UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

BIOMARCADORES NA SEPSE: PROTEÍNA C REATIVA E PROCALCITONINA

VANESSA MARTINS DE OLIVEIRA

Orientador: Prof. Dr. Airton Tetelbom Stein
Coorientadora: Profa. Dra. Eliana Márcia Wendland

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SUMÁRIO

ABREVIATURAS E SIGLAS

%	Percentual
<	Menor
>	Maior
AIDS	*Acquired Immune Deficiency Syndrome*
ALO	*Alograft*
AUC	Área sob a curva /*Area under the curve*
AUROC	Área sob a Curva *receiver operating characteristic* / *Area under the receiver operating characteristic curve*
bpm	Batidas por minuto
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CD4	Grupamento de diferenciação 4 / *Cluster of differentation 4*
CID	Classificação Internacional de Doenças
CRP	*C-Reative Protein*
CTI	Centro de Tratamento Intensivo
DMOS	Disfunção de múltiplos órgãos e sistemas
DOR	Diagnóstico da Razão de Chances / *Odds ratiodiagnostic*
FC	Frequência cardíaca
FN	*False negative*
FP	*False positive*
FR	Frequência respiratória
HAART	*Highly active antiretroviral therapy*
HIV	Vírus da imunodeficiência adquirida / *Human immunodeficiency virus*
HSCT	*After hematopoietic stem cell transplantation*
HSROC	ROC sumarizada hierarquizada / *Hierarchical summary receiver operating characteristic*
HTLV	*Human T lymphotropic vírus type 1*
I^2	Medida de inconsistência
IC	Intervalo de confiança/ *Confidence interval*
IL-6	Interleucina 6
KTTP	Tempo de tromboplastina parcialmente ativada
Likelihood	Razão de verossimilhança
LR	*Likelihood ratio*
mg/dia	Miligrama por dia
mg/dl	Miligrama por decilitro

mg/l	Miligrama por litro
mm^3	Milímetro cúbico / *Cubic millimetre*
mmHg	Milímetro de mercúrio
mmol/l	Milimol por litro
mr/min	*Respiratory movements per minute*
mrm	Movimentos respiratórios por minuto
ng/ml	Nanograma por mililitro
NPV	Negative predictive value
º C	Grau centígrado
$PaCO_2$	Pressão parcial de dióxido de carbono
PCR	Proteína C reativa
PCT	Procalcitonina / *Procalcitonin*
PDF	Produtos da degradação do fibrogênio
PPV	Positive predictive value
PRISMA	*Preferred reporting items for systematic reviews and meta-analyses*
Q	Quiquadrado
QE	Resíduo quiquadrado
QUADAS	*Quality assessment of diagnostic accuracy studies*
RBM	Revista Brasileira de Medicina
REML	*Random effects method*
ROC	*Receiver operating characteristic*
SIDA	Síndrome da imunodeficiência adquirida
SIRS	Síndrome de resposta inflamatória sistêmica / *Syndrome inflammatory systemic*
SOFA	*Sequential organ failure assessment*
TBC	Tuberculose
TN	*True negative*
TP	*True positive*
TREM	*Triggering receptor expressed on myeloid cells*
USA	*United States*
χ^2	Teste do Qui-Quadrado

DEFINIÇÕES DE TERMOS

- **Colonização**- Presença de micro-organismos em um determinado local, sem que ocorra dano ao hospedeiro.[1, 2]
- **Infecção**- Presença de um determinado agente que esteja causando danos ao hospedeiro (resposta inflamatória ao micro-organismo).[1, 2]
- **Bacteremia**- Ocorrência de bactérias viáveis no sangue, podendo ser transitória.[1, 2]
- **Síndrome de resposta inflamatória sistêmica (SIRS)** -Caracteriza-se por uma resposta inespecífica do organismo a uma variedade de situações que geram inflamação (infecção, queimaduras, pancreatite aguda, trauma e outras). Como critérios para sua detecção são necessárias duas das seguintes condições: temperatura > 38^{o}C ou < 36^{o}C, frequência cardíaca (FC)> 90 bpm, frequência respiratória (FR)> 20 mrm ou $PaCO_2$< 32 mmHg, leucocitose (leucócitos > 12.000/mm^3) ou leucopenia (leucócitos < 4.000/mm^3)ou > 10% debastões.[1, 2]
- **Sepse** - SIRS desencadeada por infecção bacteriana, viral, fúngica ou parasitária.Considera-se sepse severa quando a SIRS é complicada com uma ou mais disfunções orgânicas, hipoperfusão tissular (caracterizada, entre outros aspectos, por oligúria, distúrbio mental agudo e/ou acidose láctica) ou hipotensão arterial.[1, 2]
- **Choque séptico**- Sepse associada à hipotensão refratária à quantidade adequada de volume.[1, 2]
- **Disfunção de múltiplos órgãos e sistemas (DMOS)** - Alterações da função de órgãos do paciente, de modo que a homeostase não pode ser mantida sem intervenção terapêutica.É primáriase consequente à própria injúria, e secundária se oriunda não da injúria, mas da resposta orgânica do hospedeiro à condição mórbida.[1, 2]

RESUMO

Sepse é um importante problema de saúde pública, uma vez que seu tratamento gera altos custos a um sistema de saúde já sobrecarregado. É uma síndrome de alta mortalidade e morbidade que afeta, em geral, pacientes jovens com plena capacidade produtiva. A identificação e o tratamento precoce desta síndrome reduzem a morbimortalidade, assim como o custo. A proteína C reativa (PCR) e a procalcitonina (PCT) são bem estudadas como ferramentas para diagnóstico de infecção bacteriana em imunocompetentes, mas seu uso como ferramenta diagnóstica ainda não está estabelecido em pacientes imunossuprimidos. Portanto, a proposta deste estudo é avaliar a acurácia diagnóstica destes biomarcadores, em pacientes críticos imunossuprimidos (vírus da imunodeficiência adquirida –HIV positivos, portadores de tuberculose (TBC), cirróticos e transplantados). Como o uso da proteína C ainda não está estabelecido, a primeira questão de pesquisa investigou seu potencial diagnóstico quando comparado ao teste padrão (cultural). O segundo artigo comparou a PCR com a PCT. Para isto foram realizados dois artigos de revisão sistemática com metanálise. O primeiro artigo comparou a acurácia em determinar infecção bacteriana em imunossuprimidos da PCR ao teste padrão-ouro (as culturas). A primeira revisão incluiu 1.418 pacientes e demonstrou uma boa acurácia da PCR como biomarcador no diagnóstico de infecção bacteriana, apresentando sensibilidade de 69% e especificidade de 76% com uma área sob a curva (AUC) de 0,77. Os resultados encontrados são similares aos da literatura para imunocompetentes,[3] sensibilidade de 75%, especificidade de 67% e Área Sob a Curva *Receiver Operating Characteristic*(AUROC) de 0,92. Quando a PCT foi comparada com a PCR, ambos os biomarcadores mostraram acurácia moderada na utilização como ferrramenta de diagnóstico de infecção bacteriana, com um diagnóstico da razão de chances (DOR) de 7,24 (95% CI (2,83-14,60) para PCT e de5,56 (95% CI (5,21-10,30) para PCR.A PCT e a PCR apresentaram sensibilidade de 69% e 68% e uma especificidade de 75% e 71%, respectivamente.Ambas mostraram resultados semelhantes, podendo ser utilizadas no diagnóstico de sepse em imunossupressos.

Palavras-Chave: Imunossupressos; Procalcitonina; Proteína C reativa; Sepse.

ABSTRACT

Sepsis is a major public health problem, since its treatment generates high costs, a health system already overburdened. A high mortality and morbidity syndrome affects, in general, young patients with full production capacity. The identification and early treatment of this syndrome reduce morbidity and mortality as well as the cost. C-reactive protein (CRP) and procalcitonin (PCT) are well studied as tools for diagnosis of bacterial infection in immunocompetent patients, but its use as a diagnostic tool is not yet established in immunocompromised patients. Therefore, the purpose of this study is to evaluate the diagnostic accuracy of these biomarkers in immunosuppresses critical patients (human immunodeficiency virus,cirrhotic and transplant). As the use of the c protein is not yet established, the first research question investigated their diagnostic potential when compared to the pattern (cultural). The second article compared to CRP and PCT. For this, there were two articles of a systematic review and meta-analysis. The first article compared the accuracy in determining bacterial infection in immunosuppresses of CRP to the gold standard (cultures). Our first review included 1,418 patients and showed good accuracy of CRP as a biomarker for the diagnosis of bacterial infection presenting a sensibility of 69% and 76% specificity with an area under the curve (AUC) 0.77. The results are similar to those found in the literature for immunocompetent,[3] sensitivity 75%, specificity of 67% and *Area Under the Receiver Operating Characteristic Curve*(AUROC): 0.92. When the PCT was compared with PCR, both biomarkers showed a moderately accurate for use as tool diagnostic bacterial infection with a *Odds ratiodiagnostic* (DOR) 7.24 (95% CI (2.83-14.60) and PCT to 5:56 (95% CI (5.21-10.30) for CRP. the PCT and CRP had a sensitivity of 69% and 68% and a specificity of 75% and 71%, respectively. Both showed similar results may be used in the diagnosis of sepsis in immunosuppression.

Key words: C-reactive protein; Immunosuppressed; Procalcitonin; Sepsis.

APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada *Biomarcadores na Sepse: Proteína C Reativa e Procalcitonina*, apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul, em 24 de maio de 2016. O trabalho compõe-se de três partes, na ordem que segue:

1. Introdução, Revisão da Literatura e Objetivos
2. Artigos
3. Conclusões e Considerações Finais

Documentos de apoio estão apresentados nos Anexos A e B.

1 INTRODUÇÃO

A incidência mundial de sepse grave é extremamente elevada, superando a da síndrome da imunodeficiência adquirida (SIDA) e a dos principais tipos de câncer. Sepse é uma das principais causas de morte no mundo, estimando-se três casos por mil habitantes/ ano.[4-7]

Estudo recente observacional retrospectivo brasileiro nos anos de 2002 e 2010,que utilizou a busca pela Classificação Internacional de Doenças(CID-10) no Sistema Nacional de Notificação de Óbitos, demonstrou uma mortalidadeem 2002 de 982.294 pacientes/ano e, no ano de 2010, de 1.133.761 pacientes/ano. Em 2002, a sepse foi responsável por 9,77% de todas as causas de morte nos brasileiros e por 12,9% em 2010.[8]

Este aumento na mortalidade nos últimos 8 anos também foi observado nos Estados Unidos, sendo explicado pela melhor identificação e notificação da síndrome e pela maior expectativa de vida da população, uma vez que a mortalidade por sepse é maior no subgrupo de mais de 60 anos.[8,9]Muitos autores demonstraram que a mortalidade, a incidência e a hospitalização por sepse vêm aumentando, mas que a taxa de casos fatais ajustada para idade vem se reduzindo em países desenvolvidos, o que reflete o melhor acesso ao sistema de saúde e o melhor manejo hospitalar e adesão aos *guidelines* para tratamento da síndrome.[8,9]

A identificação precoce da sepse é essencial para um melhor prognóstico, uma vez que a implementação de intervenções, com eficácia comprovada por estudos randomizados, pode reduzir a mortalidade em 16% na sepse grave e no choque séptico.[10-12]Todavia, os sinais clínicos de sepse são similares aos de outras causas não infecciosas de inflamação sistêmica.[13]Atualmente, os médicos têm à sua disposição biomarcadores que facilitam o diagnóstico.

Entretanto,mesmo com tais ferramentas, esta situação é subdiagnosticada epoucos casos têm acesso aoCentro de Terapia Intensiva (CTI).[14,15]No Brasil, esta realidade foi confirmada por um estudo em CTIs em vários estados brasileiros onde os médicos identificaram corretamenteSIRS(78%), infecção (92%), sepse (27%), sepse severa (56%)e choque séptico (81%).[14] Nos Estados Unidos, a sepse é responsável por 3% das internações, sendo que 50% desses pacientes internam em CTI. Dez por cento das internações em CTIs têm como causa esta síndrome.[4]Na realidade brasileira, apenas 25% dos pacientes que internam na emergência com sepse têm acesso aos leitos de CTI, devido à escassez deste recurso. Sabemos, também, que o tempo de internação dos sobreviventes e não sobreviventes é o mesmo, mas que os custos são maiores em não sobreviventes. Portanto, sepse é um problema de saúde pública, sobrecarregando um sistema já esgotado.[16]

2 REVISÃO DA LITERATURA

2.1 CONCEITOS DE SEPSE

Desde sua primeira definição, em 1914, o conceito de sepse vem sofrendo modificações e, apesar das amplas discussões, as definições de sepse e SIRS ainda não apresentam consenso na comunidade científica.[15, 17]

No entanto, segundo o conceito mais aceito,SIRS caracteriza-se por uma resposta inespecífica do organismo a uma variedade de eventos que geram inflamação (infecção, queimaduras, pancreatite aguda, trauma e outras). Como critérios para sua detecção são necessárias duas das seguintes condições: temperatura > 38^{o} C ou < 36^{o} C, FC > 90 bpm, FR> 20 mrm ou pressão de dióxido de carbono ($PaCO_2$)< 32 mmHg, leucocitose (leucócitos > 12.000/mm^3)ou leucopenia (leucócitos< 4.000/mm^3)ou> 10% de bastões.[2] Considera-se sepse um processo inflamatório cujo evento desencadeante é uma bactéria, um vírus, um fungo ou um parasita. A sepse severa é uma progressão do quadro com uma ou mais disfunções orgânicas (cardiovascular, renal, hepática, neurológica ou do sistema de coagulação).[1,2]

Novo conceito foi proposto em 2016,[18]tendo o conceito de SIRS sido eliminado para tornar o diagnóstico mais específico e pelas novas definições.Sepse é definida como disfunção orgânica desencadeada por resposta inflamatória do organismo a uma bactéria. Disfunção orgânica pode ser identificada quando, ao se aplicar o escore de disfunção orgânica *Sequential Organ Failure Assessment* (SOFA), temos dois ou mais pontos, o que reflete um risco de morte de 10% nos pacientes hospitalizados com suspeita de infecção. Choque séptico é conceituado como anormalidade circulatória e do metabolismo celular, sendo identificado na presença de hipotensão refratária a volume com necessidade de vasopressor para manter

pressão arterial de 65 mmHg e elevação do lactato > 2 mmol/l. Pacientes com esta condição apresentam mortalidade que excede 40%.[18]

Contudo, o diagnóstico diferencial entre sepse e SIRS, à beira do leito, pode ser extremamente difícil, uma vez que as alterações fisiológicas que se traduzem em variáveis clínicas e laboratoriais nas duas situações são similares.[1]Infelizmente, os sintomas mais específicos de sepse, como a disfunção cardiovascular (hipotensão arterial e aumento do lactato), aparecem tardiamente. A presença de disfunção orgânica aumenta a mortalidade de 35% para 70%.[11,19-22]

O diagnóstico diferencial entre sepse e SIRS é fundamental.Esta diferenciação tem implicações não apenas no prognóstico destas condições, mas também nas decisões terapêuticas e implicações econômicas. As terapêuticas a serem ofertadas são diferentes e, algumas vezes,excludentes, e a falha ou a ausência em identificar e tratar precocemente o foco infeccioso são associadas com aumento da morbidade, altos custos do tratamento e mortalidade em 5%a 10%.[21,23-25]O uso indiscriminado de antibióticos na SIRS pode expor o paciente a potenciais efeitos colaterais das drogas na ausência de qualquer benefício.[23]O uso abusivo destas drogas favorece a emergência de patógenos resistentes e aumenta os custos do tratamento.[23]Dados da literatura demonstram que os médicos, no Canadá e nos Estados Unidos, superprescrevem antibióticos em 50% dos casos.[4]

Portanto, o uso de dados microbiológicos para diferenciar estas duas síndromes é essencial. O diagnóstico microbiológico definitivo é alcançado em não mais de 30% a 40% dos pacientes com manifestação clínicas de sepse. emesmo resultados positivos não excluem definitivamente a presença de infecção, podendo indicar colonização ou contaminação.[23,26,27]Além disso, as culturas apresentam como desvantagens o custo e o rendimento reduzido com o uso prévio deantibióticos bem como o tempo para obtenção dos resultados, que requerer no mínimo 24-48horas, retardando o início da terapêutica.[23,26,27]

O uso dos atuais métodos para diagnóstico de sepse apresenta algumas limitações, como demora no diagnóstico (culturas), sensibilidade subótima (hemoculturas), baixa sensibilidade devido à contaminação (aspirado), invasão dos métodos (por exemplo: biópsia de pulmão) ou baixa especificidade para diagnóstico de infecção (marcador inflamatório e leucocitose).[28]Tais limitaçõesna capacidade diagnóstica dos métodos podem ser explicadas pelos diferentes tipos de infecção e pela complexa interação de vários mediadores pró e anti-inflamatórios da resposta do hospedeiro em combater os patógenos invasores, que depende do tempo, do tipo, da extensão e do sítio da infecção de base.[23]

Portanto, é necessária a identificação de biomarcadores para reconhecimento precoce da infecção bacteriana, para orientar oinício do tratamento e reduzir o uso inadequadode antibióticos, o que possivelmente melhorará os desfechos a longoprazo.[10,12,22,26,29]

2.2 EPIDEMIOLOGIA DA SEPSE NO BRASIL E NO MUNDO

A despeito dos avanços no diagnóstico e tratamento da sepse, amortalidade mundial mantém-se elevada, variando em torno de 20% a 80%.[4-7,20,26]Constatam-se no mundo 215.000 mortes/ano (28,6% dos casos)[30]e,nos países da União Europeia, 150.000 óbitos/ano por sepse.[4]Estudosbrasileiros estimam a ocorrência de 400.000 casos de sepse novos/ano, sendo a principal causa de morte nas CTIs e uma das principais causas de mortalidade hospitalar tardia, superando infarto do miocárdio e câncer.[5,6,30]

A efetividade do manejo da sepse no Brasil é baixa, considerando que as taxas de letalidade nas CTIs apresentam-se maiores (56%) do que as de outros países em desenvolvimento (45%) e de países desenvolvidos (30%).O choque séptico apresenta mortalidade mundial em torno de 30% a 40% ea brasileira gira em torno de 52,2% a 65,3%.[16, 30]Vários estudos brasileiros[31]confirmam esta informação, com uma taxa de

letalidade para SIRS, sepse, sepse grave e choque séptico de 24,2%, 33,9%, 46,9% e 52,2%, respectivamente.

