Universidade do Estado do Rio de Janeiro
Centro Biomédico
Faculdade de Ciências Médicas

Mariana Carneiro Lopes

Características relacionadas ao prognóstico da sarcoidose e identificação de atividade da doença através de biomarcadores e PET CT

Rio de Janeiro
2020

Mariana Carneiro Lopes

Características relacionadas ao prognóstico da sarcoidose e identificação de atividade da doença através de biomarcadores e PET CT

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Orientador: Prof. Dr. Rogério Lopes Rufino Alves

Coorientadora: Prof.ª Dra. Thaís Porto Amadeu

Rio de Janeiro

2020

CATALOGAÇÃO NA FONTE
UERJ/REDE SIRIUS/CBA

L864 Lopes, Mariana Carneiro.
Características relacionadas ao prognóstico da sarcoidose e identificação de atividade da doença através de biomarcadores e PET CT / Mariana Carneiro Lopes. – 2020.
89 f.

Orientador: Rogério Lopes Rufino Alves
Coorientadora: Thaís Porto Amadeu

Tese (Doutorado) – Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas. Programa de Pós-graduação em Ciências Médicas.
1. Sarcoidose. 2. Biomarcadores. 3. Doença Granulomatosa Crônica. I. Alves, Rogério Lopes Rufino. II. Amadeu, Thaís Porto. III. Universidade do Estado do Rio de Janeiro. Faculdade de Ciências Médicas. IV. Título.
CDU 616-002

Bibliotecária: Angela da Silva Velho CRB7/4780

_____ _____

Assinatura Data

Mariana Carneiro Lopes

Características relacionadas ao prognóstico da sarcoidose e identificação de atividade da doença através de biomarcadores e PET CT

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Ciências Médicas, da Universidade do Estado do Rio de Janeiro.

Aprovada em 03 de dezembro de 2020.

Coorientadora : Prof.ª Dra.Thais Porto Amadeu

Faculdade de Ciências Médicas – UERJ

Banca Examinadora:

_____

Prof. Dr. Rogério Lopes Rufino Alves (Orientador)

Faculdade de Ciências Médicas – UERJ

_____

Prof.ª Dra. Cláudia Henrique da Costa

Faculdade de Ciências Médicas – UERJ

_____

Prof. Dr. Thiago Thomaz Mafort

Faculdade de Ciências Médicas – UERJ

_____

Dr. Bruno Rangel Antunes da Silva

Hospital Américas

_____

Prof. Dr. Ronaldo Adib Kairalla

Universidade de São Paulo

Rio de Janeiro

2020

DEDICATÓRIA

Dedico esta tese à memória de meu avô Nelson, que sempre esteve presente em todas as minhas conquistas, aplaudindo de pé na primeira fileira, e que tanto se orgulhava de cada vitória alcançada por mim.

AGRADECIMENTOS

Agradeço a Deus por todas as oportunidades que tive na minha vida.

Aos meus pais Fátima e Ivan por todo amor, pelos esforços para me oferecerem uma boa educação e por lutarem comigo para transformar o sonho de criança de ser médica em realidade.

Ao meu irmão Fábio e meu melhor amigo, por caminhar sempre junto comigo.

Ao meu marido Bruno que é meu grande parceiro, ouviu todas as angústias e comemorou comigo as conquistas até aqui, me apoiou, me incentivou, sempre acreditando em mim, foi fundamental para a conclusão dessa tese e na minha vida.

Ao meu tio e padrinho Carlos, presente na minha criação desde sempre e toda minha família que me apoiou e transmitiu palavras de carinho que facilitaram essa jornada.

Aos meus amigos, os de infância que acompanharam desde cedo toda essa trajetória, torceram e vibraram comigo e os que a medicina me trouxe, dividindo momentos apreensivos e muitos momentos de alegria, me fazendo orgulhar dos grandes médicos que são.

A todos professores que participaram da minha formação , desde o ensino fundamental.

À UFF pela excelente graduação e por exercer o ensino humanizado da medicina.

A todos os staffs da pneumologia UERJ , por me sentir acolhida e valorizada, por encontrar excelência e dedicação a serem tomadas como exemplo.

A todas equipes multiprofissionais pelas quais passei durante a gradução, residências médicas e até os dias de hoje , que muito me ensinaram e acrescentaram, incluindo médicos, fisioterapeutas, enfermeiros e técnicos.

A todos os pacientes, por contribuirem com o aprendizado e a ciência, mesmo em momentos de dor e sofrimento.

Ao professor Marcelo Ribeiro, que me ensinou estatística com muita paciência e esteve disponível todas as muitas vezes que precisei.

Aos meus orientadores professor Rogério Rufino e professora Thais Amadeu, vocês têm minha admiração pelo conhecimento, pela dedicação e compromisso com

a formação profissional e pessoal de seus alunos. Obrigada por me permitirem realizar esse sonho.

Só se vê bem com o coração, o essencial é invisível aos olhos.

Antoine de Saint-Exupéry

RESUMO

LOPES, Mariana Carneiro. *Características relacionadas ao prognóstico da sarcoidose e identificação de atividade da doença através de biomarcadores e PET CT.* 2020. 89 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2020.

