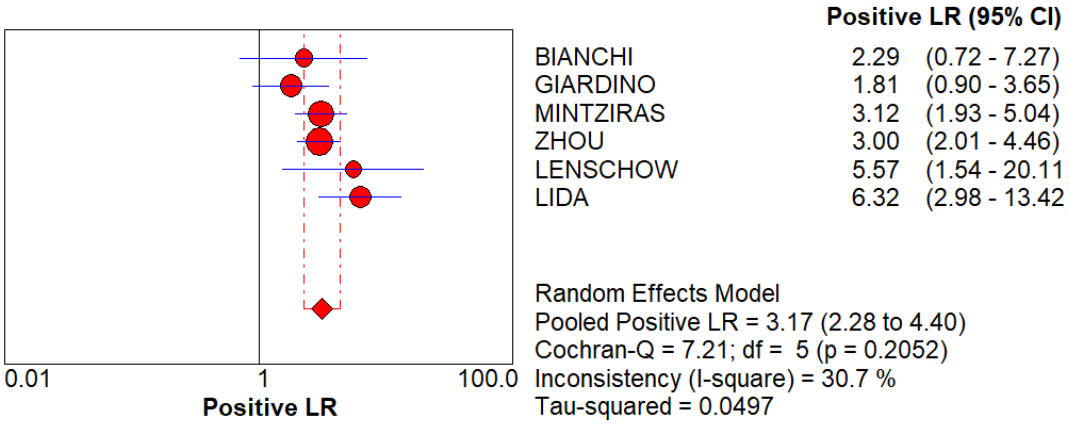


Positive likehood ratio day 5 CRP

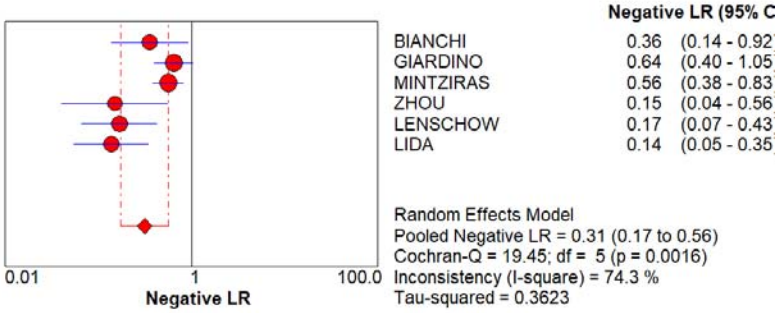


Negative like hood ratio day 5 CRP

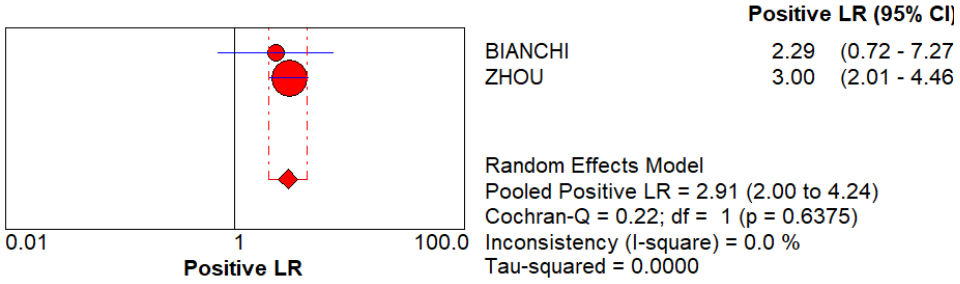
Supplement Figure 1: positive and negative like hood ratios of day 3,4,5 CRP.



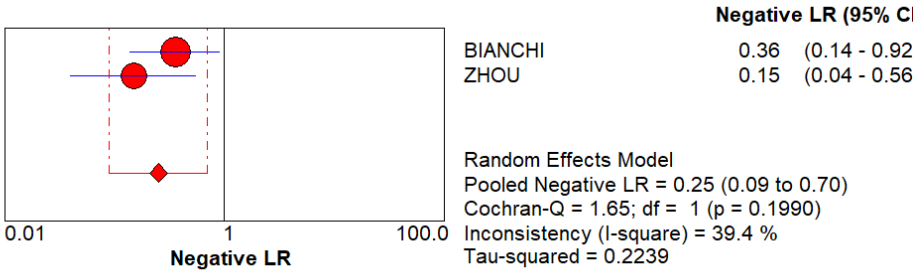
(a) POSITIVE LIKE HOOD RATIO DAY 3 PCT



(b) NEGATIVE LIKEHOOD RATIO DAY 3 PCT



FOREST PLOT FOR POSITIVE LIKEHOOD RATIO FOR PCT DAY 5



FOREST PLOT FOR NEGATIVE LIKEHOOD RATIO FOR PCT DAY 5

Supplement Figure 2. Positive and negative like hood ratio for postoperative day 3 and day 5 CRP and PCT.