2.3 CUSTOS COM A SEPSE NO BRASIL E NO MUNDO

O custo do tratamento da sepse em CTI é alto. Nos Estados Unidos, 51% dos pacientes com sepse severa internam em CTI, gerando gastos de aproximadamente US$17 bilhões por ano[4]e,na realidade brasileira, apenas 25% dos leitos em CTIs são ocupados com pacientes sépticos, apresentando uma média global de gastos de US$ 10.595 por ano.[16, 31, 32]A análise brasileira das características dos pacientes críticos internados indica uma mortalidade maior nos hospitais públicos, mesmo quando maior a gravidade dos pacientes dos hospitais privados. Uma hipótese levantada para explicar esta situação é o reconhecimento tardio do quadro de sepse e a falha em iniciar precocemente a terapêutica. Estes pacientes, talvez, pelo significativo aumento do tempo de disfunção, apresentavam maior número de disfunções orgânicas e, como consequência, maior mortalidade.[16]

2.4 BIOMARCADORES EM SEPSE

Mais de 100 moléculas distintas têm sido propostas como marcadores biológicos úteis para diagnosticar sepse, ainda que não se saiba quais traduzem uma informação verdadeira e útil.[33]Biomarcador é "uma medida para quantificar a homeostase biológica definida como normal e uma referência para predizer ou detectar o que é anormal."[33]

A utilidade do biomarcador está na capacidade de prover mais precocemente a informação do que os dados fisiológicos e o exame clínico. Esta informação adicional pode ser usada para:[34]

- **Rastreamento:** utilizado para identificar pacientes com risco aumentado para o desfecho ou candidatos à intervenção profilática.
- **Diagnóstico:** utilizado para diagnóstico. Deve ser mais rápido, mais barato e mais acurado do que os demais métodos já em uso.
- **Estratificação de risco:**utilizadapara identificar subgrupos de pacientes com um particular diagnóstico que podem experimentar maior benefício ou prejuízocomuma intervenção terapêutica.
- **Monitoramento:** utilizado para medir a resposta à intervenção para permitir adequar a dose ou duração de um tratamento.
- **Substituição de desfecho:**utilizada para se obter uma medida mais sensível da consequência do tratamento.O biomarcador ideal deve: encurtar o tempo e melhorar a acurácia do diagnóstico; facilitar a diferenciação entre causas infecciosas e não infecciosas de inflamação e sequelas de disfunção orgânica e choque; permitir a diferenciação entre infecção viral, fúngica e bacteriana; e refletir a efetividade do tratamento antibiótico.[35-37]Além disso, o marcador deve ser capaz de fornecer informação em tempo hábil com alta sensibilidade e especificidade, indicar o estágio da doença e seu prognóstico e ser de fácil realização ebaixo custo.[36-38]

Atualmente, muitos biomarcadores para sepse vêm sendo estudados: PCR, PCT, citocinas, complementos, neopterina, endocano e *triggering receptor expressed on myeloid cells* (TREM)-1entre outros, mas poucos são utilizados na prática clínica diária, devido ao custo da mensuração, ao tempo do resultado do exame e à efetividade.[35-37]Dos mais de 170 diferentes biomarcadores para sepse descritos na literatura nenhum tem mais de 90% de sensibilidade e especificidade para predizer quais pacientes têm maior risco para morrer.[33]

Os biomarcadores parecem ser mais úteis para descartar a hipótese de infecção. Três biomarcadores têm alto valor preditivo negativo: 99% para PCT (quando o ponto de corte

considerado é 0,2 ng/ml), 96% para tempo de ativação da protrombina (KTTP)e 100% para sepse por Gram-negativos pelo método ELISA para produtos da degradação do fibrinogênio (PDF).[39]Atualmente, a PCR e a PCT são os biomarcardores mais utilizados na prática clínica diária e os mais amplamente estudados.[33,36-38,40]

Portanto, devido à complexidade da resposta à sepse, nenhum marcador mostrou suficiente especificidade e sensibilidade para ser empregado rotineiramente para diagnóstico na prática clínica, e a combinação deles com outros exames laboratoriais e com a clínica do paciente parece ser mais efetiva do que o uso de um único marcador isolado.[33-37]

- **Proteína C Reativa**

Por suas características como biomarcador inflamatório, a PCR vem sendo estudada desde 1930, com o objetivo de investigar sua acurácia no diagnóstico e prognóstico de infecções bacterianas e como guia no tempo de tratamento antimicrobiano.[41]A PCR é uma proteína de fase aguda sintetizada predominantemente pelo fígado, principalmente em resposta à liberação de interleucina 6 (IL-6), havendo boa correlação entre elas. A secreção da PCR inicia dentro de 4-6 horas do estímulo, dobrando a cada 8 horas e atingindo o pico em 36-50 horas com uma meia-vida de 19horas.[42]

A elevação dos níveis de PCR depende da intensidade do estímulo e da capacidade da síntese hepática,[42, 43]e a magnitude da sua elevação tem relação direta com o risco de desenvolver disfunção multiorgânica.[44]Após remoção do estímulo, a proteína tende a cair rapidamente, podendo permanecer persistentemente elevada se a causa-base não for revertida.[42]A utilização da PCR para diagnosticar diferentes tipos de infecção (bacteriana, viral ou fúngica) ainda não está clara.Entretanto, os níveis séricos do marcador, geralmente, são mais elevados em infecção bacteriana.[45]

Outra controvérsiadiz respeito aoponto de corte que define infecção: ele varia entre os estudos e nenhum valor foi determinado.Em pacientes adultos saudáveis, a concentração

plasmática normal da PCR é em torno de 0,8 mg/dl. Durante infecção e inflamação aguda, estes valores podem aumentar em até 10.000 mg/dl.[41,42,46-48]

Portanto, o valor absoluto do nível sérico da PCR não é útil, pois, em alguns pacientes, principalmente os idosos e os pacientes críticos em que outras causas de inflamação estão presentes, seus valores podem estar elevados sem indicar presença de processo infeccioso. Nestes pacientes, dosagens seriadas demonstrando elevação ao longo do tempo parecem ser mais úteis do que um único valor mensurado.[42]Como não é um marcador específico de infecção, apresenta-se elevado, também, em situações inflamatórias crônicas, como artrite reumatoide, espondilite anquilosante, febre reumática, doença de Crohn, infarto agudo do miocárdio, pós-operatório de grandes cirurgias e neoplasias.Na prática clínica, vem sendo utilizada para controle do tratamento e monitorização dos períodos de exacerbação destas doenças.[46,49,50]

Quanto à acurácia, há variação entre os trabalhos. Por exemplo, um estudo demonstrou que, para um ponto de corte de 7,9 mg/dl, o marcador apresenta sensibilidade de 67,6% e especificidade de 61,3%.[51]Povoa e colaboradores demonstraram que, para níveis séricos superiores a 8,7 mg/dl, a sensibilidade foi de 93,4% e a especificidade de 86,1% e que a combinação de PCR superior a 8,7 mg/dl e temperatura acima de 38,2^{o} C aumentou a especificidade para 100%.[42]Em outro estudo observacional em pacientes de CTI, foi realizada mensuração diária da PCR, e a variação diária do marcador acima de 4,1 mg/dl mostrou ser um bom preditor para infecção nosocomial, apresentando sensibilidade de 92,1% e especificidade de 71,4%.[41]Sierra e colaboradores também demonstraram que, para pontos de corte acima de 8mg/dl, a sensibilidade foi de 94,3% e a especificidade de 87,3%.[46]

Contudo, a PCR é reconhecida como um marcadorde inflamação e infecção, especialmente em pacientes imunocompetentes.[40] Além disso, sua elevação correlaciona-se com risco aumentado de falência orgânica e morte, e o acompanhamento da queda de seus

valores com o tempo pode ser útil para avaliar resposta terapêutica em pacientes com sepse.[52,53]

- **Procalcitonina**

A elevação da PCT para detectar sepse bacteriana foi primeiramente relatada em 1993 e, na última década, vem ganhando importância como marcador precoce de sepse bacteriana em CTIs e em emergências.[54]

PCT é um pro-hormônio da calcitonina composto por 116 aminoácidos produzido pelas células C da glândula tireoide e liberado na circulação por uma protease específica.[38]Este biomarcador modula a resposta imune durante ainfecção e inflamação, apresenta funções quimiotáticas e modula a liberação e produção do óxido nítrico sintetase, citocinas e de proteínas que interferem no tônus vascular.[55]As endotoxinas ou mediadores liberados pelas infecções bacterianas (o fator de necrose tumoral e interleucinas) estimulam a liberação deste biomarcador.Portanto, as citocinas liberadas em resposta a uma infecção viral atenuam a liberação de PCT, tornando este marcador mais específico para infecções bacterianas do que virais.[56]

Os níveis de PCT elevam-se dentro de 2 a 4 horas com pico em 8 a 24horas após início do processo de sepse, caindo rapidamente dentro de 6 a 12 horas do controle da resposta imune do hospedeiro.[56]Sua resposta é mais rápida do que a da PCR, que aumenta mais lentamente e tem seu pico em 48horas.

PCT apresenta melhor capacidade discriminatória para diagnosticar infecção em comparação com leucograma e PCR. É importante salientar que os níveis de PCT devem ser sempre avaliados no contexto de uma avaliação clínica e microbiológica.[35]Em pacientes saudáveis, apresenta níveis circulantes baixos (< 0,1 ng/ml)e, nos pacientes sépticos, a literatura indica diferentes pontos de corte, sendoquevalores iguais ou acima de0,25 ng/mlsugerem infecção bacteriana.[38,57-62]

Níveis baixos de PCT podem ser observados durante o curso inicial ou quando a infecção está localizada. Portanto, o nível de PCT deve ser monitorizado a fim de detectar mudanças sutis aumentando a sensibilidade do teste.[63]Muitos estudos demonstram sensibilidade e especificidade da PCT para diagnóstico de sepse em torno de 80%.[64-70]

Elevações inespecíficas de níveis de PCT podem ser tipicamente vistas em situações de morte celular em massa, após traumatismo grave ou cirurgia. Nestas situações, os valores são moderadamente elevados e mostram um rápido declínio nas medições de acompanhamento. APCT também se eleva em situações não infecciosas, como SIRS após choque cardiogênico, queimaduras, insolação, doenças imunossupressoras e uso de diferentes drogas imunossupressoras (imunoglobulinas, anti-CD3, transfusão de granulócitos, anticorpos (alemtuzumab, interleucina 2, fator de necrose tumoral), e em pacientes com doença do enxerto-hospedeiro.[38,56,57,71,72]

Os primeiros estudos utilizando a PCT como marcador de sepse foram encorajadores,[54,73-75] inclusive sua dosagem foi sugerida como um dos critérios na definição de sepse pela Conferência Internacional de Sepse de 2001.[2]Entretanto, trabalhos mais recentes mostram resultados discrepantes.[34,51,57,76-79]Isto pode ser explicado pelo tipo de população incluída nos estudos, limitações da medição do biomarcador, por diferentes patógenos que podem induzir respostas distintas epelo pré-tratamento antimicrobiano que podem influenciar o valormedido da PCT.[70]

A acurácia diagnóstica deste marcador é insuficiente para uso amplo em todos os tipos de infecção e para diferentes subgrupos de pacientes. Sua utilização em algumas infecções, como a respiratória, tem evidência forte demonstrada por ensaios clínicos randomizados, mas, em outros tipos de infecção, foram avaliadas apenas por estudos observacionais.[59,64-67,80]Metanálise em pacientes críticos queavalioua acurácia da PCT no diagnóstico diferencial de SIRS e sepse demonstroubaixa acuráciado marcador, com

sensibilidade e especificidade ao redor de 71% (IC 95% 67-76) com área sob a curva de 0,78 (IC 95% 0,73-0,83). O tamanho pequeno da amostra e a heterogeneidade foram as principais limitações desse trabalho.[17, 75]

Em revisão que avaliou o valor diagnóstico da PCT em infecção pós-operatória,nenhuma conclusão pôde ser inferida devido à alta heterogeneidadedos estudos. Entretanto, ensaios clínicos randomizados demonstraram que o nível de elevação da PCT correlaciona-se com a sobrecarga bacterianaea severidade da infecção, demonstrando ter implicações prognósticas em infecções respiratórias em pacientes críticos,[53,61,62,70,78]sendo um bom preditor de mortalidade em CTI.[69,70,81]

Estudos recentes demonstraram que a utilização da PCT para guiar antibioticoterapia parece ser segura e encurtar a duração do tratamento.Por isso, tem sido proposto o seu uso não apenas para decisões sobre o início e acompanhamento da terapia antibiótica, mas, também, como guia de término da terapêutica.[82,83]

- **Comparação entre proteína C reativa e procalcitonina**

Atualmente, encontram-se, na literatura, muitos estudos comparando a acurácia em diagnosticar infecção bacteriana por PCR e por PCT. Este ainda é um ponto controverso, pois algumas evidências sugerem que a PCTseria um marcador mais acurado, mas nem todas suportam talideia.[51,84-86]Outros estudos demonstraram que a elevação da PCT correlaciona-se com a gravidade da infecção e que ela seria mais acurada do que a PCR.[3,51,79,87]

Metanálise recente demonstrou que a PCT é mais sensível do que a PCR em diferenciar causas inflamatórias das não infecciosas (sensibilidade de 88% (IC 95% = 80%-93%) *versus* 75% (IC 95% =62%-84%) e mais específica 81% (IC 95% = 67%-90%) *versus* 67% (IC95%= 56%-77%)). A sensibilidade em diferenciar infecção bacteriana de viral também é maior para PCT92% (IC 95%= 86%-95%) *versus* 86% (IC 95%= 65%-95%); e a especificidade de 73% (IC 95%=42%-91%) *versus* 70% (IC 95% =19%-96%).[3]No entanto, a revisão apresenta algumas limitações: quase a metade da população (46%) era composta por crianças e muitos pacientes tinham SIRS (57%),não tendo sido avaliados heterogeneidade ou seu efeito sobre as estimativas combinadas, tornando muito difícila generalização dos achados para outros subgrupos da população.[3]

Embora alguns estudos indiquem que a PCR é inferior em acurácia quando comparada àPCT para diagnóstico de sepse em pacientes imunocompetentes, ela ainda assim apresenta valores excelentes de sensibilidade (94%), especificidade (87,3%), valor preditivo positivo (90,4%),valor preditivo negativo (92,3%), razão de verossimilhança (Likelihood) positiva (7,41) e Likelihoodnegativa (0,065) para um ponto de corte de 8 mg/dl.[3, 85]A PCR ainda é o marcador mais utilizado na prática clínica diária pela facilidade de sua dosagem e pelo seu custo.[33,34]

2.5 MARCADORES EM IMUNOSSUPRIMIDOS

O diagnóstico precoce de sepse e o início da antibioticoterapia são fatores preditores independentes da mortalidade em pacientes imunocompetentes, e o retardo do início dos antibióticos em 24horasreduz a sobrevida de 83% para 8%.[21] Provavelmente, este cenário é mais trágico em imunossuprimidos, por isso a necessidade de testar marcadores como métodos para detecção precoce de infecção nesse grupo.

PCR e PTC foram extensamente estudadas em imunocompetentes, demonstrando que a elevação destes marcadores é acurada em diagnosticar sepse, no entanto poucos avaliaram o desempenho em imunocomprometidos.[33,35,40]Estudos com PCR em neutropênicos, cirróticos, usuários crônicos[88-93] de corticoide, tuberculosos e portadores do HIV são escassos.

Diferentes estudos têm avaliado a utilidade do PCT neste grupo de pacientes. Recente revisão sistemática em neutropênicos febris conclui que a PCT tem valor como ferramenta diagnóstica e prognóstica. Entretanto, deve-se ressaltar que os autores sugerem a realização de mais investigações, uma vez que os 30 trabalhos arrolados apresentavam importantes diferenças nas características das populações incluídas e qualidade inadequada.[94]

Recentemente, Belle demonstrou que a elevação da PCT nos pacientes imunossuprimidos (HIV, desordens hematológicas e câncer sólido), utilizando ponte de corte de 0,5 ng/ml no primeiro dia, tem acurácia de predizer infecção com sensibilidade de 100%, mas especificidade de apenas 63%.[95]

- **Marcadores de sepse na população com HIV**
  - Proteína C reativa em população com HIV

O HIV é uma infecção progressiva com destruição do sistema imune, mais especificamente depleção dos linfócitos CD4, e marcadores inflamatórios de fase aguda, como a PCR, podem estar elevados sem existir infecção bacteriana.[96]A relação entre concentração sérica de PCR e HIV ainda não está clara.[93]Curiosamente, estudos demonstraram que os níveis basais de PCR nesta população são relativamente mais baixos, em torno de 4mg/dl,o que indica que ser portador de HIV não leva a um processo inflamatório crônico de base intenso.[93,97,98]

Alguns autores demonstraram que a elevação dos níveis da PCR foi correlacionada com a progressão da infecção pelo HIV e queda do CD4. Entretanto, pontos de corte que possam discriminar a ocorrência de progressão da infecção pelo HIV da ocorrência de infecção bacteriana ainda não estão definidos.[99-101]

A PCR apresenta níveis séricos elevados, também, quando na presença de infecções oportunistas,tornando o diagnóstico diferencial mais difícil.[99-102]

– Procalcitonina em portadores de HIV

Entre pacientes com HIV, a PCT é normal ou levemente elevada, similar ao que ocorre com outras infecções virais com os vírus da hepatite C e B.[103]Este marcador apresenta-se acima dos valores normais em portadores de HIV com infecção generalizada. Entretanto, o ponto de corte utilizado para os imunocompetentes pode não ser o mais adequado para os imunossuprimidos, devendo ser reavaliado.[103,104]

A PCT é utilizada, também, como auxílio para diagnóstico de infecção nesta população. Estudo comparando pacientes com HIV negativos e positivos com sepse demonstrou que o emprego da PCT para diagnóstico de infecção reduziu o uso de antibióticos em 25% a 65%.[105]

- **Marcadores de sepse em pacientes com tuberculose**

A síntese e a liberação de PCT e PCR são determinadas pela cascata inflamatória desencadeada durante o processo de infecção. A intensidade da produção destes marcadores depende do número de organismos na circulação sistêmica. Provavelmente, o número de organismos na infecção por TBC é menor do que nas infecções bacterianas.[104]

A concentração de PCT e PCR difere entre pacientes com TBC e pneumonia bacteriana comunitária no estágio inicial da doença. O nível basal de PCT não se eleva nas infecções por TBC,sendo assim um marcador discriminatório útil. Além disso, parece ser um marcador prognóstico nos pacientes com TBC, tendo o ponto de corte acima de 0,5 ng/ml sido associado com pobre prognóstico.[106,107]

O interferon é liberado em quantidade maior na TBC do que na infecção bacteriana e atenua a secreção de PCT nas células adiposas.[108-110]A PCT parece ser um biomarcador melhor do que a PCR ou a contagem de leucócitos na diferenciação entre TBC e pneumonia em pacientes não HIV, mas faltam dados para extrapolar essa afirmação para os imunossuprimidos.

Entretanto, observa-se que a concentração sérica de PCT eleva-se levemente em infecções intracelulares como as causadas por micoplasma, vírus e *Pneumocystis jirovecii*.[108]

- **Marcadores de sepse em pacientes com cirrose**

A PCR é uma proteína de fase aguda sintetizada pelo fígado em resposta a dano tecidual, sendo difícil sua interpretação em pacientes cirróticos.[43]Portanto, a produção da PCR em resposta à infecção pode ser atenuada em pacientes com disfunção hepática mesmo em vigência de infecção bacteriana.[111]

Há escassos estudos na literatura sobre o valor da PCR como preditor de infecção nestes pacientes, mas a persistente elevação e o aumento progressivo do valor basal, mesmo em pacientes com cirrose, são preditores de pobre desfecho.[112]Park e colaboradores demonstraram que pacientes cirróticos com bacteremia por *Escherichia coli* apresentavam níveis elevados de PCR e sua redução foi associada com melhor desfecho.[113]

- **Marcadores de sepse em pacientes transplantados**

Na literatura, são reduzidos os estudos sobre o uso de biomarcadores em pacientes transplantados. Sabe-se que, em extensos procedimentos cirúrgicos abdominais, a PCT e a PCR apresentam um aumento transitório por 24 horas, mesmo sem infecção presente.[114]Estudo em transplantados hepáticos demonstrou que ocorre elevação da PCT mesmo sem evidência de infecção e que a dosagem deste marcador em dias consecutivos com elevação do seu valor basal é fortemente sugestiva de infecção.[115]

Além disso, o nível do aumento da PCT parece ser dependente do tipo de terapia imunomoduladora que o paciente recebe, sugerindo que o tipo de imunossupressor usado pode interferir na produção deste marcador.[116]

Transplantados de medula com sepse severa e choque séptico apresentam elevação da PCT e da PCR quando comparados àqueles com sepse sem sinais de severidade. O ponto de corte da PCR de 50 mg/l para diagnóstico de infecção nestes pacientes demonstrou sensibilidade de 100% e especificidade de 41%e o ponto de coorte da PCT foi mais elevado nestes pacientes (1,0 ng/ml) do que nos imunocompetentes.[117]

- **Marcadores de sepse em usuários de corticosteroide**

São poucos os estudos, na literatura, avaliando a acurácia dos biomarcadores e o uso de corticosteroides, sendo esta uma questão a ser elucidada. Segundo o mecanismo de atuação, a produção de PCT e PCR não é influenciada pelo uso de corticosteroide.[90]

Muller e colaboradores demonstraram, em estudo com 102 pacientes críticos, que os níveis de PCR e IL-6 apresentam-se mais baixos em usuários de corticosteroide (prednisona 20-1.500 mg/dia), mas sem correlação entre o uso dos corticosteroides e os níveis de PCT.[118]Tal observação foi confirmada em pacientes voluntários saudáveis, nos quais o uso de corticosteroide influenciou a dosagem de outros biomarcadores, mas não da PCT.[119]

2.6 REVISÃO SISTEMÁTICA DE TESTES DIAGNÓSTICOS

Revisão sistemática da literatura é a revisão planejada de uma questão da literatura que utiliza métodos sistemáticos para identificar, selecionar e avaliar criticamente estudos relevantes. Esta sistematização visa reduzir tantos possíveis vieses na forma de revisão da literatura e na seleção dos artigos quanto aqueles detectados pela avaliação crítica de cada estudo. O método estatístico utilizado na revisão sistemática para integrar os resultados dos estudos incluídos e aumentar o poder estatístico da pesquisa primária chama-se metanálise.[120]

Metanálises de estudos de testes diagnósticos e prognósticos desenvolveram-se na última década, depois de sua aplicação em estudos terapêuticos. Este tipo de metanálise utiliza estudos prospectivos ou retrospectivos de coorte, existindo pontos de corte diferentes para o resultado positivo ou negativo de um exame. Portanto, desenvolvem-se técnicas diferentes para combinação dos dados.[120]

Comum a todas as revisões sistemáticas, a primeira etapa é definir a questão de pesquisa (PICO, onde P = população, I = teste índex, C = teste padrão utilizado, O = desfecho). Num segundo momento, deve ser realizada ampla busca sistematizada na literatura, utilizando as principais bases eletrônicas existentes, literatura cinza, isto é, em estudos não publicados ou não indexados e na busca manual dos termos predefinidos no acrômio PICO. Os estudos escolhidos serão selecionados por dois pesquisadores e as discrepâncias são resolvidas por um terceiro pesquisador.[121]

O terceiro passo é a avaliação da qualidade dos estudos escolhidos, que será realizada pelos dois pesquisadores utilizando a ferramenta *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS 2) propostas pela Cochrane para revisões sistemáticas de estudos

diagnósticos. O quarto passo é a extração de dados, que deve ser realizada pelos dois pesquisadores.[122,123]

O quinto passo é a metanálise propriamente dita, onde aplica-se um *Receiver Operating Characteristic* (SROC), que é uma curva ROC sumarizada de todos os estudos envolvidos. Estudos de teste diagnóstico apresentam como medidas estatísticas: sensibilidade e especificidade, valor preditivo positivo e negativo, razões de probabilidade e, para definir ponto de corte do teste e acurácia do teste, uma curva (ROC). Os melhores testes de diagnóstico serão posicionados no canto superior direito do espaço ROC, onde sensibilidade e especificidade estão perto de 1.