Sarcoidose é uma doença granulomatosa, multissistêmica, com apresentação clínica e radiológica variável, assim como seu curso e resposta ao tratamento. É um grande desafio identificar a atividade da doença e prever a evolução de cada paciente para traçar o plano terapêutico individualizado. Esta tese tem a proposta de apresentar ferramentas para o acompanhamento e manejo terapêutico da sarcoidose, utilizadas de forma até então não apresentada na literatura. Três estudos foram desenvolvidos, com 105 pacientes com sarcoidose,composto por grupos em atividade, remissão e controle, no período de 4 anos (2015-2019), no centro de doenças intersticiais na Policlínica Piquet Carneiro/ UERJ. Foram dosadas chitotriosidase (CHITO), enzima conversora de angiotensina (ECA) e proteína C reativa ultra sensível (PCR us) e relizados exames de tomografia computadorizada com emissão de pósitrons (PET CT). Primeiro: biomarcadores (CHITO, ECA e PCR us) para avaliação da atividade e remissão da doença; segundo: escore de indicadores de prognóstico para sarcoidose; terceiro: PET CT e CHITO na avaliação da evolução dos pacientes. No primeiro estudo, foram encontrados os pontos de corte para cada biomarcador: CHITO = 120 U/mL, ECA = 270 ng/mL, PCR us = 0,4 mg/dL com sensibilidade e especificidade para definir atividade de doença, respectivamente, 55%, 88%, 66% e 100%, 47% e 68%. Foi realizado também um algoritmo unificando os 3 marcadores obtendo acurácia de 82%, sensibilidade de 78% e especificidade 89%, para diferenciar atividade da remissão da sarcoidose. No segundo estudo, após um período mínimo de acompanhamento de 24 meses, os pacientes foram classificados de acordo com sua evolução clínica. Quarenta e oito por cento dos pacientes evoluíram com a forma crônica da sarcoidose. A ausência dos marcadores reumatológicos, a capacidade vital forçada (%) e a presença de sintomas respiratórios iniciais (dor torácica, tosse, dispneia e sibilos)foram relacionados com melhor prognóstico. No terceiro estudo, o PET CT e a CHITO apresentaram acurácia superior a 60% para o acompanhamento da sarcoidose, auxiliando em casos selecionados. Não houve diferença estatística na acurácia, sensibilidade e especificidade entre os dois métodos (intervalo de confiança sobrepostos). Dessa forma, esta tese pretende contribuir para o manejo dos pacientes diagnosticados com sarcoidose desde o início da doença ao estabelecer o prognóstico ao longo do tratamento com a identificação de sua atividade.

Palavras-chave: Sarcoidose.Atividade.Prognóstico.Biomarcadores.CHITO.PET CT.

ABSTRACT

LOPES, Mariana Carneiro. *Characteristics related to the prognosis of sarcoidosis and identification of disease activity using biomarkers and PET CT*. 2020. 89 f. Tese (Doutorado em Ciências Médicas) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2020.

Sarcoidosis is a granulomatous, multisystemic disease, with variable clinical and radiological presentation, as well as its course and response to treatment. It is a great challenge to identify the activity of the disease and to predict the evolution of each patient to outline the individualized therapeutic plan. This thesis has the proposal of presenting tools for the monitoring and therapeutic management of sarcoidosis, used in a way not previously presented in the literature. Three studies were developed, with 105 sarcoidosis patients, composed of activity, remission and control groups, in the period of 4 years (2015-2019), at the interstitial diseases center in the Polyclinic Piquet Carneiro / UERJ. Chitotriosidase (CHITO), angiotensin-converting enzyme (ACE) and ultra-sensitive C-reactive protein (us CRP) were measured and positron emission computed tomography (PET CT) scans were performed. First: biomarkers (CHITO, ACE and us CRP) to assess disease activity and remission; second: score of prognostic indicators for sarcoidosis; third: PET CT and CHITO in assessing the patient's evolution. In the first study, cutoff points were defined for each biomarker: CHITO = 120 U / mL, ACE = 270 ng / mL, us CRP = 0.4 mg / dl with sensitivity and specificity to define disease activity, respectively, 55 %, 88%, 66% and 100%, 47% and 68%. An algorithm was also performed combining the 3 markers, obtaining an accuracy of 82%, sensitivity of 78% and specificity of 89%, to differentiate the activity of sarcoidosis remission. In the second study, after a minimum follow-up period of 24 months, patients were classified according to their clinical evolution. Forty-eight percent of patients progressed to chronic sarcoidosis. The absence of rheumatological markers, forced vital capacity (%) and the presence of early respiratory symptoms (chest pain, cough, dyspnoea and wheezing) were related to a better prognosis. In the third study, PET CT and CHITO had accuracy greater than 60% for monitoring sarcoidosis, helping in selected cases. There was no statistical difference in accuracy, sensitivity and specificity between the two methods (overlapping confidence intervals). Thus, this thesis aims to contribute to the management of patients diagnosed with sarcoidosis since the beginning of the disease by predicting the clinical evolution and identifying its activity throughout the treatment.

Keywords: Sarcoidosis. Activity. Prognosis. Biomarkers. CHITO. PET CT.

LISTA DE ABREVIATURAS E SIGLAS

ANCA	Anticorpo anti-citoplasmático de neutrófilo
ATS	*American Thoracic Society*
CEP	Comitê de Ética em Pesquisa
CHITO	*Chitotriosidase*
COS	*Clinical outcome status*
CPI	*Composite physiologic index*
CVF	Capacidade vital forçada
DCO	Difusão de monóxido de carbon
ECA	Enzima conversora de angiotensina
EDTA	*Ethylenediamine tetraacetic acid*
ELISA	Ensaio de imunoenzimático
FAN	Fator antinuclear
FAPERJ	Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
FIOCRUZ	Fundação Oswaldo Cruz
FR	Fator reumatoide
HUPE	Hospital Universitário Pedro Ernesto
PCR us	Proteína C reativa ultra sensível
PET CT	Tomografia computadorizada com emissão de pósitrons
TCLE	Termo de consentimento livre e esclarecido
UERJ	Universidade do Estado do Rio de Janeiro
UFRJ	Universidade Federal do Rio de Janeiro
VEF_1	Volume expiratório forçado no primeiro segundo

SUMÁRIO

INTRODUÇÃO

Sarcoidose é uma doença granulomatosa, multissistêmica, sem etiologia definida, considerada rara, com prevalência variando pelas populações mundiais. No Brasil, ela é estimada em 10 casos para 100.000 indivíduos.(1,2)

A apresentação da doença é variável, assim como seu curso e resposta ao tratamento. Em alguns casos, pode haver remissão espontânea, sem necessidade de drogas imunossupresoras, em outros apresentará resposta satisfatória à primeira linha de tratamento com corticoide com remissão da doença em até 2 anos. Porém uma parte dos pacientes irá evoluir com a forma crônica da sarcoidose e a necessidade de terapia imunossupressora, além do corticoide por tempo indefinido.(3,4,5) porcentagem

É um grande desafio prever a evolução de cada paciente para traçar o plano terapêutico individualizado.

Algumas características estudadas já foram apontadas como indicadores de melhor ou pior prognóstico isoladamente.(6) Neste trabalho será apresentado um escore envolvendo algumas características clínicas, laboratoriais e funcionais, de fácil realização e acesso para auxiliar no acompanhamento da evolução dos pacientes.

Outra dificuldade durante o manejo terapêutico desses pacientes é a identificação de atividade da sarcoidose, nem sempre evidente, com sintomas e achados radiológicos inespecíficos. (7)

Desde a década de 70 alguns biomarcadores são estudados com o objetivo de identificar atividade da doença, inicialmente a enzima conversora de angiotensina (ECA), posteriormente surgiram outros marcadores, entre eles, a chitotriosidase (CHITO).(7)

Além dos biomarcadores séricos, a medicina nuclear tem fornecido contribuição importante com a tomografia por emissão de pósitrons associada à tomografia computadorizada (PET CT). O PET CT tem excelente sensibilidade na detecção de sítios pulmonares e extrapulmonares de sarcoidose em atividade, sendo um bom exame para o seguimento dos pacientes em determinados casos.(8)

Esta tese tem a proposta de apresentar ferramentas para o acompanhamento e manejo terapêutico da sarcoidose, utilizadas de forma até então não apresentada na literatura.

1 REVISÃO DE LITERATURA

1.1 Definição

A sarcoidose é uma doença multissistêmica de causa desconhecida caracterizada pela formação de granulomas não caseosos constituídos de células epitelioides.Frequentemente,afeta adultos jovens, e se apresenta muitas vezes por adenopatia hilar bilateral, assintomática, infiltrado intersticial pulmonar ou com manifestações extrapulmonares, podendo acometer qualquer órgão. (1,9) O seu prognóstico é variável dependendo da forma de apresentação inicial e extensão da doença. (6)

1.2 Epidemiologia

Até nos dias de hoje a epidemiologia da sarcoidose é de difícil definição. O diagnóstico tardio, as formas de apresentação que mimetizam outras doenças, os casos com remissão espontânea, paucissintomáticos e assintomáticos, fazem com que a sarcoidose seja uma doença subestimada. (1)

Apesar de poder acometer qualquer pessoa, a maior incidência é em adultos até 40 anos, variando entre as populações do mundo. Nos países escandinavos e no Japão acontece um segundo pico de apresentação em mulheres acima de 50 anos.(1)

Nos países do norte da europa encontramos as maiores incidências – 5 a 40 casos/100.000 indivíduos, já no Japão 1 a 2 casos/100.000 indivíduos.(10) Entre os americanos é observada uma incidência maior nos afrodescendentes (35.5/100.000) comparado aos caucasianos (10.9/100.000). No Brasil não há estudos suficientes que possam predizer a prevalência nacional, porém acredita-se que seja em torno de 10/100.000. (2)

A mortalidade geral varia de 1 a 5 %, com alguns estudos sugerindo maior gravidade nos afroamericanos e na sua maioria devido à fibrose e hipertensão pulmonar.(11-13) É observada uma discreta preponderância do sexo feminino nas

populações mundiais e no Brasil. A situação socioeconômica parece não ser fator de risco para a doença.(14,15)

1.3 **Etiologia**

A etiologia da sarcoidose ainda não é conhecida, mas especula-se que exista a participação de agentes ambientais em indivíduos geneticamente predispostos.(16,17,18)

Entre os fatores ambientais até agora identificados como possíveis agentes causais estão alguns vírus (herpes vírus, Epstein-Barr, retrovírus, citomegalovirus e coxsackie B), pólen de pinheiro, zircônio, argila, alumínio, talco, Micobactérias, Mycoplasma, *Borrelia burgdorferi* e *Propionibacterium acnes*. (19,20)

Os genes de antígeno leucocitário humano, do inglês human leukocyte antigen (HLA), são responsáveis por codificarem as moléculas apresentadoras de antígenos. Já foi estudada a relação do HLA com o desenvolvimento da sarcoidose, assim como o fenótipo da doença. O HLA-DRB1*01 e DRB1*04 são fatores de proteção em populações caucasianas, enquanto DRB1*03, DRB1*11, DRB1*12, DRB1*14 e DRB1*15 são fatores de risco para sarcoidose. Quadros de síndrome de Löfgren foram associados ao HLA-B8/DR3 e outros alelos se relacionaram com o curso crônico da doença. (18)