A sumarização das várias ROCs adquiridas dos estudos selecionados é chamada de ROC sumarizada hierarquizada (HSROC), que utiliza o modelo de regressão linear para a construção de curvas ROC resumo proposto por Moses e colaboradores,[124] baseado em regressão do Log do *odds ratio* de teste diagnóstico chamado de DOR. DOR é a razão de chances do teste diagnóstico, sendo uma combinação estatística da sensibilidade, da especificidade e dos valores de Likelihood positiva e negativa.[123]No entanto, o modelo Moses tem suas limitações: não considera a precisão das estimativas do estudo, não estima a heterogeneidade entre os estudos e a variável explicativa na regressão é medida com erro.[121]

Duas abordagens foram recentemente desenvolvidas para superar essas limitações: o modelo ROC hierarquizado e o modelo de efeito aleatório bivariado. O primeiro se concentra em identificar a curva ROC subjacente, estimando a precisão média, utilizando para isso a razão de chances diagnóstica. O segundo se concentra em estimar a sensibilidade média e a especificidade, mas também estima a variação não explicada e a correlação entre eles. Os dois modelos básicos são matematicamente equivalentes na ausência de covariáveis. Fornecem uma estimativa válida do resumo da curva ROC subjacente e o ponto de operação média.

Também permitem a exploração da heterogeneidade. Os dois modelos podem ser analisados com *software* estatístico para modelos mistos de ajuste.[124-126]

A variabilidade é uma característica esperada em estudos de testes diagnósticos, uma vez que haverá diferenças no desenho, na condução, nas características dos participantes, nas intervenções, na gravidade da doença e no teste índice ou padrão de referência (tempo de aplicação/submissão, aspectos técnicos dos equipamentos ou materiais utilizados, variações laboratoriais ou inter/intraobservadores).[123,125, 127, 128]

Outra peculiaridade nos estudos de teste diagnóstico é a avaliação do viés de publicação que, em revisões de estudos de intervenção, utiliza o gráfico em funil, que não é recomendado pela Cochrane para este tipo de estudo, sendo recomendado o teste de regressão de Egger.[123,129]

3 OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar a acurácia dosbiomarcardores PCR e PCTem detectar sepse em pacientes críticos imunossuprimidos.

3.2 OBJETIVOS ESPECÍFICOS

Determinar a característica daPCR como marcador de infecção bacteriana em relação ao exame microbiológico (padrão-ouro) em pacientes críticos portadores de HIV, tuberculosos, transplantados, usuários crônicos de corticosteroide e cirróticos.

Determinar as características da PCT como marcador de infecção bacteriana em relação àPCRem pacientes críticos portadores de HIV, tuberculosos, transplantados, usuários crônicos de corticosteroide e cirróticos.

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5 ARTIGO 1

Acurácia da Proteína C Reativa como Marcador de Infecção Bacteriana em Pacientes Críticos Imunossupressos: Uma Revisão Sistemática e Metanálise

Accuracy of the C Reactive Protein as Bacterial Infection Marker in Immunosuppressed Critical Patients: A Systematic Review and Metanalysis

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ABSTRACT

Background: There is a need to have a better understanding on the role of C-reactive protein (CRP) as a valid marker for detecting bacterial infection in sepsis patients.In order to rule out the diagnosis of sepsis and bacterial infection in immunocompetent patients, there is a need for a high negative predictive value of CRP.However, few studies have evaluated its performance in immunocompromised hosts. The aim of the present study was evaluated the performance of CRP as marker of infection in immunocompromised patients. **Methods:**The inclusion criteria werein immunosuppressed patients which c reactive protein was used as bacterial infection marker by searching the Cochrane Register, MEDLINE, EMBASE, SCOPUS, WEB OF SCIENCE, LILACS and CINAHL. We applied Quality Assessment of Diagnostic Accuracy Studies Tool 2 (QUADAS 2) to evaluate the quality of the articles in this review. We evaluated test accuracy parameters with the use of forest plots, hierarchical summary receiver operating characteristic (HSROC) curves, and bivariate random effect models.**Results:** From 21 references, only 13 studies have data for quantitative results. We analysed all studies as immunocompromised patients by random effects method (REML)leads to a joint *Odds ratiodiagnostic* (DOR) of 3.04 of (95% IC 1.71-5.40), but with a very high heterogeneity $I^2 = 91$ %, $Q = 181.48$ ($p < 0.001$). Therefore, a bivariate model was use then to account for different thresholds. The use of this model up confirming the hypothesis that its cause would be different cut off studies. It was not possible analysis of the following groups' carrier tuberculosis, steroid user, presence of opportunistic infection proposals to the protocol for lack of this information in articles. **Conclusions:**C-reactive protein seems to be a good screening tool for sepsis in immunosuppresses.
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Keywords: Bloodstream infection; C-reactive protein;Diagnostic accuracy; Immunosuppressed;Sepsis.

INTRODUCTION

Sepsis is a syndrome with high mortality, morbidity and costs. It is a leading cause of death worldwide accounting for 751,000 cases/year in the United States and its incidence exceeds the Acquired Immune Deficiency Syndrome (AIDS) and the main types of cancer [1-3]. Early identification of sepsis is essential to a better prognosis, since the implementation of interventions with proven efficacy in randomized trials, can reduce mortality by 16% in severe sepsis and septic shock [4].

Unfortunately, the clinical signs of sepsis are similar to other non-infectious causes of systemic sepsis and ideal method diagnosis, there is still [4, 5]. Currently, the value of CRP has been used in medical practice to rule out the diagnosis of sepsis and bacterial infection in immunocompetent patients [6-9].

However, studies with CRP in immunocompromised patients as neutropenic, cirrhosis, chronic corticosteroid users, tuberculosis and carriers of human immunodeficiency virus (HIV) are scarce and controversial results [10-16]. In recent years, two meta-analysis in hematological and cirrhotic patients have been published, in which CRP have a good accuracy in differentiating bacterial from other no infective cause of inflammation in this subgroup of immunocompromised patients [8, 9] but patients included in the analysis are not critical patients.

Therefore, the objective of the present study is to investigate whether CRP is a valid marker for detecting bacterial infection in critical immunocompromised patients.

METHODS

We performed this systematic review using the guidelines proposed by the Cochrane Handbook for Systematic Reviews of Diagnostic test [17]. We used the preferred reporting items for systematic reviews and meta-analyses(PRISMA) statement methodology [18]. Submitted PROSPERO 2015: CRD42015019329

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of study

We have included all cohort and case-control studies published which have assessed CRP levels as a marker of bacterial infection in immunosuppressed patients compared with cultures or clinical signs of sepsis. Severe sepsis and septic shock were also included. Raw data from the articles were used to construct 2 x 2 tables; when unavailable, the tables were constructed using given measures of sensitivity and specificity to derivate row data.

Experimental animals' studies, narrative reviews, correspondences, case reports, expert opinions and editorials and studies for which complete data was unavailable were excluded. No limitation was placed on the language of the article.

Condition or domain being studied

Although recently the concept of sepsis has been updated with some modifications, in our study we used the concept of 2001 [19] since the articles published until 2015 used this [20].

Target condition was the presence of bacterial infection at any stage: sepsis, severe sepsis or septic shock. The concept used of sepsis was that established by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference in 2001 [19]. According to this consensus: **microbiological infection** should be confirmed or

clinically suspected by at least one or more characteristics: white cells in sterile body fluids, drilling viscera, radiographic evidence of healing in combination with purulent sputum, and syndromes associated with high risk for infection. **Syndrome inflammatory systemic (SIRS)** was set when at least two of the criteria are present: heart rate > 90 bpm / min, respiratory rate > 20mr/min. or need for mechanical ventilation, body temperature > 38º C or < 36º C, leukocytes > 12,000/mm^3 or < 4,000/mm^3. **Sepsis** was defined as SIRS secondary infection documented by microbiological diagnosis. **Severe sepsis** was defined as sepsis in the presence of hypotension, hypoperfusion or organ dysfunction. **Septic shock** was defined as sepsis with refractory hypotension associated with the appropriate amount of volume.

Participants/population

Patients over 18 years with immunosuppression HIV with any level of CD4 or not using antiretroviral, any progression of the disease, presence or absence of opportunistic diseases (tuberculosis, pneumocystis). Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid.

Outpatients, pregnant women, post-operative major surgery, acute myocardial infarction, cancer sufferers, rheumatologically, autoimmune and other diseases that cause immunodeficiency were excluded.

Index Test

C-reactive protein was evaluated by any method except ultra-sensitive CRP.

Comparator

The gold standard test was considered any microbiological examination (sputum culture, bronchial lavage, urine, peripheral blood or catheter or body secretions) with bacterial growth [12].

Outcomes

Theprimary outcomes was to assess the sensitivity, specificity, positive and negative predictive value of CRP in detecting sepsis in critical immunosuppressed patient in relation to the gold standard: HIV positive with tuberculosis, transplant on chronic corticosteroid and cirrhotic. Secondary outcomes are assessing the best cut off point for CRP as a marker of bacterial infection.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

The electronic search was conducted for Cochrane Central Register of Controlled Trials (CENTRAL–The Cochrane Library, MEDLINE; 1966 to August 2014), EMBASE (1980 to August 2014), CINAHL (1982 to August 2014), and SCOPUS (until August 2014), LILACS (1982 to August 2014) and Web of Science (until August 2014). Date, language restriction or publication status did not apply.

A Boolean strategy was applied, cross-searching of the following MeSH Terms had been conducted ((HIV) OR “HIV” [MeSH Terms]) OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus [MeSH Terms]) OR Acquired Immunodeficiency Syndrome Virus) OR AIDS)) OR ((tuberculosis) OR “tuberculosis” [MeSH Terms])) OR ((liver cirrhosis) OR “liver cirrhosis” [MeSH Terms]) OR liver cirrhosis)) OR ((“transplants” [MeSH Terms]) OR transplants) OR “transplantation” [MeSH Terms] OR transplantation)) OR ((“glucocorticoids” [MeSH Terms]) OR glucocorticoids) OR corticosteroids)) AND

((sepsis) OR “sepsis” [MeSH Terms]) OR infection) OR “infection” [MeSH Terms]) OR “C-reactive protein”) OR sepses) OR sepse) OR sepsi)) AND ((“C-reactiv protein”) OR “protein C-reactive”) OR “C-Reactive Protein” [Mesh]) OR “C-reative protein”) OR “C-reactive protein”).

The search of the grey literature was conducted through the databases: Bank of Theses (PROQUEST and CAPES) and protocols repository (PROSPERO). We contacted the authors if the information of the selected articles was insufficient to abstract data or were inaccurate.

DATA EXTRACTION (SELECTION AND CODING)

The selection and data extraction were performed by 2 independent reviewers (Vanessa Martins de Oliveira and Rafael Barbena Moraes), and disagreements, if any, were resolved by a third reviewer (Eliana Márcia Wendland). We used the PRISMA statement methodology [18] to report the systematic review and meta-analysis. The details are summarized in Figure 1.

A data collection instrument was developed for the study, in which variables were collected as general characteristics of publication (year, publication journal), general characteristics of the population (age, gender, ethnicity, type of immunosuppression (HIV, tuberculosis, cirrhotic or transplanted), study design (emergency site, floor and intensive care unit), disease severity (APACHE, *Sequential Organ Failure Assessment*–SOFA), severity of infection (infection sepsis or severe sepsis), characteristics of the tests (measurement method and cohort points used), laboratory measurements as leukocyte and lymphocyte types of infection (bacterial, fungal and tuberculosis), comorbidities, use of immunosuppressant, corticosteroids (dose and chronic use), HIV (CD4 count, a measure of human T lymphotropic vírus(HTLV) / II and use of highly active antiretroviral therapy–HAART).

QUALITY ASSESSMENT

We evaluated the methodological quality of the included studies by applying the QUADAS 2, as the criteria for assessing the studies [21]. When there was different evaluation on the articles, a consensus was obtained through a third reviewer opinion. The summary of risk of bias assessment are described on Figures 2 and 3.

DATA ANALYSIS

The data extracted from the articles were grouped in a 2 x 2 table to evaluate the sensitivity and specificity of the test. The pretest probability (positive and negative predictive values) were extracted from the studies. The post-test probability was estimated by likelihood ratio was calculated starting the sensitivity and specificity of the test: (likelihood ratio) (LR + = sensitivity / (1-specificity) and LR = (1-sensitivity) / specificity). A random effect summary diagnostic chances (DOR) was used as the summarization measure of test accuracy index. DOR was estimated by the restricted maximum-likelihood estimator (REML) calculated from the likelihood ratio. In contrast to univariate meta-analysis, diagnostic meta-analysis often requires a bivariate model. In diagnostic test, is common to have different thresholds used in different studies. Moreover, when there is a significant correlation between sensibility and specificity due to the different thresholds, pooling sensitivity and specificity separately leads to a biased results. The bivariate approach adjust for the correlation between sensitivity and specificity and assumes a bivariate distribution for the logit-transformed sensitivity and specificity, adjusting the equation for the covariance between the correlated parameters to estimate the DOR [22]. The parameters of the bivariate model, model sensitivity, specificity

and the direct correlation between them, while the parameterization of ROC HSROC models sensitivity and specificity functions to set a summary ROC curve. The summarized ROC (SROC) will be obtained by summarizing the sensitivity, specificity and diagnostic odds ratio (DOR). Forest Plot graph represented the value of each individual study of positive and negative predictive values, sensitivity and specificity of the test, along with their 95% confidence intervals [23,24].

ASSESSMENT OF HETEROGENEITY AND REPORTING BIAS

The heterogeneity in this meta-analysis was evaluated in two ways: I-squared test (Higgins) and Cochran Q-test were calculated to quantify the between-study variation and by visual analyses of the forest plots When the arrangement of studies in plots were inspected visually and may suggest the presence of heterogeneity that can be exploited by sensitivity / subgroup analyzes [17]. The publication bias were assessed using Egger regression test[17].

Outcome measures summarized and heterogeneity of research through modeling was carried out with R software version 3.2.4 (metafor and mada packages) [25].

SENSITIVITY ANALYSIS

We have defined subgroup analysis based on 1) Patient characteristics: immunosuppression type: carrier tuberculosis, cirrhotic, transplanted, and HIV, presence of opportunistic infection (pneumocystis, fungi and tuberculosis), corticosteroids (dose, chronic use or not); 2) For patients with HIV: CD4 measure, and HTLV II and viral load if they are measured, use of antiretroviral informed.; 3) Performance Characteristics: method used to measure CRP and different cut off tests; 4) The condition: site of infection: lung, urinary,

abdominal, catheter, skin or without a defined focus; 5) The design of the study: case-control and prospective or retrospective cohort.

RESULTS

After excluding duplicates 601 publications were retrieved and 58 studies were selected for full text reading. We excluded 38 studies. The most common causes of exclusion of studies were not meeting the criteria of sepsis, severe sepsis and septic shock and measurement of CRP by ultrasensitive method. Twenty articles were included in qualitative syntheses and 12 have available data for quantitative analysis (Figure 1). A description of studies included in the qualitative syntheses of systematic review shown in Table 1. The majority of studies were from Europe , 6 from Asia [10,13,14,26-28] and USA [29], Latin America [30,31] and South Africa [11] contribuited with one studies, respectively. We found 5 case-control [10,26,28,32,33] and the others were cohorts' studies being the majority prospective. The number of participants included in each study varies from 17 to 890 (Table 1).

We included in the quantitative syntheses 5 studies with cirrhotic population [12,28,30,34,35], 2 with HIV[11,36] population and 5 studies whom participants submitted to transplant [13,14,32,37,38]. The studies in transplanted patients are, in general, heterogeneous: some report the data as events (545) and some as individual patients (1,418) (Tables 1 and 2).

It was not possible analyse of the following groups: carrier of tuberculosis, steroid user, presence of opportunistic infection due to the lack of information described on the articles on this subject;Groups included HIV patients, cirrhotic and transplant some of the information planned to be collected in the protocol had no data available.

Overall, there is a low risk of applicability concerns and unclear or high risk of bias. Most studies did not report lost to follow up or discrepancies between included and analyse participants neither the time between interval and index reference test (Figure 2). No significant evidence of potential publication bias was noted using the Egger's () test.

DIAGNOSTIC ACCURACY INDICES

Overall population

When a summary of raw data from all studies of immunocompromised patients was estimated by REML, leads to a joint DOR of 3.04 of (95% IC 1.71-5.40), but with a very high heterogeneity I^2 = 91 %, Q =181.48 ($p < 0.001$) (Figure 3). We have attribute this heterogeneity due to different cut offs points of the studies. It has also been investigated whether this could be a source of heterogeneity by using a meta regression. The different cut-off significant influence the diagnostic accuracy and explain only 44.6% of the heterogeneity. The test for residual heterogeneity is significant (QE = 68.7; $p< 0.001$), indicating that other moderators not considered in the model are influencing the CRP accuracy.

Subgroup analysis

In order to explain the high heterogeneity found, we had performed a subgroup analysis by restricting studieswith similar population, type of study, and used bivariate model.

Type of Population

Summary of the subgroup analysis of the included type of population (Table 3). Combining the two studies with HIV patients[11,36], the accuracy of CRP was DOR6.24 (2.09-18.63), with an I^2 of 0%; Q = 0.27; p = 0.60. Observed an improvement in performance had been observed on the screening test. The HIV population had only two studies in which

different cut offs points have lead for not being able to conduct a subgroup analysis. The two HIV studies show the same type of study design (prospective cohort) and type of test, the same location (lung) and severity of infection (sepsis without multiple organ dysfunction). It had not been possible to analyse by subgroup the following measures: CD4, HTLV II, viral load and use of antiretroviral, as there was a lack of this information on these exams. A REML had been applied in order to analyse the cirrhotic population[12,28,30,34,35]. Pooled DOR was 3.52 (1.98-6.26), with a significant drop in the heterogeneity for all (I^2 = 85.2%, Q = 24.3, P < 0.001)(Figure 4). All studies included patients with immunocompromised HSCT (after hematopoietic stem cell transplantation)[13,14,32,37,38]. In some included studies, analyse had been carried out taking into account the individual, but not events. For transplanted, DOR was1.99 (0.92- 4.30) with high heterogeneity I^2 = 92.04 %; Q = 69.00, p = < 0.001(Figure 4).

Splitting the analysis by subgroup of population (HIV, cirrhosis and transplanted) could not explain the total amount of heterogeneity. The heterogeneity in cirrhotic and transplanted population still very high (I^2 = 85.2% and I^2 = 92, 5%), respectively (Figure 4).

Type of studies

Met analysis had 7 prospective cohort studies [11-13,30,34-37], 2 retrospective cohort [14,38] and 3 case-control studies [26,28,32]. The effect of type of study in the DOR can be observed in Figure 6. For prospective cohort studies was DOR 3.61 (1.81-7.21) high heterogeneity I^2 = 82.19%, Q = 44.05 p < 0.001and 3 retrospective cohort was DOR2.55 (1.27-5.11) substantial heterogeneity com I^2 = 95.62%; Q = 22.81, p < 0.0001. Case-control studies was DOR 1.80 (0.50-6.54) and I^2 = 0%, Q = 0.03, p = 0.86(Figure 6). CPR only can predict infection in on cohort studies not in case-control ones (Figure 5).

Bivariate Model

In order to explain and solve the heterogeneity we applied the hierarchical bivariate model who takes in account the different cut off and assume that specificities and sensitivities are different in it study. A bivariate model was use then to account for different thresholds.