1.4 **Imunopatogênese**

A interação entre células T ativadas e macrófagos desencadeada através da presença de um antígeno constitui a origem dos granulomas sarcóides. Os macrófagos se diferenciam em células epitelióides mediante o estímulo pelas citocinas e se fundem formando células gigantes multinucleadas. Em granulomas maduros, fibroblastos e colágeno englobam o aglomerado de células. As células T CD4+ são as responsáveis pela interação com as células apresentadoras de antígenos dando início à formação do granuloma e sua manutenção, constituindo a

área central do granuloma, enquanto as células CD8+ estão presentes mais na sua periferia. Na maioria das vezes os granulomas não são neclrotizantes, porém podem ser observadas pequenas áreas de necrose em até 1/3 dos pacientes. Cabe ressaltar que o granuloma é uma lesão inespecífica e sua identificação não é suficiente para confirmação diagnóstica da sarcoidose.(9,21)

Nenhum estudo mostrou porque a doença persiste em alguns casos, em outros, remite ou progride para fibrose. (3,4) Porém, já foram identificadas características associadas com pior prognóstico como a etnia afroamericana, idade avançada, alterações da função pulmonar, hipertensão pulmonar e a presença de fibrose. (6, 22,23)

1.5 **Manifestações clínicas**

Por se tratar de uma doença sistêmica, a apresentação clínica e sua evolução podem ser bastante variáveis, como formas agudas e crônicas. (1,24)

Dentre as manifestações agudas da sarcoidose estão a síndrome de Löfgren – linfadenomegalia hilar bilateral, febre, artralgia e eritema nodoso – e a síndrome de Heerfordt – uveíte, paralisia facial e aumento de parótidas. (1) O tempo de doença para definição de sarcoidose crônica é ponto de discordância entre autores. Baughman et al sugeriu uma classificação de acordo com a evolução clínica dos pacientes após 5 anos de doença, considerando crônicos aqueles que permaneceram em tratamento e os que não estavam tratando porém com doença persistente.(24)

O pulmão está acometido em cerca de 90% dos casos. Os principais sintomas são tosse, dispneia e desconforto torácico, mais raramente também pode ocorrer hemoptise. Na ausculta pulmonar é pouco provável a presença de estertores, assim como baqueteamento digital.(1)

Em torno de 1/3 dos pacientes cursam com sintomas constitucionais como febre, fadiga e perda ponderal. (1)

Sintomas extrapulmonares estão presentes em 30% dos casos. Na pele podem se manifestar de diversas formas , com predileção por áreas de cicatriz e tatuagem. As lesões cutâneas se dividem em específicas, quando há presença do

granuloma e em inespecíficas, quando não há o granuloma, como acontece no eritema nodoso. As lesões específicas encontratadas mais frequentemente são as máculas, pápulas, placas, nódulos subcutâneos, lúpus pérnio e infiltrações em cicatriz e tatuagens, geralmente, não pruriginosas. (25)

Nos olhos podemos encontrar diversos tipos de lesão, sendo a uveíte anterior, olho seco e nódulos conjuntivais mais comuns. Os sintomas relacionados à uveíte incluem hiperemia, perda de acuidade visual, dor ocular e fotofobia. A uveíte pode evoluir com catarata e elevação da pressão intraocular. (26)

A linfonodomegalia mediastinal é característica marcante da sarcoidose, mas também pode ser encontrada em cadeias cervicais, axilares e inguinais, na maioria das vezes indolores e móveis.(27)

O acometimento hepático na sarcoidose é caracterizado por granulomas dispersos no parênquima. A maioria dos pacientes são assintomáticos podendo apenas apresentar aumento das enzimas hepáticas, especialmente a fosfatase alcalina em torno de 5 a 10 vezes o limite superior da normalidade. A dor abdominal é um sintoma presente quando há distensão da cápsula de Glisson. Raramente a sarcoidose hepática pode se apresentar com hipertensão porta, colestase intra ou extra-hepática ou evoluir com cirrose. (28)

Hipercalciúria ocorre em mais da metade dos pacientes e hipercalcemia em menos de 20% devido à alteração do metabolismo do cálcio. Os granulomas aumentam a produção de calcitriol estimulando a absorção de cálcio pelo intestino. A hipercalciúria pode acarretar nefrolitíase e mais raramente nefrocalcinose levando à insuficiência renal. (29)

A incidência de sarcoidose cardíaca é estimada em 5% dos pacientes, porém especula-se que esse valor esteja subestimado de acordo com as análises de autópsia. A doença pode se manifestar com insuficiência cardíaca, distúrbios de condução como bloqueios de ramo, atrioventriculares, taquicardias atriais e ventriculares e até morte súbita.(30,31)

O principal acometimento do sistema nervoso central é a paralisia de nervo craniano, mais frequentemente o facial. Outras formas de apresentação são o diabetes insipidus e pan-hipopituitarismo quando envolve o eixo hipotálamo-hipófise. Lesões expansivas cerebrais são causa de crises convulsivas ou sinais focais neurológicos. A neurossarcoidose ainda pode se apresentar como neuropatia

periférica incluindo mononeurite e mononeurite multiplex,meningite asséptica e mielite. (32,33)