The pooled DOR was was 7.34 (95% IC 1.95-27.69), with an area under curve of 0.74 (HSROC) (Figure 6). CPR showed moderate performance with screening tool with sensitivity 0.70 (95% IC 0.58-0.81) and specificity = 0, 74 (0.58-0.85), + LR = 2.81 (1.53-4.88) and - LR 0.42 (0.25-0.65) (Figure 6).

DISCUSSION

A comprehensive systematic review had been conducted including 1.418 critical immunosuppressed patients and has shown that CRP is a good accuracy-screening test for bacterial infections had sensitivity 0.69 (0.53-0.60) and specificity 0.76 (0.71-0.76) , with an HSROC of 0.77 to detect bacterial infection. Overall CRP present a slightly lower sensitivity and specificity in immunosuppressed critical patients then in immunocompetent population (sensitivity 75% (95% CI: 62-84%), specificity 67% (95% IC: 56-77%) and *Area Under the Receiver Operating Characteristic Curve*(AUROC): 0.92 (95% CI: 0.89-0.94)[8]. The review with immunocompetent population has some limitations: almost half the population (46%) consisted of children and many patients had SIRS (57%), not having been assessed heterogeneity or its effect on the combined estimates, making it very difficult to generalize the findings to other subgroups of the population [8].

No meta-analyzes in the literature on HIV population and in our metanalysis only two studies were included.

In cirrhotic patients, we had estimated by bivariate model with poor performance CPR with a sensitivity 0.57 (95% IC: 0.31-0.80), a specificity 0.75 (95% IC: 0.59-0.86) and a good performance when we used an HSROC (0.74). Comparing our results with previous meta-analysis that included 858 patients and 275 bacterial infection episodes (32.1%), this meta-analysis found that CPR has a superior performance in the diagnosis of systemic infection. The results showed moderate performance of CPR (sensitivity of 0.77 (95% CI: 0.69-0.84) and specificity of 0.85 (95% CI: 0.76-0.90), and AUROC 0.87 (95% CI: 0.84-0.90) [39]. These difference could be explained by the fact that Lin *et al*. [39] included septic's patients and patients with localized infection.

In the group of transplant population, recent meta-analysis published by Lyu *et al*. [40] was using pooled data from 6 studies (1,344 immunocompromised HSCT, two studies were carried out among paediatric populations and the other 4 were in adult populations. Two studies in this meta-analysis focused on patients with febrile neutropenia. This was our exclusion criterions. Some limitations observed in this meta-analysis: lack of homogeneity in the selection criteria of the included studies; small sample size; did subgroup analysis or meta-regression; jointly analyzed studies with population data and events that influence the summarization of the estimated accuracy. Both metanalysis applied bivariate model. Compared our results presents a high sensitivity (0.84, 95% CI: 0.69-0.92) and specificity (0.76%, 95% CI: 0.59-0.88; HSROC 0.85) similar a previous metanalysissensitivity 0.80 (95% CI 0.54-0.93), specificity 0.73 (95% CI 0.56-0.86), and area under the curve(AUC) 0.82 (95% CI: 0.79-0.86)[40].

A comprehensive literature review had been carried out, in, which included all immunosuppresses groups, which is a strength of the present study. We have applied the risk of bias evaluation for the included studies. Another strong point in our study was to apply the bivariate model. Bypassing a common problem in the meta-analysis of diagnostic studies that

a wide range of different cut-off values we did not pool the sensitivity and specificity directly. Instead, we constructed the HSROC curve, which consists of pairs of sensitivities and false-positive rate (1-specificity) from each included study. In addition, we used a bivariate modelling approach that allows adjustment of dependency inherent in the paired sensitivity and specificity, and can derive the summary sensitivity and specificity independent of the threshold effect caused by different cut-off values used that resolved our heterogeneity between studies.

As there were few studies on the topic, this could have led to lack of power and this is the limitation of the present study. Most of the included studies did not clearly presents a description of when the índex test had been evaluated the pattern and loss of patients and the different cohort of points used by studies to establish infection. Variation in clinical criteria used to define severe systemic infection across studies and the differing aetiologies of fever among the groups compared and different cut-offs values in the selected studies were also a sources of heterogeneity. Another limitation may be the relatively small number of studies and pooled sample size. Studies with small sample sizes may have allowed for Type II error and wide confidence intervals. The less precise estimates of pooled effect make a definitive conclusion difficult.

CONCLUSION

PCR appears to be a good screening test for sepsis in critical imunossupressos patients, with the same accuracy than in immunocompetent. However, it should not be used, as a single marker in diagnosing sepsis should be associated with clinical and other tests**.**

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Drafting of the manuscript: Vanessa Martins de Oliveira; Eliana Márcia Wendland and Airton Tetelbom Stein

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Table 1 - Characteristics of the twenty included studies that used biomarkers to assess patients with sepsis, severe sepsis and septic shock

Author, year	Country	Age (years)	SEX (M/F)	Population	Study Design	Outcome definition
Walker 1984	United Kingdom	NA	NA	HSCT	Prospective Cohort	Sepsis
Chasty 1993	EUA	32.5	8/11	HSCT	Prospective Cohort	Sepsis
Arber 2000	Switzerland	40	36/35	HSCT	Retrospective Cohort	Severe sepsis
Hambach 2002	Germany	40	37/24	HSCT ALO	Prospective Cohort	Sepsis
Pihusch 2006	Germany	40	206/144	HSCT ALO	Retrospective Cohort	Severe sepsis/septic shock
Mori 2011	Japan	54	NA	HSCT ALO	Case-control	Sepsis
Kanda 2011	Japan	47	49/63	HSCT ALO	Retrospective Cohort	Pulmonary sepsis and bacteraemia
Koya 2012	Japan	NA	NA	HSCT	Prospective Cohort	Severe sepsis and sepsis
Yepes 2014	Spain	48,47	17/12	HSCT	Cohort prospective case-control nest	Sepsis
Viallon 2000	France	58.8 ± 2.4*	53/8	Liver cirrhosis	Prospective Cohort	Sepsis/severe sepsis/septic shock
Park 2004	Chorea	53.0 ± 11.8*	46/14	Liver cirrhosis	Prospective case-control	Bacteraemia/ severe sepsis/septic shock
Bota 2005	Belgium	56	414/450	Liver cirrhosis	Prospective case-control	Pulmonary, abdominal sepsis
Tsiakalos 2009	Greece	59	67/21	Liver cirrhosis	Prospective Cohort	Abdominal, pulmonary sepsis and bacteraemia
Young 2011	Chorea	58	138/64	Liver cirrhosis	Retrospective Cohort	Bacteraemia
Paap 2011	Hungray	58	204/164	Liver cirrhosis	Prospective Cohort	Pulmonary, abdominal, ITU sepsis
Yuan Li 2013	China	54.81 ± 6.42*	45/39	Liver cirrhosis	Prospective case-control	Abdominal sepsis and bacteraemia
Lazarotto 2013	Brazil	54	44/20	Liver cirrhosis	Prospective Cohort	Pulmonary, abdominal, sepsis
Schleicher 2005	South Africa	33.5	32/35	HIV	Prospective Cohort	Pulmonary sepsis
Perello 2010	Spain	43	77/41	HIV	Prospective Cohort	Pulmonary sepsis
Silva 2009	Brazil	42	NA	HIV	Prospective Cohort	Sepsis

*Mean age (DP).
Abbreviations: HSCT = after hematopoietic stem cell transplantation, ALO = alograft

Table 2- Diagnostic characteristics of the twelve studies include in the quantitative analysis

Author, year	Prevalence	PCR assay	Cut off (mg/ml)	TP	FP	TN	FN	Sensivity (%)	Specificity (%)
Koya 2012	0.92	Immunoturbidimetric assay	4	64	11	13	15	83	57
Lazzaroto 2013	0.54	Nephelometry	5	11	14	3	53	78	79
Paap 2012	0.37	Integra 700 Automated analyser system	10	117	21	22	208	84	90
Pihusch 2006	0.56	Methods on automatic analyzer (Hitachi, Roche)	50	23	69	81	23	22	25
Schleircher 2005	0.49	Nephelometry	24.6	26	6	7	28	78	82
Hambach 2002	0.67	Turbidimetry	10	23	18	14	59	62	76
Yepes 2014	0.62	Cobas® c501 Roche	7.5	16	5	2	6	88	54
Tsiakalos 2009	0.21	Nephelometry	5.58	15	3	4	66	78	95
Viallon 2000	0.34	NA	8	13	17	8	23	61	57
Perello 2010	0.24	NA	10	23	51	4	34	85	40
Yuan Ly 2013	0.50	Immunoturbidimetric assay	16.15	27	2	15	40	64	95
Kanda 2011	0.16	Latex agglutination assay	0.3	9	19	10	74	47	79

Abbreviations: TP=true positive; FP=false positive; TN=true negative; FN=false negative

Table 3 - Summary of accuracy indicators of the eight studies included Summary of accuracy indicators of the twelve studies included

Variable	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	AUC (95% CI)	AUC Parcial (95% IC) *	DOR (95% CI)
Overall population	12	0.74 (0.58-0.86)	0.72 (0.20- 0.38)	2.63 (1.81- 3.65)	0.36 (0.20- 0.57)	0.778	0.734	7.98 (3.28- 16.10)
T76Cirrhotic	5	0.84 (0.69- 0.92)	0.77 (0.11- 0.41)	3.84 (1.97-6.94)	0.22 (0.10-0.41)	0.88	0.79	21 (5.50-52-80)
Transplanted	5	0.59 (0.27- 0.85)	0.71 (0.20- 0.41)	1.68 (0.63-3.55)	0.70 (0.24-1.50)	0.64	0.68	3.57 (0.43-13.10)

*Partial AUC (restricted to observed FPRs and normalized)
Abbreviations: CI = confidence interval; AUC = area under receiver operating characteristic; DOR = *odds ratio* diagnostic; LR = likelihood *ratio*

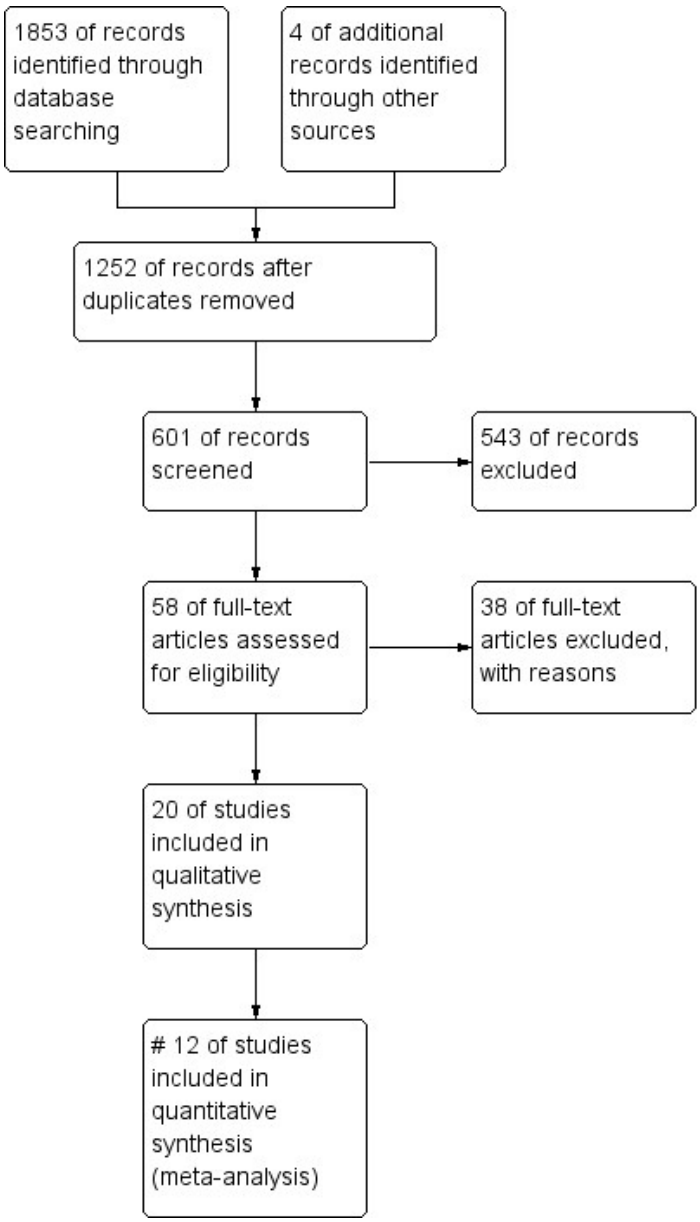
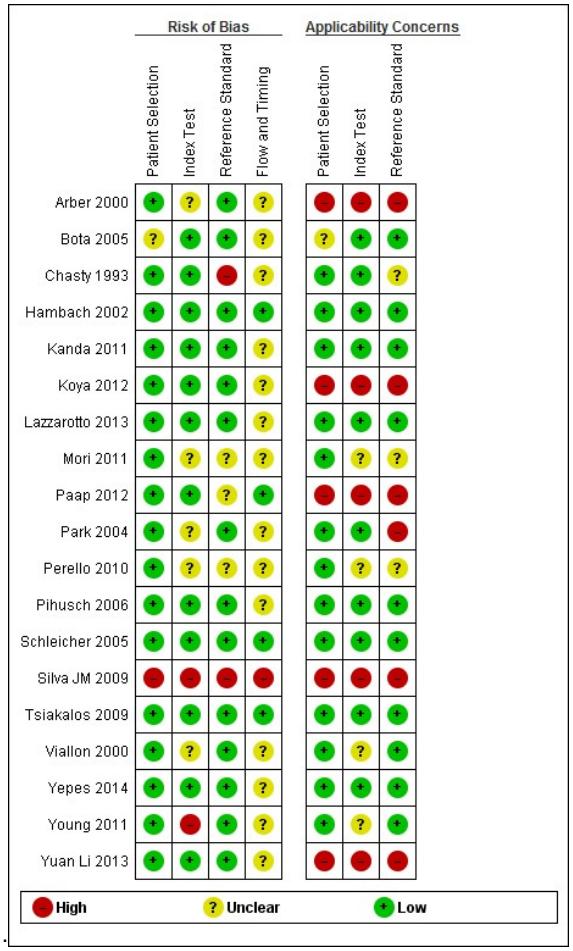


Figure 1 - Flow chart of study identification and inclusion.



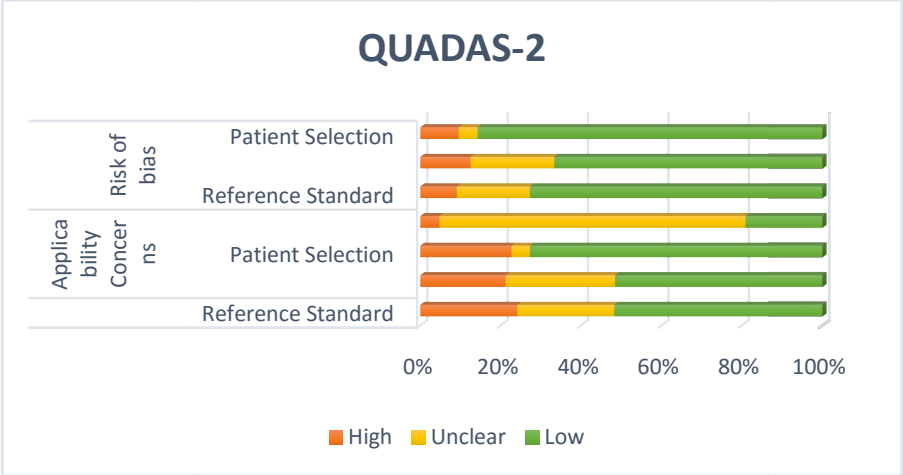


Figure 2 - Quality Assessment of Diagnostic Accuracy Studies criteria for included studies. The consensus judgment of quality criteria is shown as cumulative percentages across the twenty studies included.

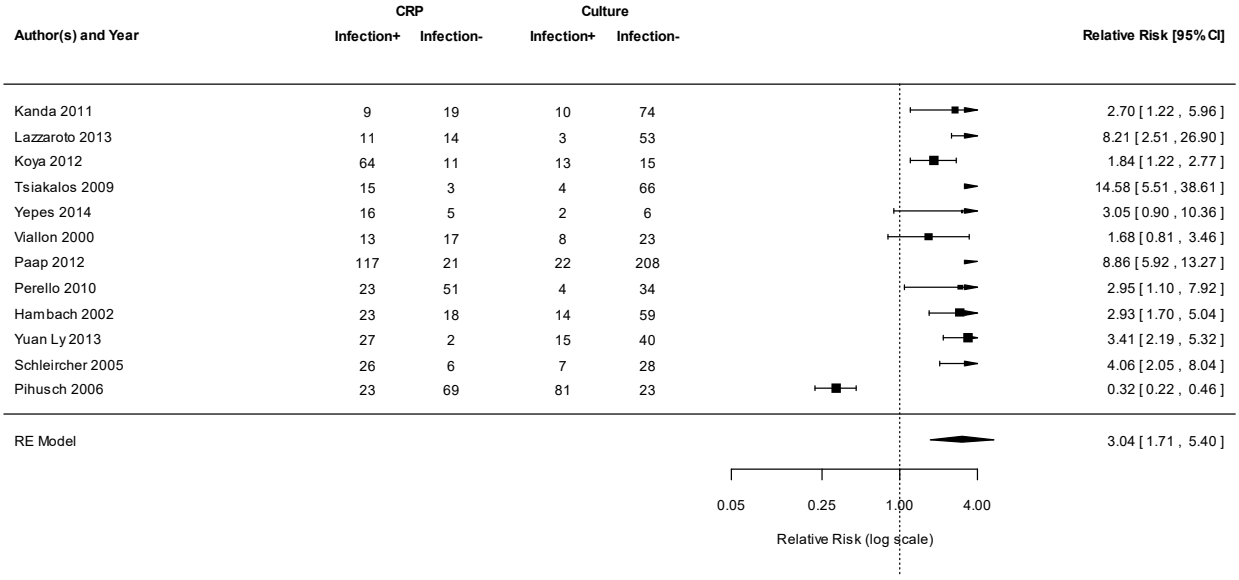


Figure 3 - Forest plot of the diagnostic ORs of studies that used CRP compared with culture.

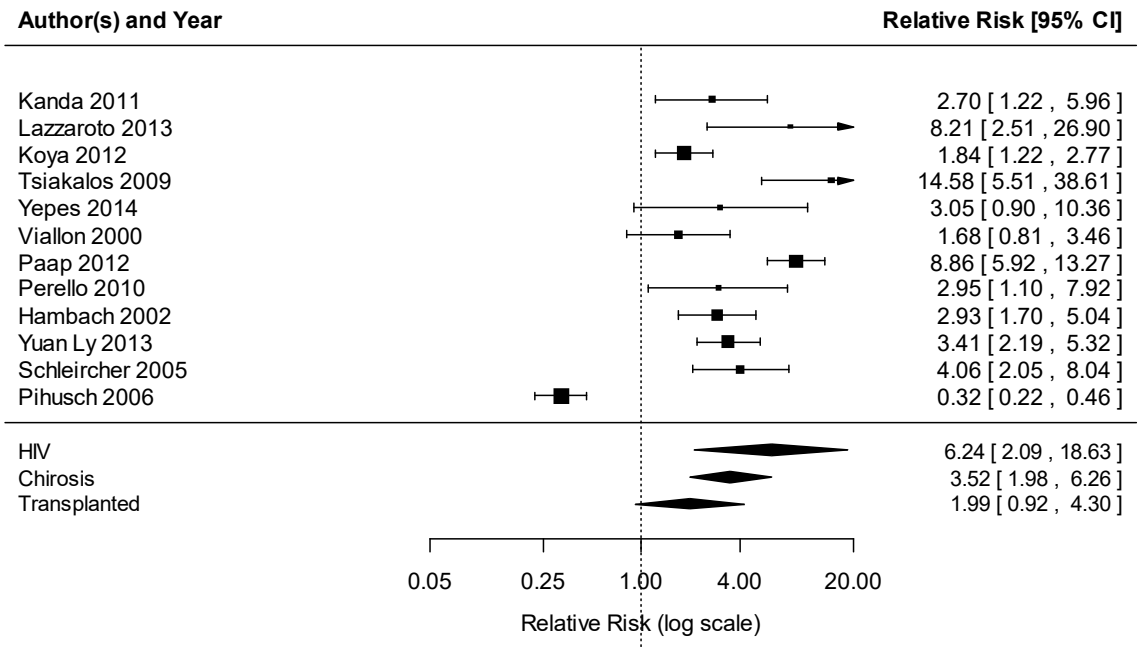


Figure 4-Analysis subgroups for type of population.

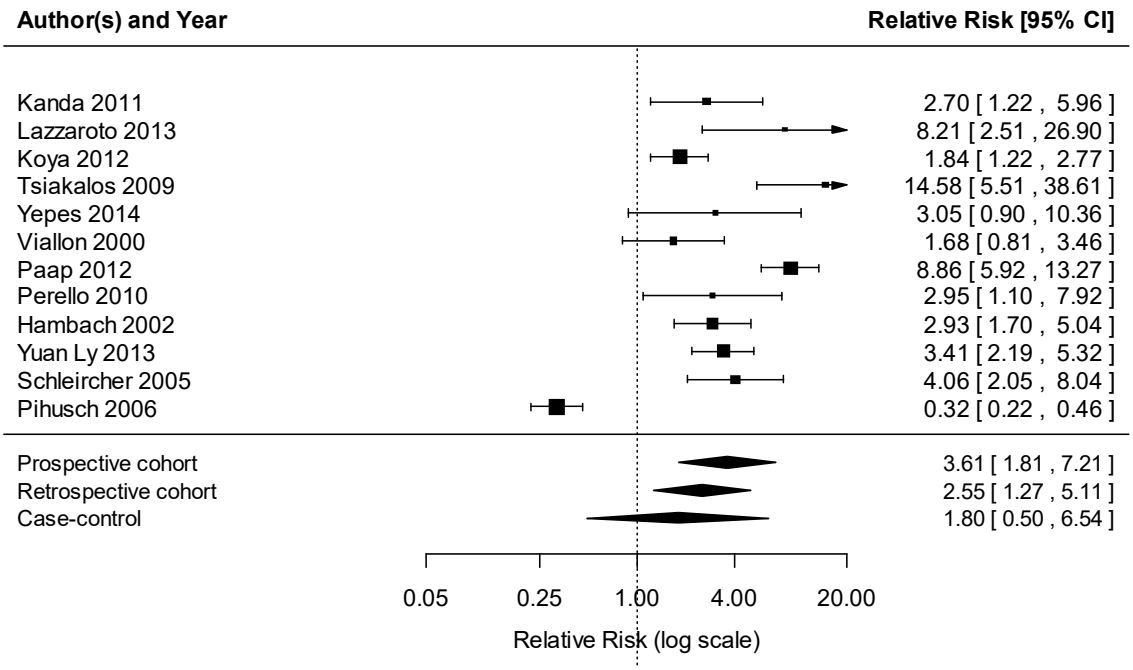
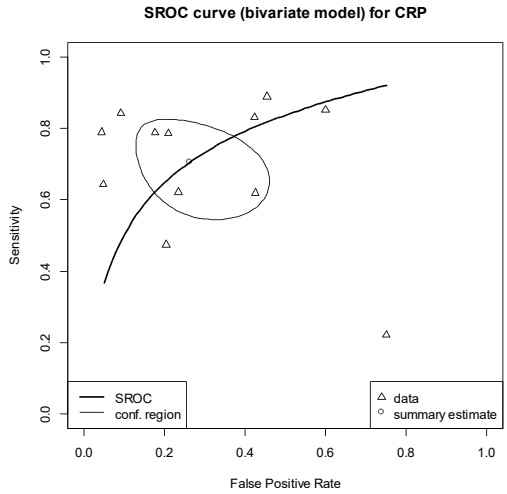
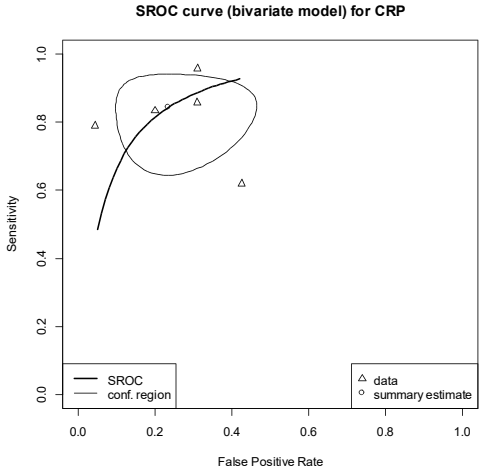


Figure 5- Analysis subgroups for type of study.

Curve A



Curve B



Curve C

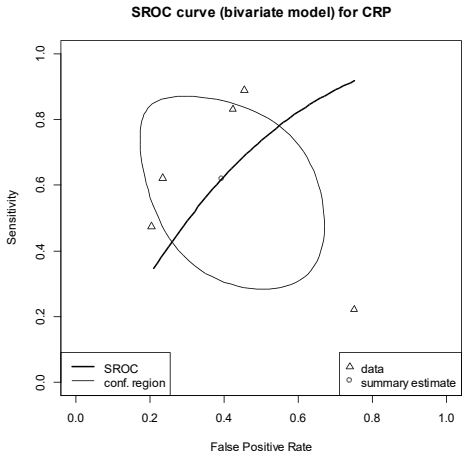


Figure 6- Hierarchical summary receiver operating characteristic (HSROC)curve using CRP for all population (A), CRP for cirrhotic (B) and CPR for the detection of bacterial infection immunocompromised HSCT (after hematopoietic stem cell transplantation) patients (C) for the detection of bacterial infection among patients with chronic liver disease. Solid square: summary estimate; inner dashed line: 95% confidence ellipse; outer dotted

line: 95% prediction ellipse. The symbol size for each study is proportional to the study size.

6 ARTIGO 2

Acurácia da Proteína C Reativa e Procalcitonina como Marcador de Infecção Bacteriana em Pacientes Críticos Imunossupressos: Uma Revisão Sistemática e Metanálise

Accuracy of the C Reactive Protein and Procalcitonin as Bacterial Infection Marker in Immunosuppressed Critical Patients: A Systematic Review and Metanalysis

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Accuracy of the C Reactive Protein and Procalcitonin as Bacterial Infection Marker in immunosuppressed critical patients: a systematic review and metanalysis

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ABSTRACT

Purpose: Sepsis is a major cause of mortality and morbidity in critically ill patients. Procalcitonin (PCT) and C-reactive protein (CRP) are the most frequently used biomarkers in sepsis. We investigated changes in PCT and CRP concentrations in critically ill patients with sepsis to determine the accuracy of PCT, compared with C-reactive protein, to identify bacterial infection in immunosuppressed patients. **Methods:** We searched EMBASE, MEDLINE, LILACS, SCOPUS, Cochrane database, and lists of relevant articles, with no language restrictions, published from inception through October 2015. We selected original research that have reported the diagnostic performance of PCT when compared with CRP to diagnose infectious complication among immunosuppressed critical patients. We used quality assessment of diagnostic accuracy studies tool 2 (QUADAS 2) to evaluate the risk of bias and quality of the articles in this review. We summarized the test performance characteristics by using forest plots, hierarchical smmary receiver operating characteristic curves, with a bivariate random effects model. **Results:** The substantial heterogeneity estimated by the analysis of PCT using random effects methods (REML) indicate that the model was not suitable.So we decided to use the bivariate model. Procalcitonin test had a greater area under the ROC curve value (AUC) (0.78) compared with CRP (0.72). Procalcitonin test showed a pooled sensitivity 0.69 (0.56-0.79) and specificity 0.75 (0.18-0.34) and CPR test, pooled sensitivity 0.68 (0.51-0.81) and specificity 0.71 (0.25-0.34).Procalcitonin had greater specificity and specificity than CRP. The diagnostic ORs for procalcitonin and CRP were 7.24(95% CI (2.83- 14.60) and 5.56 (95% CI (5.21-10.30), respectively. **Conclusions:** The available evidence indicated only a moderate rule out value of both PCT and CRP testing in discriminating bacterial infection following immunosuppressed critical patients.

The protocol was submitted to the PROSPERO register CRD42015019330

Keywords: Bloodstream infection; C-reactive protein; Diagnostic accuracy; Immunosuppressed; Procalcitonin; Sepsis.

BACKGROUND

Sepsis is a major cause of mortality and morbidity in critically ill patients. Early confirmation of systemic inflammation and sepsis, as carried out by PCT measurement, is most relevant for a better prognostic. There are several studies that have confirmed the survival rate of patients with sepsis, who canbe significantly improved, when appropriated antibiotic and therapy had been initiated, as soon as an early diagnostic can be defined [1]. It is more relevant to apply in immunosuppressed patients. Procalcitonin (PCT) and C reactive protein (CRP) are the most frequently used biomarkers for critically ill patients with sepsis[2, 3].

PCT is synthesized physiologically by thyroid C cells but in sepsis has an extra thyroidal origin. The origin of PCT in the inflammatory response is not yet fully understood, but it is believed that PCT is produced ubiquitously during infections, by tissues like the liver, among others [4]. The sensitivity and specificity of serum PCT for diagnosing bacterial sepsis was about 80% in most studies in immunocompetent. Presently, a number of studies and metanalysis point out that PCT is a superior marker than CRP for diagnosis of sepsis and infection in immunocompetent patients[5-7]. Immunocompromised patients can produce high serum PCT concentrations during bacterial sepsis [7].Whether PCT is more specific for infection than cytokines is still debatable[8].

However, few studies have evaluated the diagnostic performance of PCT in immunocompromised patients [8-10]. There is some meta-analyses comparing PCT and CRP in immunocompromised, but not in critically ill patients [11-14]. The objective of the present meta-analysis is to determine whether PCT is more accuracy than CRP as diagnostic marker of sepsis, severe sepsis or septic shock in immunosuppressed adults.

METHODS

We performed this systematic review, in which the guidelines proposed by the Cochrane Handbook for Systematic Reviews of Diagnostic test [15] had been applied. The study protocol was published on PROSPERO register CRD42015019330.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of study to be included

We included all cohort and case-control studies, which have compared C-reactive protein levels, and procalcitonin as a marker of bacterial infection in immunosuppressed patients with the following outcomes: sepsis, severe sepsis and septic shock. Experimental animals' studies, narrative reviews, correspondences, case reports, expert opinions, editorials and studies for which complete data was unavailable were excluded. No limitation was placed on the language of the article.

Condition or domain being studied

Although recently the concept of sepsis has been updated with some modifications, in our study we used the concept of 2001[16] since the articles published until 2015 used this.Outcome condition was the presence of bacterial infection at any stage: infection, sepsis or severe sepsis. The concept of sepsis was that established by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference [16-18]. According to this consensus: microbiological infection should be confirmed or clinically suspected by at least one or more characteristics: white cells in sterile body fluids, drilling viscera, radiographic evidence of healing in combination with purulent sputum, and syndromes

associated with high risk for infection. SIRS (syndrome inflammatory systemic) was set when at least two of the criteria are present: heart rate > 90 bpm /min, respiratory rate > 20 mr /min. or need for mechanical ventilation, body temperature > 38ºC or < 36ºC, leukocytes > 12,000/mm^3 or < 4,000/mm^3. Sepsis was defined as SIRS secondary infection documented by microbiological diagnosis. Severe sepsis was defined as sepsis in the presence of hypotension, hypoperfusion or organ dysfunction. Septic shock was defined as sepsis with refractory hypotension associated with the appropriate amount of volume [16,17]. We include any definition listed above.

Participants/ population

Patients over 18 years with immunosuppression from HIV infection, with any level of CD4, using or no antiretroviral, with any progression of the disease, presence or absence of opportunistic diseases (tuberculosis, pneumocystis); patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid.

Outpatients, pregnant women, post-operative major surgery, acute myocardial infarction, cancer sufferers, rheumatologic conditions, autoimmune and other diseases that cause immunodeficiency were excluded.

Index Test

We include procalcitonin and c reactive protein evaluated by any analytical method described in the individual articles, except ultra-sensitive.

Comparator

C-reactive protein. Studies done with high-sensitivity C-reactive protein were excluded.

Outcomes

The primary outcomes are sensitivity and specificity for the different thresholds. Positive and negative predictive value of procalcitonin with C-reactive protein in detecting sepsis in immunosuppressed patients: HIV positive, tuberculosis, transplant on chronic corticosteroid and cirrhotic were also evaluated.

Search methods for identification of studies

We conducted electronic searches without language or publication status restrictions in the MEDLINE; 1966 to October 2015), EMBASE (1980 to October 2015), SCOPUS (until October 2015) and LILACS (1982 to October 2015), Web of Science (until October 2015) and Cochrane Central Register of Controlled Trials (CENTRAL-The Cochrane Library. The search of the grey literature was conducted through the databases: Bank of Theses (PROQUEST and CAPES) and protocols repository (PROSPERO). We contacted the authors if the information of the selected articles was insufficient to abstract data or were inaccurate.

A Boolean strategy was applied, cross-searching of the following MeSH Terms was done (HIV OR "HIV" [MeSH Terms] OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus [MeSH Terms] OR Acquired Immunodeficiency Syndrome Virus OR aids OR (tuberculosis OR "tuberculosis" [MeSH Terms] OR (liver cirrhosis OR "liver cirrhosis" [MeSH Terms] OR liver cirrhosis) OR ("transplants" [MeSH Terms] OR transplants OR "transplantation"[MeSH Terms] OR transplantation) OR ("glucocorticoids" [MeSH Terms] OR glucocorticoids OR corticosteroids) AND (sepsis OR "sepsis" [MeSH Terms] OR infection OR "infection" [MeSH Terms] OR sepses OR sepse OR sepsi) AND ("c-reactiv protein" OR "protein c-reactive" OR "C-Reactive Protein"[Mesh] OR "c-reative protein" OR "c-reactive protein") AND Procalcitonin (Appendix 1).

Data extraction, (selection and coding)

The selection and data extraction were performed by 2 independent reviewers (VMO and WN), and disagreements, if any, were resolved by a third reviewer (EMW). We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement methodology [19] to report the systematic review and meta-analysis. The details are summarized in Figure 1.

A data collection instrument was developed for the study, in which variables were collected as general characteristics of publication (year, publication journal), general characteristics of the population (age, gender, ethnicity, type of immunosuppression (HIV, tuberculosis, cirrhotic or transplanted), study design (cohort or case-control), severity of infection (sepsis or severe sepsis), and characteristics of the tests (measurement method and thresholds).

Quality assessment

The risk of bias and quality of the studies was evaluated based on t the Quality Assessment of Diagnostic Accuracy Studies Tool 2 (QUADAS 2), which allows for the identification of important design elements in diagnostic accuracy studies[20].The summary of risk of bias assessment are described on Figures 2 and 3.

Data analysis

The following data were extracted from each study included in the meta-analysis were extracted: author, year of publication, place of study, gender, age and number of participants, method of diagnosis, study design, sensitivity and specificity data, positive predictive value (PPV) and negative predictive value (NPV). The data to be extracted were analysed in the following subgroups: classification of type population, type of test, severity of infection.

Forest Plot graph represented the value of each individual study of positive and negative predictive values, sensitivity and specificity of the test, along with their 95 % confidence intervals [15]. R software version 3.2.2 with metafor and mada packages[21, 22] was used to conduct the meta-analysis.

We constructed 2 x 2 contingency table with raw data. The sensitivity (true positive rate), specificity (true negative rate), positive likelihood ratio and negative (LR+, or LR-, is estimated by the ratio of the proportion of positive, or negative, tests in the diseased versus no-diseased subjects) and diagnostic odds ratio (DOR is calculated as the LR+ divided by the LR), with a confidence interval (CI) of 95%, were obtained for each study and subsequently combined. Cochran Q chi-square test and the I^2 statistic were calculated to assess the heterogeneity of the included studies. Random-effects model was used in all analysis, to assume a conservative approach. Additionally, a hierarchical summary receiver operating characteristic (HSROC) curve of the selected studies was plotted. The HSROC curve is a bivariate model that provides information on the overall performance of a test through different thresholds. As the studies presented different thresholds, we used a hierarchical bivariate model to calculate the diagnostic odds ratio (DOR) [15].

Assessment of heterogeneity and reporting bias

We quantified the extent of between-study variations (e.g., heterogeneity) by calculation of the I^2 statistics. The I^2 statistics describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Significant heterogeneity was considered present at $I^2 > 50$ % and extended hierarchical regression models the SROC the arrangement of studies in ROC plots were inspected visually and may suggest the presence of heterogeneity [14-16]. The publication bias were assessed using with Egger regression test[15-17].

Sensitivity analysis

We have defined subgroup analysis based on:

1) Patient characteristics: immunosuppression Type: Carrier tuberculosis, cirrhotic, transplanted, HIV or steroid user, presence of opportunistic infection (pneumocystis, fungi and tuberculosis), corticosteroids if they are measured; 2) For patients with HIV: CD4 measure, and HTLV II and viral load if they are measured, use of antiretroviral informed; 3) Performance Characteristics: method used to measure CRP and procalcitonin and different cut off tests; 4) The design of the study: case-control and prospective or retrospective cohort.

RESULTS

After excluding duplicates 1,573 publications were retrieved and 57 studies were selected for full text reading. The qualitative syntheses included 22 articles and 12 have available data for quantitative analysis (Figure 1). A description of studies included in the systematic review is shown in table 1. The most common causes of exclusion of studies were not meeting the criteria of sepsis, severe sepsis and septic shock and measurement of CRP or procalcitonin for ultrasensivel method.

The quantitative syntheses included four studies with cirrhotic population [13, 23-26], two studies with HIV [27,28] and seven studies with transplant population [29-33]. The studies in transplanted patients are, in general, heterogeneous: some report the data as events (545) and some as individual patients (1.061).

The majority of studies were from Europe, six from Asia [10, 13, 14, 23-25] and USA [26], Latin America [27,28] and South Africa [11] contributed with one study each, respectively. We found four case-control and fifteen cohort studies, being the majority, prospective. The number of participants included in each study varies from 17 to 864 (Tables 1 and 2).

It was not possible analyse of the following groups: carrier of tuberculosis, steroid user, presence of opportunistic infection due to the lack of information described on the articles on this subject;Groups included HIV patients, cirrhotic and transplant some of the information planned to be collected in the protocol had no data available.

Most of the studies used a LumiTest (Brahms Diagnostic) for PCT measurement and different methods for CPR (Tables 2 and 3).

Overall, a low risk of bias, in the applicability domain, had been identified in the studies (Figure 2). Some studies used clinically documented infection as an outcome definition but did not clearly describe whether clinical diagnosis was independent of the biomarker tests. None of the included studies described whether the physicians were blinded with regard to the index tests when they made the diagnosis of bacterial infection. In addition, none of the included studies explicitly provided explanations for withdrawal, and none showed uninterpretable results. No significant evidence of potential publication bias was noted using the Egger's test($z = 3.24$; $p < 0.01$).

Diagnostic accuracy indices

It was estimated by random effects methods (REML) with 12 studies simultaneously with DOR 3.04 (1.71-5.40) (Figure 3). We observe evident of significant heterogeneity (I^2: 92.44%, $Q = 155.61$, $p < .0001$). Heterogeneity is common in diagnostic studies and attribute to different cut offs of the studies. We used a Meta regression to investigate the role of these different thresholds in heterogeneity. The different cut-off significant influence the diagnostic accuracy and explain 10% of the heterogeneity. The test for residual heterogeneity is significant ($I^2 = 80.67\%$; $p < 0.001$), indicating that other moderators not considered in the model are influencing the PCT accuracy (Figure 3).

Subgroup analysis

In order to explore the high heterogeneity found, we performed subgroup analysis by restricting studieswith similar population, type of study and bivariate model. It was not possible analysis of the following groups: carrier tuberculosis, steroid user, presence of opportunistic infection proposals to the protocol for lack of this information in articles.

Type of Population

Two studies were with HIV population [27, 28] with DOR for procalcitonina was 11.76 (95% IC 3.29-41.98), I^2=0%, Q= 0, p= 1. It had not been possible to analyse by subgroup the following measures: CD4, HTLV II, viral load and use of antiretroviral, as there was a lack of this information on these exams. The diagnostic OR for procalcitonin was 4.79(95% IC 2.52-9.10), I^2= 52.78%, Q=6.59, p< 0.09 in four studies with cirrhotic patients[13, 23-26].Most of the studies with transplanted patients included hematologic stem cell transplantation [29, 30, 31, 32, 33]with a DOR of 1.96 (95% IC 1.08-3.54), I^2= 91.24%, Q=83.57, p< 0.0001). The heterogeneity, however, did not change transplanted, but shows a slightly decrease for cirrhotic population(52.78%; p = 0.08) (Figure 4).

Type of studies

When we stratified the data by type of studies, analysing only the prospective cohort studies[11-13, 27, 29, 30], we found a DOR of 3.19(95% IC 1.56-6.52), but the heterogeneity still high (I^2: 80.01%, Q= 32.36; p<0.0001). The same was observed for retrospective cohort [14, 31] (DOR 2.93; 95% CI 1.50-5.72; Q=0; p=1) and case-control studies[23, 25] (DOR = 2.69, 95% (IC 0.83-8.70);I^2:79.03%, Q=7.43;p=0.02) (Figure 5).

Even using subgroup analysis for population and type of study heterogeneity remained substantial, so we decided to use the bivariate model raising the hypothesis that heterogeneity would be caused by the different cut off for the included studies.

In order to explain and solve the heterogeneity we applied the hierarchical bivariate model who takes in account the different cut off and assume that specificities and sensitivities are different in it study. A bivariate model was use then to account for different thresholds.