1.6 **Diagnóstico**

O diagnóstico é composto por um quadro clínico e radiográfico compatível e demonstração histopatológica de granulomas não caseosos, excluídas outras possíveis doenças granulomatosas. Quando a sarcoidose se apresenta nas formas de síndrome de Löfgren ou síndrome de Heerfordt a confirmação anatomopatológica não será necessária para a definição da enfermidade. O local a ser biopsiado deverá ser o de mais fácil acesso e o menos invasivo. (34) É possível a broncoscopia ser um substitudo da biópsia pulmonar para o diagnóstico da sarcoidose. A análise da composição celular e da citometria de fluxo do lavado broncoalveolar pode ser útil para o diagnóstico da sarcoidose quando houver linfocitose e a razão de linfócitos CD4+ /CD8+ for maior que 3,5. Este valor de corte tem sensibilidade para confirmar a sarcoidose em 53% com especificidade de 94%.(35) Além do lavado, a broncoscopia possibilita outras modalidades diagnósticas através da biópsia transbrônquica convencional e guiada por ultrassonografia endoscópica, biópsia endobrônquica e criobiópsia. O rendimento da biópsia transbrônquica aumenta de acordo com o número de fragmentos e com a presença de infiltrado pulmonar , variando de 44% a 90%. Quando há presença de linfonodomegalia intratorácica, a biópsia por ultrassonografia endoscópica tem rendimento em torno de 90%. Já o sucesso da biópsia endobrônquica depende da visualização de alterações em mucosa , nessa situação em quase 100% das vezes é possível confirmar a presença de granuloma, enquanto em apenas 40% dos casos quando o aspecto macroscópico da mucosa é normal. (36, 37)

Os achados radiográficos foram classificados e relacionados ao prognóstico da doença por Scadding e incluem estágios de 0 a IV, onde 0- normal, I- adenomegalia hilar, II- adenomegalia hilar e lesão parenquimatosa, III- lesões parenquimatosas sem adenomegalias, IV- fibrose pulmonar. O prognóstico piora e a chance de remissão reduz à medida que aumentam as lesões no parênquima.

Dessa forma, os pacientes em estágio I alcançam resolução completa em 50-90% dos casos, no estágio II 30-70% , estágio III 10-20% e no estágio IV 0%.(38,39)
A maior prevalência de pacientes encontra-se no estágio I (45-65%), seguido do estágio II (30-40%), estágio III (10-15%) , estágio 0 (5-15%) e por último estágio IV (5%). (40)

A apresentação clássica da sarcoidose pulmonar na tomografia computadorizada é o predomínio de nódulos peribroncovasculares, em lobos superiores, e nas cisuras, espessamento septal e linfonodomegalia hilar e mediastinal. No entanto, podemos observar várias outras apresentações tomográficas, tais como: calcificação linfonodal em casca de ovo, consolidações, padrão micronodular, aprisionamento aéreo, distorção arquitetural do parênquima com bronquiectasias de tração e faveolamento.(41)

Os testes de função respiratória na sarcoidose podem apresentar um distúrbio restritivo, por se tratar de uma doença com acometimento intersticial, e também obstrutivo, devido aos granulomas peribrônquicos.(42)

Aqueles com doença fibrosante predominam com distúrbio restritivo com capacidade vital forçada (CVF) e difusão de monóxido de carbono (DCO) reduzidas nas fases mais avançadas. A DCO também pode ser útil no diagnóstico de sarcoidose com hipertensão pulmonar, quando observamos redução acentuada da DCO em relação a CVF, inferindo um possível distúrbio vascular associado.. Com frequência observamos valores funcionais no limite inferior da normalidade e quando comparados a controles saudáveis os pacientes com sarcoidose têm resultados inferiores. (43-45) A CVF, o volume expiratório forçado no primeiro segundo (VEF1) e a DCO já foram apontadas como preditores de mortalidade na sarcoidose de forma isolada ou em associação, como no escore de Walsh et al, que é constituído pelo índice fisiológico composto (91 – (0.65 × %DCO) – (0.53 × %CVF) + (0.34 × %VEF1)) , pela razão do diâmetro de artéria pulmonar/ aorta e pela extensão de fibrose no parênquima pulmonar. (46,5)

Outros exames para acompanhamento dos pacientes com sarcoidose incluem eletrocardiograma e ecocardiograma, além de hemograma, função renal, enzimas hepáticas, calcemia, devido aos distúrbios do cálcio, e avaliação por oftalmologista. (47)

1.7 **Tratamento**

O tratamento da sarcoidose é instituído nos pacientes sintomáticos. Alguns podem cursar com resolução espontânea, como ocorre nas apresentações agudas. Quando há a presença de doença parenquimatosa, com disfunção importante, envolvimento do sistema nervoso central, hipercalcemia acentuada, hipercalciuria, doença cardíaca, hepatopatia grave e doença ocular não controlada, o tratamento sistêmico é sempre indicado. A dose de prednisona inicial será entre 20 e 40 mg.(48,49)

Alguns pacientes podem apresentar recidiva após a retirada completa do medicamento. Ainda podemos associar imunossupressores poupadores de corticoide como metotrexato, azatioprina ciclofosfamida, hidroxicloroquina, leflunomida e infliximabe quando os sintomas não são controlados apenas com corticoide e os efeitos colaterais não são tolerados ou o paciente depende de doses altas do medicamento.,. O tratamento deve sempre ser individualizado, de forma que não há um esquema terapêutico superior, e sim uma necessidade de adequação da terapia de acordo com cada caso, levando em consideração a adesão, os efeitos colaterais e o sítio de atividade da doença.(50-52)

1.8 Atividade da sarcoidose e marcadores

A definição da atividade de doença na sarcoidose é um grande desafio. Desde a década de 70 tem-se estudado potenciais marcadores para essa caracterização. Alguns biomarcadores têm sido estudados para tentar determinar a atividade da sarcoidose, tais como a ECA, a CHITO, a PCR, a amiloide A e o receptor de interleucina 2 sérico, porém nenhum deles até então demonstrou elevada sensibilidade e especificidade isoladamente. O objetivo da utilização desses marcadores é guiar o tratamento, identificando as recidivas e impedindo a progressão para a fase fibrótica da doença.(53-55, 7)