A bivariate model was used to estimate the pooled effect size for procalcitonin and CRP. The AUC for PCT (0.79) is lightly higher than the CRP (0.73) curve. PCT test showed a pooled sensitivity 0.69 (0.56-0.80) and specificity 0.75 (0.65-0.83) (Figure 6) and CPR test, pooled sensitivity 0.70 (0.51-0.83) and specificity 0.71 (0.67-0.76) (Figure 6).Both measures have similar specificities and sensitivity. Procalcitonin had a high positive likelihood ratio LR + 2.83 (95% IC: 1.74-4.53) than CRP (LR+ 2.39[95% CI (1.66-3.08)making it and little better test for the diagnosis of infectious complications in immunosuppressed critical patients. The diagnostic ORs for PCT and CRP were 7.58(95% CI (2.69- 17.07) and6.04(95% CI (2.36-3.30) (Figure 6).

DISCUSSION

Procalcitonin and CRP presented a good capacity differentiate effectively between infection and systemic inflammatory response syndrome of non-infectious origin. PCT have a better diagnostic property than CRP to diagnose infection.

Previously, two meta-analyses have investigated the diagnostic accuracy of procalcitonin in immunocompetent critically ill patients[5,7], with conflicting results Uzzanand colleagues [5] in metanalysis in critically ill adults (2,966 patients) with trauma. It had reported for PCT (2,966 patients), sensitivities ranged from 42% to 97% and specificities ranged from 48% to 100%. The optimal cut off values for PCT, determined from the ROC

curves, ranged from 0.78 (0.71-0.84) to 5 ng/mL and for CRP sensitivities ranged from 35% to 100%, and specificities ranged from 18% to 85%. Cutoff values for CRP ranged from 39 mg/L to 180 mg/L. The SROC for procalcitonin was better than for C-reactive protein for identification of sepsis. (Q* value for PCT 0.78; 95% CI, 0.71-0.84 vs. Q* value for CRP 0.71; 95% CI, 0.64-0.76). However, the investigators restricted the population to surgery or trauma patients and applied a univariate model in spite of high heterogeneity between studies. Tang and colleagues [7](1,602 patientes) concluded that the diagnostic accuracy of PCT was sensitivity and specificity were both 71% (95% IC:0.67-0.76) and AUC was 0.78 (95% CI 0.73-83) in immunocompetent patients, similar to the values found in our analysis for immunosuppressed. This metanalysis had some limitations: ruled out packages with septic shock and studies with typical sources of sepsis (abdominal focus, meningitis and pancreatitis) and thepatients with infection and sepsis were not separated.

Wacker *et al.* in recent metanalysis [34] in 3,244 immunocompetent critically ill patients showed, PCT is a helpful biomarker for diagnosis of sepsis with pooled sensitivity was 0.77 (95% CI 0.72-0.81) and pooled specificity was 0.79 (95% CI 0.74-0.84); AUC 0.85 (95% CI 0.81-0.88).Bivariate model was applied, but heterogeneity was not explored. In our metanalysis in immunosuppressed showed procalcitonin test showed a pooled sensitivity 0.69 (0.56-0.80) and specificity 0.75 (0.65-0.83) with AUC 0.78 and CPR test showed a pooled sensitivity 0.70 (0.51-0.83) and specificity 0.71 (0.67-0.76) with AUC 0.79 and 0.73, respectively, similar literature for immunocompetent critical patients.

Lin *et al.*[11], metanalysis in cirrhotic patients, showed higher performance of biomarkers when comparing our results. The bivariate of metanalysis of cirrhotic patients a pooled in sensitivity estimates were 79% (95% confidence interval [CI]: 64%-89%) for PCT tests and 77% (95% CI: 69%-84%) for C-reactive protein (CRP) tests. Pooled specificity estimates were higher for both PCT and CRP tests (PCT, 89% [95% CI: 82%-94%]; CRP,

85% [95% CI: 76%-90%]). The results showed good performance of PCT with AUC 0.92 and CPR with AUC 0.87.This meta-analysis has selection problems where patients were mixed with spontaneous bacterial peritonitis and sepsis

In group of transplant population, recent meta-analysis published by Lyu *et al*.[12]was using pooled data of six studies from 1,344 immunocompromised HSCT (after hematopoietic stem cell transplantation) applied bivariate model. Bivariate pooled sensitivity and specificity were 0.66 (95% confidence interval [CI] 0.60-0.72) and 0.72 (95% CI 0.65-0.79) for PCT, and 0.80 (95% CI 0.54-0.93) and 0.73 (95% CI 0.56-0.86) for CRP. In terms of area under the curve (AUC), CRP was superior to PCT in detecting infectious complications, with an AUC of 0.82 for CRP versus an AUC of 0.69 for PCT. This result is different our results that PCT had moderate performance and CPR had better performance PCT.Explain these different results by the difference of the population selected in this meta-analysis (2 studies in children are exclusion criteria of our study), studies include dates with population data and events which can influence summarization of the estimated accuracy.

There is not in the meta-analysis literature with the population of HIV patients.

The strengths of our study is the extensive literature search and the attempt to include all immunosuppresses groups and on its compliance with criteria for performing, a rigorous systematic review and we have used a standard tool to evaluate the risk of bias for the included study. The statistical method used is another strong point of this meta-analysis. Bypassing a common problem in the meta-analysis of diagnostic studies that a wide range of different cut-off values we did not pool the sensitivity and specificity directly. Instead, we constructed the hierarchical summary receiver operating characteristic curve, which consists of pairs of sensitivities and false-positive rate (1–specificity) from each included study. In addition, we used a bivariate modelling approach that allows adjustment of dependency

inherent in the paired sensitivity and specificity, and can derive the summary sensitivity and specificity independent of the threshold effect caused by different cut-off values used.

As weaknesses of our study, the limitation may be the relatively small number of studies and pooled sample size. The small number of studies available for our review prevented us from performing more extensive subgroup analysis. The less precise estimates of pooled effect make a definitive conclusion difficult. Most of the included studies did not clearly presents a description of when was the index test evaluate, as was the pattern and loss of patients and the different cohort of points used by studies to establish infection. Variation in clinical criteria used to define severe systemic infection across studies and the differing aetiologies of fever among the groups compared and different cut-offs values in the selected studies were also a source of heterogeneity.

CONCLUSION

In conclusion, based on the available studies, the diagnostic performance of PCT is not compromised in immunosuppressed critical patients, independent of the type of immunosuppression. The results showed good accuracy of biomarkers for both PCR as procalcitonin in immunosuppressed critical patients, but should not be used in isolation but must be interpreted in the context of history, physical and microbiological examination. Analysis of the pooled data suggests that procalcitonin is slightly more specific indicator of bacterial infection than CRP.

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Author contributions: Acquisition of data: O.V.M. Selection and analysis risk of bias studies: O.V.M; N.W.L and W.E.M. Analysis and interpretation of data: O.V.M and W.E.M Drafting of the manuscript: O.V.M; W.E.M and S.A.T

Conflict of interest: None declared.

Table 1 - Characteristics of the twenty included studies that used biomarkers to assess patients with sepsis, severe sepsis and septic shock

Author, year	Country	Age (Median)	Sex (M/F)	Population	Study Design	Outcome definition
Blijlevens 2000	Netherlands	NR	5/7	HSCT	Prospective Cohort	Skin Sepsis, sepsis without focus
Hambach 2002	Germany	40	37/24	HSCT ALO	Prospective Cohort	Sepsis
Pihusch 2006	Germany	40	206 /144	HSCT ALO	Retrospective Cohort	Severe sepsis/septic shock
Prat2008	Germany	47 (15-69)	31/30	HSCT	Prospective Cohort	sepsis
Mori 2011	Japan	54	NR	HSCT ALO	Case-control	Sepsis
Koivula 2011	Finland	56(18-70)	46/23	HSCT ALO	Prospective Cohort	Severe sepsis/septic shock/sepsis
Sato2014	Japan	NR	45/34	HSCT	Prospective Cohort	sepsis
Yepes 2014	Spain	48,47	17/12	HSCT	Cohort prospective case-control neast	Sepsis
Schuttrumpf 2003	Germany	53 (18-69)	43/52	HSCT	Prospective Cohort	Sepsis
Connert 2003	Dorsten	57(19-92)	77/50	Liver cirrhosis	Prospective Cohort	Abdominal sepsis
Bota 2005	Belgium	56	414/450	Liver cirrhosis	Prospective case-control	Pulmonary, abdominal sepsis
Li2011	Taiwan	62 (57–67)	66/32	Liver cirrhosis	cross-sectional diagnostic study	Abdominal sepsis
Paap 2011	Hungray	58	204/164	Liver cirrhosis	Cohort prospective	Pulmonary, abdominal, ITU sepsis
Lazarotto 2013	Brazil	54	44/20	Liver cirrhosis	Prospective Cohort	Pulmonary, abdominal, skin sepsis
Schleicher 2005	South Africa	33.5	32/35	HIV	Prospective Cohort	Pulmonary sepsis
Mikula 2011	Poland	35	60/42	HIV	Prospective Cohort	Severe sepsis/septic shock/sepsis
Polzin 2003	Germany	NR	NR	tuberculosis	Prospective Case-control	sepsis

* Hematologic or other malignancy treated by high-dose chemotherapy and/or stem cell transplantation; solid organ transplantation; AIDS; long-term corticosteroid therapy (*ie*,20mg/d prednisone equivalent for 2 months); and current use of immunosuppressive or cytotoxic medication for indications other than organ or stem cell transplantation.

*Mean age (DP). Abbreviations: HSCT= after hematopoietic stem cell transplantation, ALO = allograft

NR-not reported

Table 2 - Diagnostic characteristics of thetwelve studies with procalcitonin included in the quantitative analysis

Author, year	Prevalence	Procalcitonin assay	Cut off (ng/ml)	TP	FP	TN	FN	Sensivity (%)	Specificity (%)
Koya 2012	0.92	Chemiluminescent enzyme immunoassay	0.5	59	5	18	21	76	80
Lazzaroto 2013	0.54	Chemiluminescent enzyme immunoassay	1.1	11	13	3	54	78	80
Paap 2012	0.37	Immunoluminometric assay LUMItest PCT	0.5	100	37	39	192	71	83
Pihusch 2006	0.56	Immunoluminometric assay LUMItest PCT	5.7	23	69	81	23	22	25
Schleircher 2005	0.49	Immunoluminometric assay LUMItest PCT	0.3	27	6	6	28	81	82
Hambach 2002	0.67	Immunoluminometric assay LUMItest PCT	0.5	26	30	11	47	70	61
Yepes 2014	0.62	Chemiluminescent enzyme immunoassay	0.0005	12	3	6	8	66	72
Connert 2003	0.36	Immunoluminometric assay LUMItest PCT	0.58	33	14	3	50	91	78
Koivula 2011	0.31	Immunochromatographic rapid procalcitonin test PCT-Q	0.5	12	12	9	52	57	81
Li 2011	0.27	NA	0.49	40	9	2	33	95	78
Prat 2008	0.53	Immunoluminometric assay LUMItest PCT	0.5	16	6	26	31	38	83
Sato 2014	0.81	Electrochemiluminescence immunoassay method	0.07	17	10	9	43	65	81

TP=true positive; FP=false positive; TN=true negative; FN=false negative

Table 3 - Diagnostic characteristics of the twelve studies with CRP included in the quantitative analysis

Author, year	Prevalence	PCR assay	Cut off (mg/ml)	TP	FP	TN	FN	Sensivity (%)	Specificity (%)
Koya 2012	0.92	Immunoturbidimetric assay	4	64	11	13	15	83	57
Lazzaroto 2013	0.54	Nephelometry	5	11	14	3	53	78	79
Paap 2012	0.37	Integra 700 automated analyser system	10	133	71	6	158	84	90
Pihusch 2006	0.56	Methods on automatic analyzer (Hitachi, Roche).	50	24	16	127	29	22	25
Schleircher 2005	0.49	Nephelometry	24.6	26	6	7	28	78	82
Hambach 2002	0.67	Turbidimetry	10	23	18	14	49	62	76
Yepes 2014	0.62	Cobas® c501 Roche	7.5	15	5	2	7	88	54
Connert 2003	0.28	Immunoturbidimetric assay	0.5						
Koivula 2011	0.23	Cobas® c501 Roche	10	11	24	10	43	52	64
Li 2011	0.26	NA	2.4	21	14	5	57	80	80
Prat 2008	0.40	(TRACE) (CRPus KRYPTOR)	2	10	7	16	31	38	81
Sato 2014	0.48	Latex agglutination assay	0.25	22	13	16	28	57	68

TP=true positive; FP=false positive; TN=true negative; FN= false negative

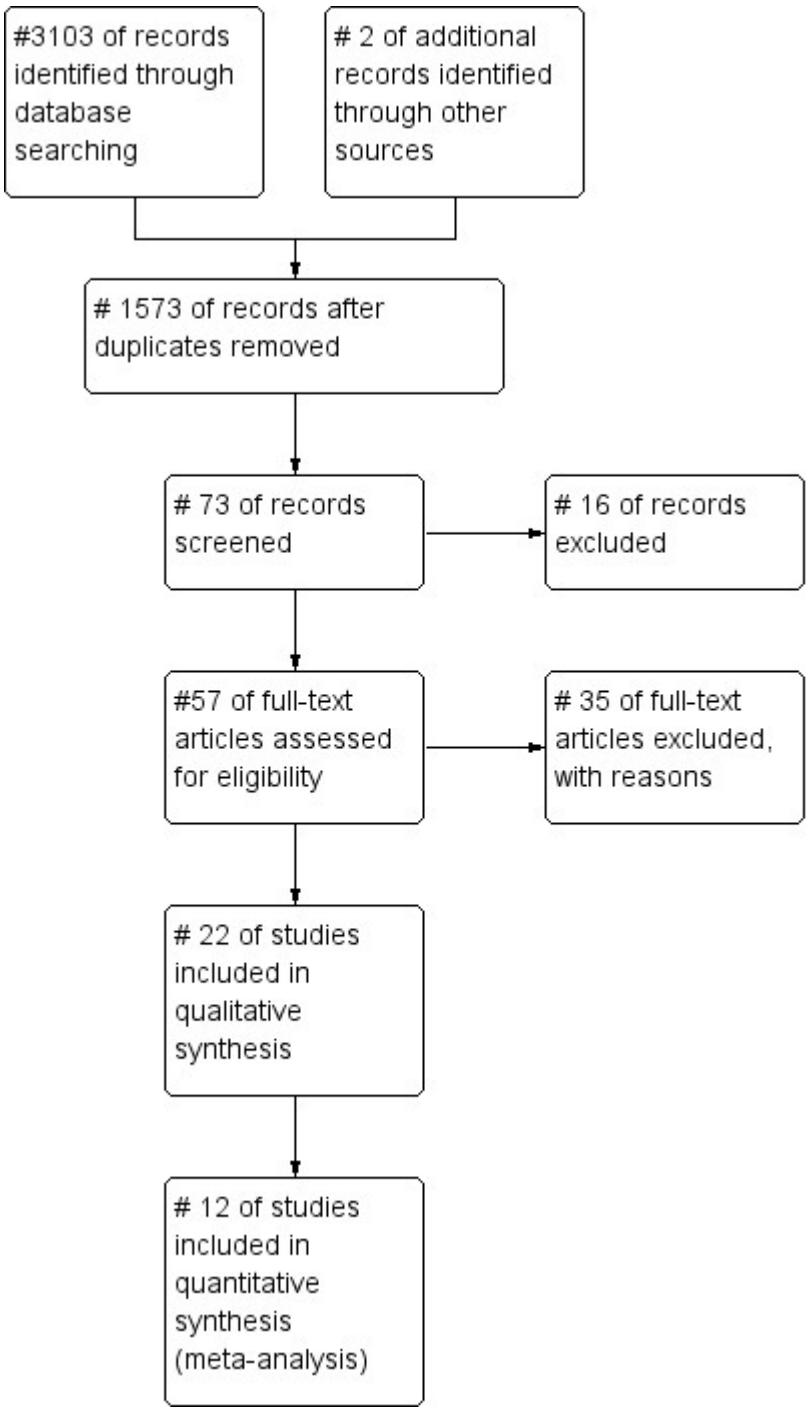


Figure 1 -Flow chart of study identification and inclusion.

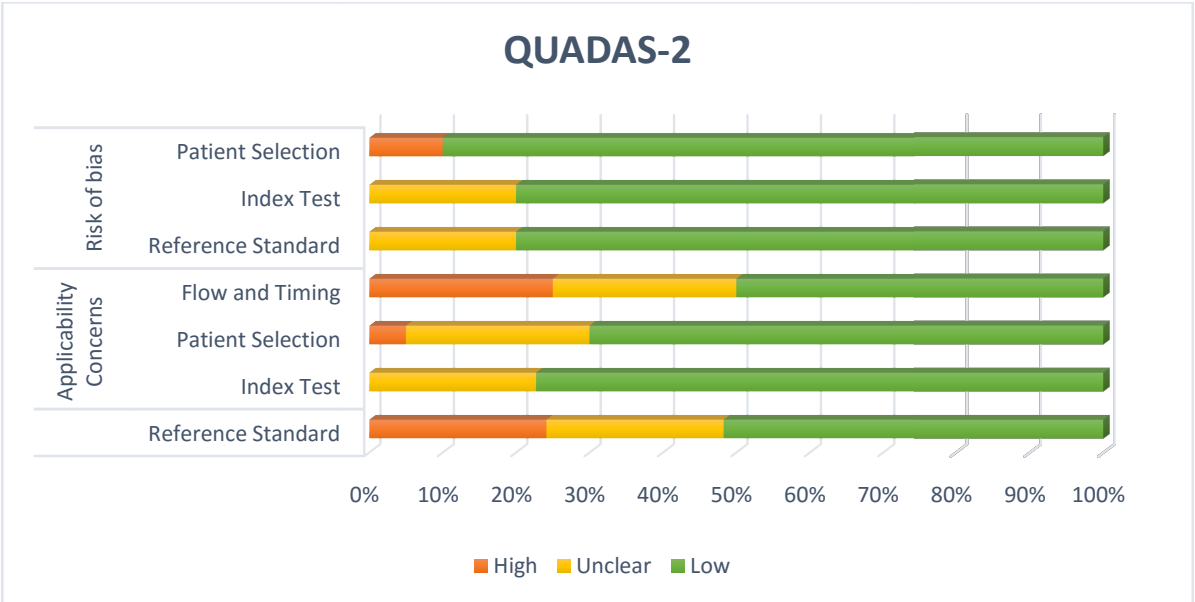


Figure 2 - Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

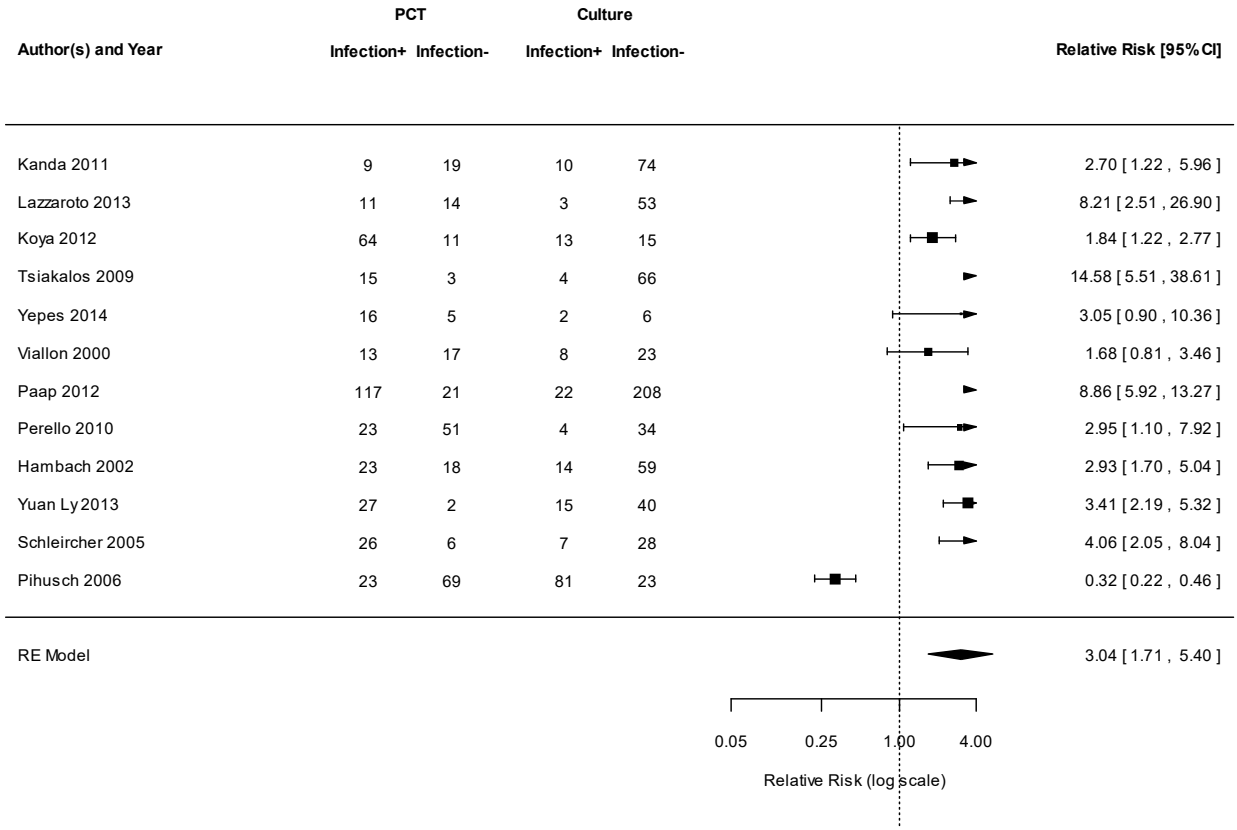


Figure 3 - Forest plot of the diagnostic ORs of studies that used procalcitonin compared with culture.

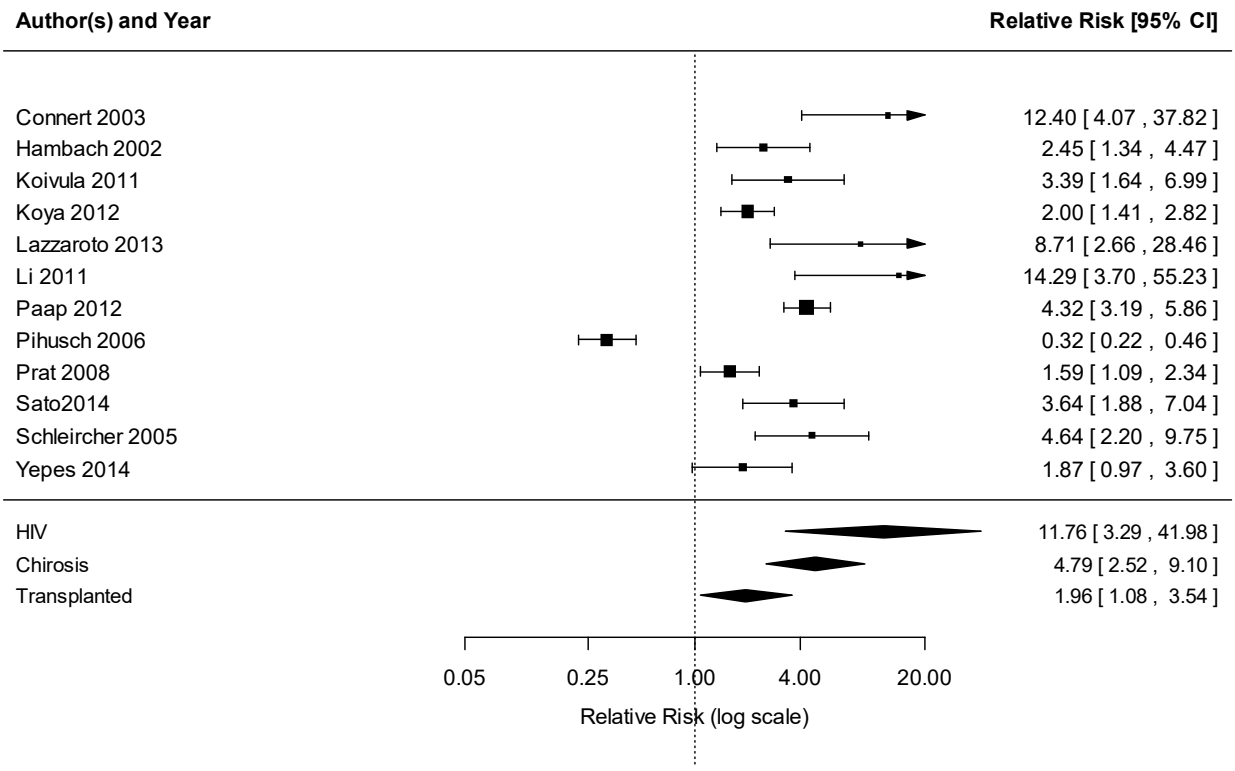


Figure 4 -Analysis subgroups for type of population.

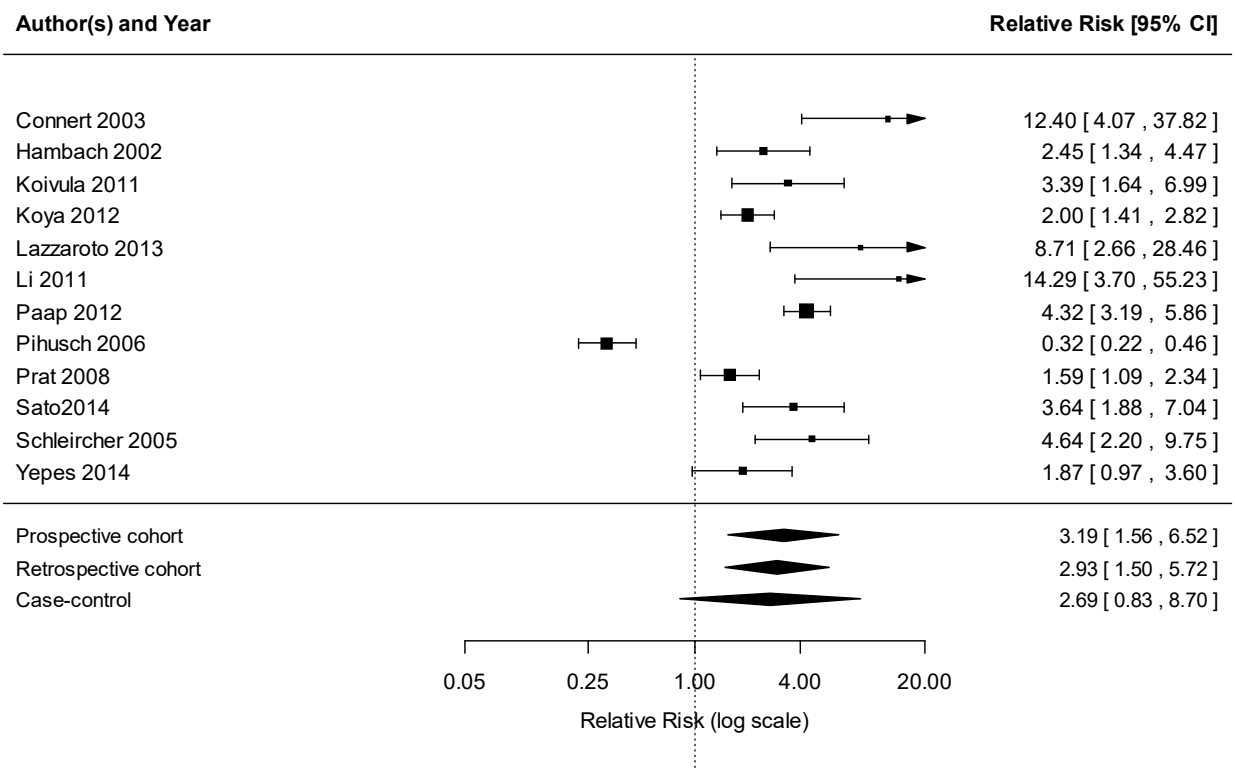
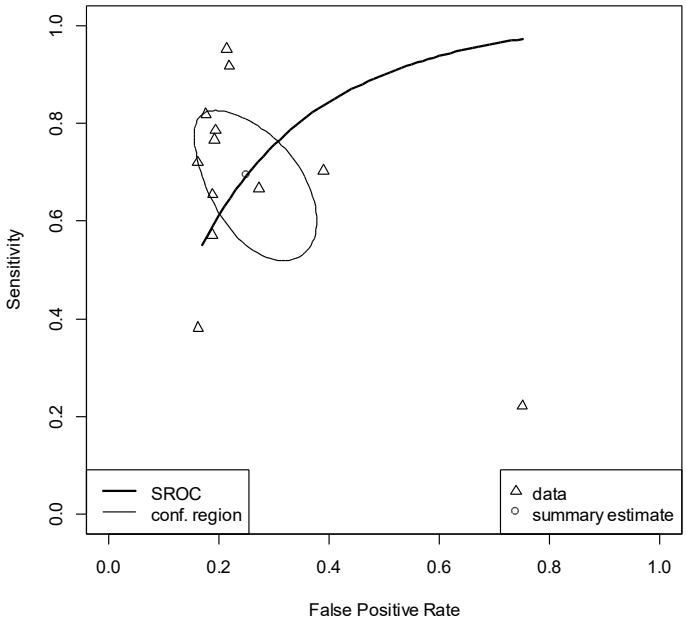


Figure 5 - Analysis subgroups for type of study.

A - SROC curve (bivariate model) for PCT



B e C - SROC curve (bivariate model) for CRP and PCT

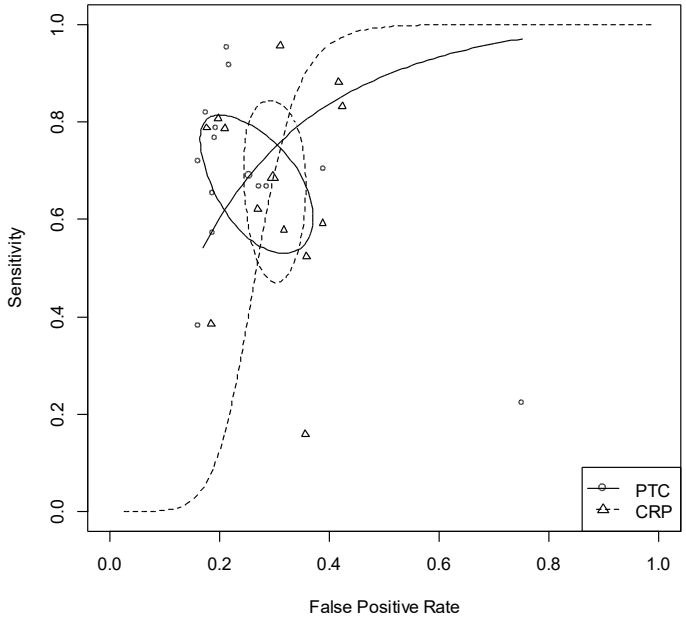


Figure 6 - Hierarchical summary receiver operating characteristic (HSROC) curve using procalcitonin for all population (A), CRP for all population (B) and SROC curve using bivariate model compared for PCT and CPR inimmunocompromised (C) for the detection of bacterial infection among patients with chronic liver disease. Solid square: summary estimate; inner dashed line: 95% confidence ellipse; outer dotted line: 95% prediction ellipse. The symbol size for each study is proportional to the study size.

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APPENDIX 1

Electronic search strategies

MEDLINE

#11	(Search ((((((((((HIV) OR "HIV"[MeSH Terms]) OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus[MeSH Terms]) OR Acquired Immunodeficiency Syndrome Virus) OR aids))))) OR (((HIV) OR "HIV"[MeSH Terms]) OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus[MeSH Terms]) OR Acquired Immunodeficiency Syndrome Virus) OR aids))))) OR (((tuberculosis) OR "tuberculosis"[MeSH Terms])))) OR ((("glucocorticoids"[MeSH Terms]) OR glucocorticoids) OR corticosteroids)))) OR ((("transplants"[MeSH Terms]) OR transplants) OR "transplantation"[MeSH Terms]) OR transplantation))))) AND ((((sepsis) OR "sepsis"[MeSH Terms]) OR infection) OR "infection"[MeSH Terms])))))) AND ((((((procalcitonin[Text Word]) OR calcitonin[MeSH Terms]))))) AND ((((("c-reactiv protein") OR "protein c-reactive") OR "C-Reactive Protein"[Mesh]) OR "c-reative protein") OR "c-reactive protein"))))))	**1067**
#10	Search((((((((((HIV) OR "HIV"[MeSH Terms]) OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus[MeSH Terms]) OR Acquired Immunodeficiency Syndrome Virus) OR aids)))) OR (((((liver cirrhosis) OR "liver cirrhosis"[MeSH Terms]) OR liver cirrhosis))))) OR ((((tuberculosis) OR "tuberculosis"[MeSH Terms])))))) OR ((((("glucocorticoids"[MeSH Terms]) OR glucocorticoids) OR corticosteroids))))) OR ((((("transplants"[MeSH Terms]) OR transplants) OR "transplantation"[MeSH Terms]) OR transplantation))))	1650882
#9	Search (((((sepsis) OR "sepsis"[MeSH Terms]) OR infection) OR "infection"[MeSH Terms]))	1367965
#8	Search (#6 OR #7)	68521
#7	Search (procalcitonin[Text Word]) OR calcitonin[MeSH Terms]	15263
#6	Search (((((("c-reactiv protein") OR "protein c-reactive") OR "C-Reactive Protein"[Mesh]) OR "c-reative protein") OR "c-reactive protein")	54838
#5	Search ((("transplants"[MeSH Terms]) OR transplants) OR "transplantation"[MeSH Terms]) OR transplantation)))	622525
#4	Search((("glucocorticoids"[MeSH Terms]) OR glucocorticoids) OR corticosteroids)))	381099
#3	Search(((tuberculosis) OR "tuberculosis"[MeSH Terms])))	221747
#2	Search((((liver cirrhosis) OR "liver cirrhosis"[MeSH Terms]) OR liver cirrhosis)))	98493
#1	Search(((((((HIV) OR "HIV"[MeSH Terms]) OR Human Immunodeficiency Virus) OR Human Immunodeficiency Virus[MeSH Terms]) OR Acquired Immunodeficiency Syndrome Virus) OR aids))	394625

EMBASE

		Resultados
#12	('human immunodeficiency virus'/exp OR 'acquired immune deficiency syndrome' OR ('acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp) OR 'transplantation'/exp OR 'glucocorticoid'/exp OR 'alcohol liver cirrhosis'/exp OR 'tuberculosis'/exp) AND 'sepsis'/exp AND 'c reactive protein'/exp AND 'procalcitonin'/exp	157
#11	'procalcitonin'/exp	6258
#10	'c reactive protein'/exp	105960
#9	'sepsis'/exp	190931
#8	'human immunodeficiency virus'/exp OR 'acquired immune deficiency syndrome' OR ('acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp) OR 'transplantation'/exp OR 'glucocorticoid'/exp OR 'alcohol liver cirrhosis'/exp OR 'tuberculosis'/exp	1800524
#7	'tuberculosis'/exp	213313
#6	'alcohol liver cirrhosis'/exp	7696
#5	'glucocorticoid'/exp	598552
#4	'transplantation'/exp	823426
#3	'acquired immune deficiency syndrome'/exp OR 'human immunodeficiency virus'/exp	254926
#2	'acquired immune deficiency syndrome'	128288
#1	'human immunodeficiency virus'/exp	152292

LILACS

Population		
#1	HIV [Descritor de assunto]or Human Immunodeficiency Virus$ [Palavras]orAcquired Immunodeficiency Syndrome Virus$ [Palavras]	3407
#2	Transplantation$ [Palavras]orTransplantation [Palavras]or transplantation [Descritor de assunto]	9027
#3	"corticosteroids" [Descritor de assunto]or "glucocorticoids" [Descritor de assunto]or"glucocorticoids" [Palavras]	655
#4	"tuberculosis" [Descritor de assunto]ortuberculose [Palavras]ortuberculosis [Palavras]	7470
#5	"cirrose do figado" [Descritor de assunto]orcirrose [Descritor de assunto]ocirrose do figado [Palavras]	1405
Test		
#6	"proteina c-reactiva" [Palavras]or"proteina c-reativa" [Descritor de assunto]or"c reactive protein" [Palavras]	467
#7	procalcitonina [Descritor de assunto]orprocalcitonina or procalcitonin [Palavras]orprocalcitonin [Descritor de assunto]	48
Outcome		
#8	sepse$ or sepsi$ [Palavras]or"sepse" [Descritor de assunto]or"sepsis" [Descritor de assunto]	4649
#1 OR #2 OR #3 OR #4 OR #5 AND #6 AND #7 AND #8	**"cirrose" or "cirrose do figado" or "tuberculosis" or hiv or transplantation or "corticosteroids" or "glucocorticoids" [Palavras]andsepse$ or sepsi$ or "sepse" or "sepsis" [Palavras]and" procalcitonina [Descritor de assunto]orprocalcitonina or procalcitonin [Palavras]orprocalcitonin [Descritor de assunto]**	**0**

CENTRAL

#"c-reactive protein and procalcitonin 53

WEB OF SCIENCE

#12	#11 AND #10 AND #9 AND #8	95
#11	Tópico:((Sepse) OR("sepse") OR (Sepsis) OR ("sepsis"))	78.767
#10	**Tópico:**((procalcitonin) OR ("procalcitonin") OR (calcitonin))	27.434
#9	**Tópico:**((c reactive protein) OR ("c reactive protein"))	94.646
#8	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	736.130
#7	**Tópico:**(("liver cirrhosis") OR (liver cirrhosis) OR (liver cirrhosis$))	56.265
#6	**Tópico:**(("tuberculosis") OR (tuberculosis) OR (tuberculosis$))	112.906
#5	**Tópico:**(Tópico: ("tuberculosis") OR Tópico: (tuberculosis) OR Tópico: (tuberculosis$))	0
#4	**Tópico:**(("glucocorticoids") OR (Glucocorticoids) OR (“Corticosteroids”) OR (Corticosteroids) OR (corticosteroids$))	103.290
#3	**Tópico:**(Tópico: ("glucocorticoids") OR Tópico: (Glucocorticoids) OR Tópico: (“Corticosteroids”) OR Tópico: (Corticosteroids) OR Tópico: (corticosteroids$))	0
#2	**Tópico:**((Transplantation) OR (Transplantation$))	378.120
#1	**Tópico:**((Human Immunodeficiency Virus) OR Tópico: (Human Immunodeficiency Virus$) OR Tópico: (Acquired Immunodeficiency Syndrome Virus) OR Tópico: (Acquired Immunodeficiency Syndrome Virus$) ORTópico: (Aids) OR Tópico: (Aids$))	113.951

SCOPUS

#22	(("sepsis")) AND (procalcitonin) AND (("c reactive protein")) AND ((("liver cirrhosis")) OR (("cirrhosis"))) OR ((("tuberculose")) OR (("tuberculosis"))) OR ((("glucocorticoids")) OR (("Corticosteroids")) OR (("Corticosteroides"))) OR ((("Transplantation")) OR (("Transplant"))) OR ((("HIV")) OR (("Human Immunodeficiency Virus")) OR (("Acquired Immunodeficiency Syndrome Virus"))))	1.731
#21	("sepsis")	271.399
#20	procalcitonin	11.874
#19	("c reactive protein")	177.076
#18	((("livercirrhosis")) OR (("cirrhosis"))) OR ((("tuberculose"))OR (("tuberculosis"))) OR ((("glucocorticoids")) OR (("Corticosteroids")) OR (("Corticosteroides"))) OR ((("Transplantation")) OR (("Transplant"))) OR ((("HIV")) OR (("Human Immunodeficiency Virus")) OR (("Acquired Immunodeficiency Syndrome Virus")))	3.081.847
#19	(("liver cirrhosis")) OR (("cirrhosis"))	236,833
#17	("cirrhosis")	236,833
#16	("liver cirrhosis")	147,326
#15	(("tuberculose")) OR (("tuberculosis"))	413,828
#14	("tuberculosis")	411,357
#13	("tuberculose")	18,886
#12	(("glucocorticoids")) OR (("Corticosteroids")) OR	514,747
#11	(("Corticosteroides"))	984
#10	("Corticosteroids")	398,448
#9	("glucocorticoids")	178,300
#8		
#7	(("Transplantation")) OR (("Transplant"))	1,405,799
#6	("Transplant")	546,184
#5	("Transplantation")	1,283,750
#4	(("HIV")) OR (("Human Immunodeficiency Virus")) OR (("Acquired Immunodeficiency Syndrome Virus"))	873,987
#3	("Acquired Immunodeficiency Syndrome Virus")	628
#2	("Human Immunodeficiency Virus")	485,224
#1	("HIV")	770,963

7 CONCLUSÕES E CONSIDERAÇÕES FINAIS

Sepse é uma síndrome de alto custo em que o retardo no diagnóstico e tratamento contribui para mortalidade elevada. As metanálises fornecem importante informação para pacientes críticos imunossuprimidos nos quais o diagnóstico e a conduta precoce são extremamente importantes. Os resultados demonstraram boa acurácia dos biomarcadores, tanto PCR quanto PCT, no diagnóstico da infecção bacteriana à beira do leito em pacientes imunossuprimidos críticos. Estes biomarcadores nãos se mostraram perfeitos, mas marcador ideal não existe, uma vez que sepse é um processo fisiopatológico complexo mais do que uma síndrome específica para ser mensurado por um simples marcador.