A cintilografia com gálio 67 e a tomografia computadorizada com emissão de pósitrons (PET CT) são exames de medicina nuclear utilizados na sarcoidose para detectar atividade da doença. O PET CT tem sensibilidade superior a cintilografia, respectivamente 97% e 88%, e desde a década de 90 tem sido utilizado no diagnóstico e acompanhamento da sarcoidose. (56-59)

1.8.1 Chitotriosidase (CHITO)

A CHITO é uma enzima da família das chitinases que degrada quitina, um polímero que compõe a parede celular de fungos, exoesqueletos de insetos e alguns parasitas. É secretada por neutrófilos e macrófagos pulmonares ativados após estímulo de receptores do tipo Toll, do interferon-γ, fator de necrose tumoral e do fator estimulante de colônias de granulócitos e macrófagos.(60) Sua dosagem foi utilizada principalmente nos pacientes com Doença de Gaucher, porém pode estar alterada em outras condições patológicas, tais como a malária, leishmaniose, tuberculose, talassemia e aterosclerose.(61-63)

Alguns relatos de casos demonstraram maior susceptibilidade de indivíduos com variações genéticas da chitotriosidase às infecções por patógenos portadores do Chitin, como é o caso da filariose, malária, criptococo e cândida.(64–67)

Nos pacientes com sarcoidose, desde 2004 já foi demonstrada a utilização da CHITO como biomarcador de atividade da doença.(68–70) Em indivíduos considerados em remissão da doença a concentração sérica se reduz. Esse decréscimo também foi observado após o início do tratamento com corticoide ou imunossupressores.(70,71)

No entanto, dependendo da população estudada, podemos encontrar diferentes prevalências de indivíduos homozigotos para a duplicação do alelo 24-bp, que não apresentam qualquer atividade da CHITO.(72,73)

1.8.2 Enzima Conversora de Angiotensina (ECA)

A ECA é uma proteína presente na membrana das células epiteliais capilares, principalmente nos pulmões, responsável pela conversão da angiotensina I em angiotensina II e degradação da bradicinina.(74)

Em 1974, pela primeira vez foi constatado por Lieberman o aumento dos níveis séricos da ECA nos pacientes com sarcoidose em atividade (75). Tal fato foi atribuído à produção aumentada pelas células epitelioides dos granulomas. (75,76)

Esta enzima pode estar elevada em outras doenças granulomatosas, tais como tuberculose e histoplasmose, silicose, asbestose, no linfoma de Hodgkin, no hipertireoidismo, entre outras.(75, 77-80)

Na literatura, os dados mostram a presença de ECA aumentada em 40% a 86% dos pacientes com sarcoidose.(81,82) Importante ressaltar que a detecção de polimorfismo no gene da ECA altera os níveis da enzima podendo acarretar em resultados falsamente reduzidos em indivíduos com produção insuficiente da enzima.(83)

No acompanhamento dos pacientes em remissão ou em uso de corticoide, após algumas semanas, seus níveis podem reduzir até valores normais, assim como nasrecidivas, os níveis podem voltam a elevar.(78,84) Alguns estudos correlacionam a atividade da sarcoidose e evolução crônica com valores elevados da ECA, porém outros não encontraram essa mesma correlação, não nos permitindo assumir que a ECA possa ser um adequado biomarcador de atividade e prognóstico.(9)

1.8.3 Proteína C reativa ultra sensível

A proteína C reativa é uma proteína de fase aguda ,produzida pelos hepatócitos, relacionada à inflamação tecidual não específica, podendo estar elevada em diversas situações..(85-90) Na sarcoidose, não observamos importantes alterações nos níveis séricos da PCR us, a não ser em pacientes na fase aguda, como na síndrome de Löfgren.(86,91,92) Ela também foi relacionada com sintomas de fadiga e com a alteração da função pulmonar (redução da CVF). (93-95) Sugere

que pode haver queda da PCR com uso de infliximabe em pacientes com sarcoidose crônica..(96) Até o momento, considera-se que a PCR não é suficiente para predizer gravidade. O método também apresenta baixa sensibilidade para diagnóstico e acompanhamento . (97)

1.8.4 PET CT

A tomografia por emissão de pósitrons utiliza o radiotraçador fluoro-deoxiglicose, um análogo de glicose, que se acumula em tecidos com intenso metabolismo glicolítico utilizando a mesma via da glicose , sendo convertido em FDG 6 fosfato que não é metabolizado, ficando aprisionado na célula. (58) Inicialmente, utilizado nos tumores malignos para estadiamento e avaliação de resposta à quimioterapia e à radioterapia, tem sido aplicado na sarcoidose como instrumento para detectar sítios de doença em atividade, auxiliando no diagnóstico e manejo terapêutico pela identificação de locais mais apropriados para biópsia, extensão da doença e reconhecimento de áreas de atividade nos pacientes com doença fibrosante.(8,59)

2. **JUSTIFICATIVA**

Embora a sarcoidose pulmonar seja uma doença de bom prognóstico na maioria dos casos, alguns pacientes cursam com a forma crônica evoluindo para fibrose pulmonar e aumentando sua morbimortalidade. Algumas características já foram apontadas como preditoras de prognóstico favorável ou desfavorável, porém não há critérios definidos que possam prever o curso da doença. A CHITO, a PCR us e a ECA são biomarcadores séricos estudados para avaliar a capacidade de determinarem atividade de doença, auxiliando no tratamento e seguimento da sarcoidose. Assim como o PET CT através da medicina nuclear.