PCR e PCT são úteis no diagnóstico de sepse, mas não devem ser usadas isoladamente, devendo ser interpretadas no contexto de história, exame físico e, se possível, exame microbiológico.

ANEXOS

ANEXO A

PROTOCOLOS

Proteína C reativa como marcador de infecção em pacientes imunossupressos críticos

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Evaluation of the accuracy of the C Reactive Protein Bacterial Infection Marker in immunosuppressed patients (patients with cirrhosis, syndrome adult immunodeficiency, tuberculosis, transplant and steroid users)

vanessa oliveira, Rafael Moraes, Airton Stein, Eliana Wendland

Citation
vanessa oliveira, Rafael Moraes, Airton Stein, Eliana Wendland. Evaluation of the accuracy of the C Reactive Protein Bacterial Infection Marker in immunosuppressed patients (patients with cirrhosis, syndrome adult immunodeficiency, tuberculosis, transplant and steroid users). PROSPERO 2015:CRD42015019329 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015019329

Review question(s)
Evaluation of the accuracy of the C Reactive Protein Bacterial Infection Marker in immunosuppressed patients (patients with cirrhosis, syndrome adult immunodeficiency, tuberculosis, transplant and steroid users)

Searches
Electronic Search:

The search for the studies will be carried out on the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, MEDLINE (1966 to August 2014), EMBASE (1980 to August 2014), CINAHL (1982 to August 2014), and SCOPUS LILACS (1982 to August 2014), Web of Science (until August 2014). There will be no date restriction, language or publication status.

Other Search Strategies:

Studies will be sought in the reference lists of review articles and studies. The search of the grey literature will be conducted through the databases: Bank of Theses (PROQUEST and CAPES) and protocols repository (PROSPERO).

We will contact the authors if the information of the selected articles are insufficient or inaccurate.

Types of study to be included
Cohort studies and case-control that assess C-reactive protein levels as a marker of bacterial infection in imunossupressos compared with cultures or clinical suspicion from sepsis concepts, severe sepsis and septic shock.

Included studies should have sufficient information to build a contingency table 2 × 2 (true and false positive and negative).

Articles with experimental animals, narrative reviews, correspondence, case reports, expert opinions and editorials will be excluded.

Condition or domain being studied
Target condition: presentation of bacterial infection at any stage: infection, sepsis or severe sepsis.

The concept of sepsis will be that established by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference. (12,13). According to this consensus:

microbiological infection should be confirmed or clinically suspected by at least one or more characteristics: white cells in sterile body fluids, drilling viscera, radiographic evidence of healing in combination with purulent sputum, and syndromes associated with high risk for infection.

SIR is set when at least two of the criteria are present: heart rate> 90 bpm / min, respiratory rate> 20mr / min. or need for mechanical ventilation, body temperature> 38ºC or <36ºC, leukocytes> 12,000 / mm^3 or <4,000 / mm^3.

Sepsis is defined as SIRS secondary infection documented by microbiological diagnosis.

Severe sepsis is defined as sepsis in the presence of hypotension, hypoperfusion or organ dysfunction.

Septic shock is defined as sepsis, refractory hypotension associated with the appropriate amount of volume.

Participants/ population

Patients over 18 years with immunosuppression: HIV with any level of CD4, or not using antiretrovirals, any progression of the disease, presence or absence of opportunistic diseases (tuberculosis, pneumocystosis, ...) , patients with tuberculosis, cirrhosis, transplant and chronic corticosteroid.

Outpatients, pregnant women, post-operative major surgery, acute myocardial infarction, cancer sufferers, rheumatological, autoimmune and other diseases that cause immunodeficiency will also be excluded.

Intervention(s), exposure(s)

Index test: C-reactive protein will be evaluated by immunoturbodimetric method or nephelometry method or any other method presented in the articles.

Comparator(s)/ control

Gold standard: the gold standard test will be be considered to be any microbiological examination (sputum culture, bronchial lavage, urine, peripheral blood or catheter or body secretions) with bacterial growth.

Outcome(s)

Primary outcomes

Assessing the accuracy of C-reactive protein in detecting sepsis in immunossupressed patient in relation to the gold standard and compare the two markers each other in patients: HIV positive with tuberculosis, transplant on chronic corticosteroid and cirrhotic.

Secondary outcomes

Assessing the best cut off point for CRP as a marker of bacterial infection;

Investigating whether the increase in PCR cut off point serves as a marker of bacterial infection in these patients.

Investigating the difference in CRP cutting bridges to viral disease, pneumocystosis and tuberculosis.

Data extraction, (selection and coding)

The selection of studies will be performed by two independent reviewers (VMO And RBM) and disagreements will be reresolved by a third reviewer (EW). A flow diagram of the articles found as the PRISMA method will be built. (129) The assessment of the quality of the selection of studies will be performed using the Kappa statistical test to determine the agreement between observers.

The data extraction will be performed by two independent reviewers (VMO and RBM). A data collection instrument will be developed for the study, in which variables will be collected as general characteristics of publication (year, magazine site), general characteristics of the population (age, gender, ethnicity, type of immunosuppression (HIV, tuberculosis, cirrhotic or transplanted), study (emergency site, floor and intensive care unit), disease severity (APACHE, SOFA), severity of infection (infection sepsis or severe sepsis), characteristics of the tests (measurement method and cohort points used), laboratory measurements as leukocyte and lymphocyte types of infection (bacterial, fungal and tuberculosis), comorbidities, use of immunosuppressants, corticosteroids (dose and chronic use), eto HIV (CD4 count, a measure of HTLV / II and use of HAART)

Risk of bias (quality) assessment

The risk of bias of the selected studies will be assessed by the Quality Assessment of Diagnostic Accuracy Studies Tool 2 (QUADAS 2).

The publication bias will be assessed using the ratio of diagnostic odds (DOR) with Egger regression test. This analysis will be performed in the R Development Core Team program. A: language and environment for statistical computing.

Strategy for data synthesis

After extraction of the data, they will be evaluated for the possibility of statistical synthesis. If the data is judged as having general heterogeneity not important, they are statistically aggregated.

The data extracted from the articles will be grouped in a 2 x 2 table to evaluate the sensitivity and specificity of the test. The pretest probability (positive and negative predictive values) will be extracted from the studies. Eventually, if not clear in the article, will be inferred from the sensitivity, specificity and the outcome occurrence values.

The post-test probability is estimated by likelihood ratio is calculated starting the sensitivity and specificity of the test: (likelihood ratio) (LR + = sensitivity / (1-specificity) and LR = (1-sensitivity) / specificity).

Diagnostic chances (DOR) will be used as the summarization measure of test accuracy index. DOR will be calculated from the likelihood ratio. (DOR = LR + / LR)

The study will be evaluated also with multilevel models (hierarchical) for considering the variability in the study (sampling error) and the variability between studies (heterogeneity). Two methods are used: the model bivariate model, and the hierarchical model of SROC (HSROC). The bivariate model and the model HSROC differ in parameterization. The parameters of the bivariate model, model sensitivity, specificity and the direct correlation between them, while the parameterization of HSROC models sensitivity and specificity functions to set a summary ROC curve.

The summarized ROC (SROC) will be obtained by summarizing the sensitivity, specificity and diagnostic odds ratio (DOR). The method models the bivariate sensitivity and specificity in two related directly to changes in the levels of research and studies.

The discriminatory ability test will be calculated by the SROC curve (ROC -curva (Receiver Operating Characteristic) summarized) by linear regression method of Moses-Littenburg. This method is ideal because the articles may apresentes different cut off points for sensitivity and specificity, so the presence of the effect of the cut-off point will be investigated using HSROC.

Forest Plot graph represent the value of each individual study of positive and negative predictive values, sensitivity and specificity of the test, along with their 95 %% confidence intervals.

Heterogeneity: the heterogeneity in this meta-analysis will be explained in two ways: I-squared test (Higgins) and extended hierarchical regression models (modeling SROC using bivariate and hierarchical model (HSROC). When the meta-analytic approach used is the SROC the arrangement of studies in ROC plots will be inspected visually and may suggest the presence of heterogeneity that can be exploited by sensitivity / subgroup analyzes. Outcome measures summarized and heterogeneity of research through modeling will be carried out with the software

RevMan and METADISC (http://www.hrc.es/investigacion/metadisc_en.htm).

Analysis of subgroups or subsets

We will consider subgroup analysis based on:

1) Patient characteristics: immunosuppression Type: Carrier tuberculosis, cirrhotic, transplanted, HIV or steroid user, presence of opportunistic infection (PCP, fungi and tuberculosis), corticosteroids (dose, chronic use or not)

2) For patients with HIV: CD4 measure, and HTLV II and viral load if they are measured, use of antiretroviral informed.

3) Performance Characteristics: method used to measure CRP and procalcitonin and different cutoffs tests

4) The condition: site of infection: lung, urinary, abdominal catheter, skin or without a defined focus; concurrent infections (fungi, viruses)

5) The design of the study: case-control and cohort

Contact details for further information
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Organisational affiliation of the review
UFRGS

Review team
Dr vanessa oliveira, UFRGS
Dr Rafael Moraes, HCPA
Professor Airton Stein, UFRGS
Professor Eliana Wendland, UFRGS

Collaborators
Professor AIRTON STEIN,
Professor ELIANA WENDLAND,
Dr RAFAEL MORAES,

Anticipated or actual start date
02 March 2015

Anticipated completion date
31 July 2015

Funding sources/sponsors
Dr Vanessa Martins de Oliveira post graduate epidemiology of UFRGS/

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Brazil.

Professor Airton Stein post graduate epidemiology of UFRGS

Professor Eliana Wendland post graduate epidemiology of UFRGS

Conflicts of interest
None known

Language
English

Country
Brazil

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Adult; Bacterial Infections; Biological Markers; C-Reactive Protein; Humans; Liver Cirrhosis; Tuberculosis

Stage of review
Ongoing

Date of registration in PROSPERO
10 April 2015

Date of publication of this revision
10 April 2015

DOI
10.15124/CRD42015019329

Stage of review at time of this submission	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Procalcitonina em comparação com proteína c reativa como marcador de infecção bacteriana em pacientes imunossupressos críticos

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Accuracy of the C Reactive Protein an procalcitonin as Bacterial Infection Marker in immunosuppressed patients: a systematic review

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
27/06/2013

4 Anticipated completion date
Give the date by which the review is expected to be completed.
30/06/2014

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Vanessa Martins de Oliveira

7 Named contact email
Enter the electronic mail address of the named contact.
vanessa.oliveira480@gmail.com

8 Named contact address
Enter the full postal address for the named contact.
maranguape 81 apt 802

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
05192513723

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

none

Website address:

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Vanessa	Martins de Oliveira	post graduate epidemiology of UFRGS/ Physician Hospital de Cli ´nicas de Porto Alegre, Intensive Care Unit, Porto Alegre/RS, Brazil.
Dr	Wagner Luis	Nedel	Physician Hospital de Clinicas de Porto Alegre, Intensive Care Unit, Porto Alegre/RS, Brazil.
Professor	ELIANA MARCIA	WENDLAND	Post graduate epidemiology of UFRGS//Ufcscpa
Professor	Airton Tetelbom	Stein	Post graduate epidemiology of UFRGS/Grupo Hospitalar Conceicao/Ulbra/Ufcscpa

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Vanessa Oliveira- Student of the Epidemiology Phd Program UFRGS Master in Clinica Medica. Physician of Hospital de Clinicas de Porto Alegre, Intensive Care Unit, Porto Alegre/RS, Brazil. Physician Wagner Nedel- Physician of Hospital de Clinicas de Porto Alegre, Intensive Care Unit, Porto Alegre/RS, Brazil. .PHD Eliana Márcia Wendland- post graduate epidemiology of UFRGS/Porto Alegre/RS, Brazil. PH.D Airton Stein- post graduate epidemiology of UFRGS/Porto Alegre/RS, Brazil.

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

What is the accuracy of c-reactive protein in detecting bacterial infection in immunosupressed patients(carriers of human immunodeficiency virus (HIV) Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid?

What is the accuracy of procalcitonin in detecting bacterial infection in immunosupressed patients(carriers of human immunodeficiency virus (HIV), Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid?

Which is the most accurate marker, procaltinonina or c-reactive protein, to detect bacterial infection in immunosupressed patients (carriers of human immunodeficiency virus (HIV), Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid?

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library; MEDLINE (1966 to march 2013); EMBASE (1980 to march 2013); CINAHL (1982 to march 2013), SCOPUS e LILACS(1982 to march 2013), WEB OF SCIENCE, Health Technology Assessment Database, conference proceedings, Internet resources (GOOGLE ACADEMIC) and PROQUEST. The search strategy for MEDLINE is available in the published protocol. The search terms will be adapted for use with other bibliographic databases. We did not restrict our search for trials by date, language or publication status.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

http://www.crd.york.ac.uk/PROSPEROFILES/4783_STRATEGY_20130505.pdf

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Bacterial Infection in immunosupressed patients (carriers of human immunodeficiency virus (HIV) , Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid?

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Patients over 18 years with immunosuppression HIV with any level of CD4 or not using antiretroviral, any progression of the disease, presence or absence of opportunistic diseases (tuberculosis, pneumocystis....). Patients with tuberculosis, cirrhosis, submitted to any kind of transplant, and chronic corticosteroid. Outpatients, pregnant women, post-operative major surgery, acute myocardial infarction, cancer sufferers, rheumatologically, autoimmune and other diseases that cause immunodeficiency were excluded.

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

This review will evaluate and compare CRP levels (C reactive protein) and/or procalcitonin levels, as diagnostic markers for bacterial infection in hospitalized patients.

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

We have defined sepsis as the reference standard. Sepsis has been defined using the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference. In accordance with this definition, the presence of infection has to be microbiologically confirmed or at least clinically suspected, as well as the following characteristics: white blood cells in a normally sterile body fluid, perforated viscus, radiographic evidence of pneumonia in association with production of purulent sputum and syndrome associated with a high risk of infection.

22 Types of study to be included initially

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

We will include randomised trials and observational studies. CRP levels and/or procalcitonin levels will be evaluated as diagnostic markers for bacterial infection in hospitalized patients.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

We will include studies in which the inclusion criteria were inpatients from emergency room and intensive care unit.

24 Primary outcome(s)

Give the most important outcomes.

Accuracy of determination of procalcitonin and C reative protein levels for the diagnosis of bacterial infections in hospitalized patients.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
Type of bacterial infection. Best cut off value. Timing.

Give information on timing and effect measures, as appropriate.
Sensitivity, specificity, likelihood ratio, ROC curve.

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
The selection and data extraction will be performed by two independent reviewers (V.M.O and WN). Discrepancies will be decided in a consensus meeting or, if agreement cannot be reached, they will be decided by a third investigator (TDP). The extracted data will include the following: recruitment and study completion rates; outcomes measurement; information for assessment of the risk of bias, characteristics of the study population (age), baseline characteristics, admission category (surgical or medical), study setting (unit, emergency and intensive care unit), severity of illness (sepsis, severe sepsis, or septic shock), and details of the C-reactive protein and procalcitonin assays and cutoffs applied. In addition, each investigator will record the number of true and false positives. We will contact the corresponding authors, if further information is needed.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Two review authors will independently assess the risk of bias in included studies.Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author, when necessary. We will assess the methodological quality of the studies with the Quality Assessment of Diagnostic Accuracy. Kappa agreement will be used.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
To synthesis data, we will estimate mean logit sensitivity and specificity with their standard error and 95% CI. We will transform these quantities to the original receiver operating curve scale to obtain summary sensitivity, specificity and diagnostic odds ratios. We will then use derived logit estimates of sensitivity, specificity and variances to construct a hierarchical summary receiver operating curve for C-reactive protein and procalcitonin with summary operating points for sensitivity and specificity on the curves and a 95% confidence. Heterogeneity between the studies in effect measures will be assessed using the I-squared statistic. If heterogeneity among studies was recorded, the potential source of heterogeneity will be investigated by meta regression. We will also assess evidence of publication bias. We will construct effective sample size funnel plots versus the log diagnostic odds ratio and will carry out a regression test of asymmetry. We plan to perform a sensitivity analysis to explore the causes of heterogeneity and the robustness of the results.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
We will use subgroup analysis in which the following characteristics will be taken into account: different degrees of immunity, antiretroviral usage, type of bacterial infection, timing of inclusion performance of the test, or other types of infection, such as tuberculosis.

Review general information

30 Type of review
Select the type of review from the drop down list.
Epidemiologic

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Brazil

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
This paper will be submitted to a leading journal in this field. Furthermore, should the findings of the review warrant a change in practice, a one page summary report will be prepared and sent to lead clinicians and healthcare professionals in the National Health Service.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
systematic review

Human Immunodeficiency Virus

Procalcitonin

C-Reactive Protein

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

ANEXO B

QUESTIONÁRIOS E FORMULÁRIOS

Tabela 1 -Questionário de avaliação de risco de viés da qualidade dos estudos (QUADAS 2)

	Sim	**Não**	**Não claro**
1. O espectro dos pacientes foi representativo dos que irão utilizar o teste na prática?			
2. Os critérios de inclusão estão claramente descritos?			
3. O padrão de referência é capaz de classificar corretamente a condição-alvo?			
4. Toda amostra ou uma seleção aleatória da amostra recebeu o padrão de referência para o diagnóstico?			
5. Todos os pacientes receberam o mesmo padrão de referência independentemente dos resultados do teste índice?			
6. O padrão de referência foi independente do teste índice (Quer dizer, o teste índice não faz parte do padrão de referência)?			
7. A aplicação do teste índice está descrita em detalhes suficientes para permitir a replicação do teste?			
8. A aplicação do teste padrão de referência está descrita em detalhes suficientes para permitir a replicação do teste?			
9. Os resultados do teste índice foram interpretados sem o conhecimento dos resultados do padrão de referência?			
10. Os resultados inconclusivos/intermediários foram reportados?			
11. Os motivos para retiradas de pacientes do estudo foram explicados?			

Tabela 2- Resultados da avaliação do risco de vieis dos estudos pelo QUADAS 2

Estudo	**Risco de viés**				**Aplicabilidade**		
	Seleção dos Pacientes	**Teste índice**	**Teste padrão**	**Fluxo e tempo**	**Seleção dos pacientes**	**Teste índice**	**Teste padrão**
Estudo 1							
Estudo 2							
Estudo 3							
Estudo 4							

□Baixo risco □□Alto risco □□ - Risco intermediário

Tabelas 3- Ficha de extração dos dados

Autor/ID	
Titulo	

Características dos estudos

Tipo de estudo	País do estudo	Local do estudo (UTI/emergência/ andar)	N	Qual marcador utilizou?	Qual tipo de paciente?	Escore de mortalidade
Estudo 1						
Estudo 2						
Estudo 3						

Características da população HIV

Sexo	Idade	CD4	HTVL I/II	Uso de antiretrovirais	Leucócitos	Linfócitos
Estudo 1						
Estudo 2						
Estudo 3						
Carga viral	Uso de coticosteroide (dose)	Pneumocistose	TBC	Fungos		
Estudo 1						
Estudo 2						
Estudo 3						

Outros imunossupressos

Sexo	Idade	Tipo de imunossupresso	Comorbi dades	Uso de vasopressor	Leucócitos	Linfócitos
Estudo 1						
Estudo 2						
Estudo 3						

Características dos testes PCR

Tempo do teste (admissão?)	Repetição do teste	Método de diagnóstico de infecção	Ponte de corte médio	Melhor ponte de corte definido	Sen	Esp
VP+	VP-	LH+	LH-			
Estudo 1						
Estudo 2						
Estudo 3						

Procalcitonina

Tempo do teste (admissão)	Repetição Do teste	Método de diagnóstico de infecção	Ponte de corte médio	Melhor ponte de corte definido	Sen	Esp
Estudo 1						
Estudo 2						
Estudo 3						
VP+	VP-	LH+	LH-			
Estudo 1						
Estudo 2						
Estudo 3						

CHECK LIST PRISMA PARA OS ARTIGOS

CHECK LIST PRISMA ARTIGO 1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	52
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	52
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	53
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	54-55
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	56
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	54-55-56
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	55-56
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	55-56
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	56
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	56
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	54-55
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	56-57
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	57
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	57
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	57-58
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	57-58

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	58-62
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	58-63,64,65
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	63,64
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7,8,9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	63
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	59,60
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	59
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	59
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	60
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	60

CHECK LISTS PRISMA ARTIGO 2

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	89
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	89
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	90
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	90
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	90
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	91
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	91
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	92
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	92
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	92-93
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	92-93
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	94
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	94
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	94
	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	94
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	94

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	95
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	95
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	95
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	95-96
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	96
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	96
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	97
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	97
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	98
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	98
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	99