Por se tratar de uma doença com diversas formas de manifestação, evolução e prognóstico, os marcadores de atividade devem ser exames de fácil realização e acesso à população interessada, para que dessa forma possamos oferecer cuidados individualizados.

3. **HIPÓTESE**

A sarcoidose é uma doença clínica, em geral com curso benigno, podendo apresentar remissão espontânea ou após terapia medicamentosa. Não há um marcador sérico efetivo de atividade da doença. Esta tese tem a hipótese de que a dosagem de biomarcadores incluindo CHITO, ECA e PCR, o PET CT e determinadas características clínicas, funcionais e laboratoriais são instrumentos paraidentificação de atividade da sarcoidose, auxiliando nas decisões terapêuticas.

4. **OBJETIVOS**

4.1 **Objetivo geral**

Identificar fatores relacionados com atividade de doença e prognóstico da sarcoidose durante o acompanhamento dos pacientes com sarcoidose..

4.2 **Objetivos específicos**

4.2.1 Estudo 1

Avaliar atividade sérica de CHITO, nível sérico de ECA e PCR us e determinar um algoritmo pela combinação desses marcadores para diferenciar a sarcoidose em atividade e em remissão.

4.2.2 Estudo 2

Identificar características relacionadas ao prognóstico da sarcoidose e estabelecer um escore preditor de progressão da doença.

4.2.3 Estudo 3

Avaliar PET CT e CHITO como ferramentas para seguimento dos pacientes com sarcoidose, correlacionando atividade metabólica e sérica com a evolução clínica.

5. METODOLOGIA

5.1 **Desenho do estudo**

Estudo observacional constituído por pacientes com sarcoidose atendidos e acompanhados no ambulatório de doenças intersticiais da Policlínica Piquet Carneiro/ UERJ, por 4 anos (2015-2019). Todos os participantes foram informados sobre o projeto de pesquisa e consentiram a realização do trabalho que foi aprovado pelo Comitê de Ética em Pesquisa do Hospital Universitário Pedro Ernesto (CAAE: 46767915.8.00005259). (ANEXO A)

5.2 **Critérios de inclusão e exclusão**

5.2.1 Estudo 1 e Estudo 2

Critérios de inclusão:

a) Maiores de 18 anos;
b) Consentimento formal ao estudo;
c) Ter o diagnóstico de sarcoidose.

Critérios de exclusão:

Estudo1:

a) Abandono de tratamento;
b) Asma grave em uso de corticoide;
c) Doença auto imune associada;

d) Tuberculose em atividade;
e) Doença neoplásica

Estudo 2:

Abandono de tratamento

5.2.2 Estudo 3

Critérios de inclusão:

a) Diagnóstico confirmado de sarcoidose em acompanhamento
b) Realizado PET CT e dosagem de CHITO

Critérios de exclusão:

a) Perda de seguimento ambulatorial
b) Não realização do PET CT em 2 momentos
c) Não realização da dosagem da CHITO em 2 momentos

5.3 **Exames realizados**

5.3.1 Espirometria

A espirometria foi realizada em um sistema computadorizado, modelo *Collins Plus Pulmonary Function Testing Systems* (Warren E. Collins), do Setor de Provas de Função Pulmonar do Serviço de Pneumologia do HUPE – UERJ. As medidas foram realizadas conforme padronização da *American Thoracic Society* (ATS). (98)

A Capacidade vital forçada (CVF) é representada pelo volume de ar exalado em manobra expiratória forçada após uma inspiração máxima. É realizada,

solicitando ao indivíduo que expire rápida e intensamente após realizar uma inspiração máxima.O Volume expiratório forçado no primeiro segundo (VEF1) é o volume máximo que um indivíduo consegue expirar no primeiro segundo de uma expiração máxima. A relação VEF1/CVF é resultado da fração que representa o VEF1 em relação à CVF.

5.3.2 Exames radiológicos

Os pacientes apresentavam os exames de radiografia ou tomografia computadorizada de tórax da manifestação inicial da sarcoidose e do momento da avaliação clínica, classificando em estágios radiológicos, segundo *Scadding,* em 0, 1, 2, 3 ou 4.(38) Os padrões radiológicos foram divididos em vidro fosco, consolidações, linfonodomegalia hilar e mediastinal, infiltrado micronodular ou opacidades nodulares, espessamento septal, espessamento peribroncovascular, bronquiectasias de tração, faveolamento e fibrose. (99) inserir figura dos estagios

5.3.3 Coleta e processamento das amostras

Amostras de sangue periférico obtidas por meio de punção venosa foram coletadas em tubos Vacuntainer® não heparinizados, para obtenção do soro, e em tubos contendo EDTA, para obtenção do plasma. No laboratório, após a centrifugação, as amostras de plasma e soro foram devidamente identificadas e armazenadas a -20ºC até a realização das dosagens.

5.3.3.1 Dosagem sérica da atividade da chitotriosidase

A atividade de CHITO foi determinada pelo método fluorométrico usando o Kit da SIGMA (catálogo CS1030, Sigma Chemical Co, St Louis, MO, EUA), seguindo as

recomendações do fabricante. A atividade da CHITO foi avaliada em espectrofotômetro automatizado (FlexStation 3 Multi-Modo; Molecular Devices, Califórnia, EUA). A fluorescência foi medida com comprimento de excitação de 365nm e um comprimento de onda de emissão de 450 nm a 37ºC. A atividade da CHITO foi expressa em U/mL. (100)

5.3.3.2 Dosagem sérica da proteína C reativa ultra sensível (PCR us)

As concentrações de PCR us foram determinadas por método de imunoensaio por turbidimetria (BioSystems S.A., Barcelona, Spain). O método é sensível para detectar valores de PCR acima de 0,1 mg/L. Os resultados foram expressos em mg/dL. (101)

5.3.3.3 Dosagem Sérica da Enzima Conversora de Angiotensina (ECA)

Para dosagem de ECA foi utilizado o kit de ELISA comercial (R&D Systems, Minneapolis, USA - cat.DY929), onde os soros diluídos 1:100 (em PBS/BSA1%) foram processados, conforme orientação do fabricante. O ensaio foi realizado em duplicatas. A leitura de absorbância foi obtida a 450nm em espectrofotômetro (Thermo Fisher Scientific - Multiskan FC, catálogo: 51119000). Os resultados foram expressos em ng/mL. (102)

5.3.3.4 Marcadores reumatológicos

O fator antinuclear (FAN), fator reumatoide (FR) e anticorpo anti-citoplasmático de neutrófilo (ANCA) dos pacientes foram dosados no momento do diagnóstico e durante o acompanhamento. Consideramos positivo quando FR ou ANCA foram reagentes ou FAN $\geq$ 1/160.

5.3.3.5 PET CT

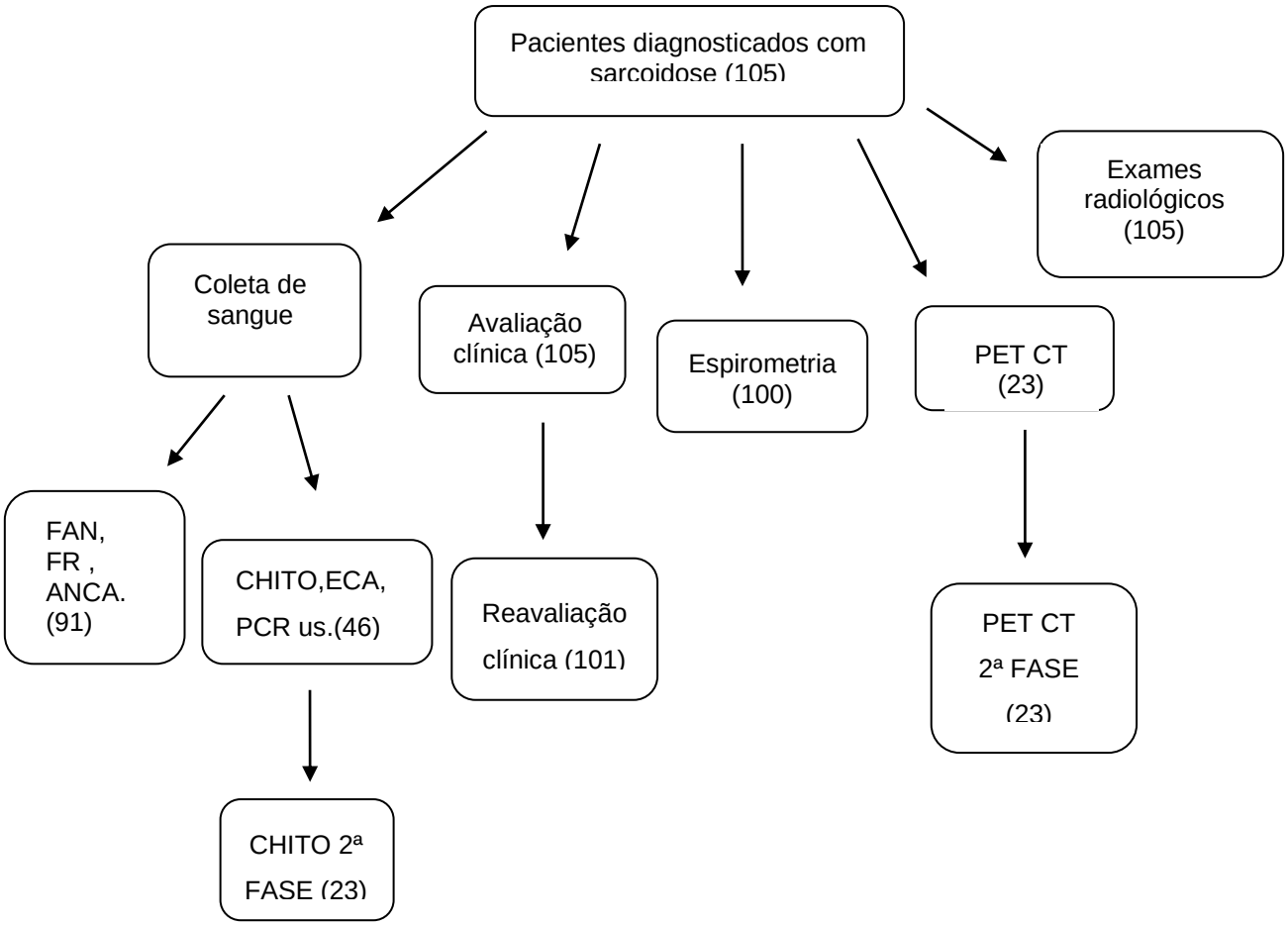
O exame foi realizado no Instituto Nacional do Câncer (INCA). O paciente foi posicionado no equipamento 60 minutos após a injeção do radiofármaco 18F-fluorodeoxiglicose. Foram obtidas imagens de tomografia sem contraste e, em seguida, imagens volumétricas tridimensionais de PET, ambas do vértex do crânio até o meio das coxas com o equipamento Philips Gemini TF w/ToF 64 (Cleveland, OH, USA). As imagens foram revisadas nos planos transaxial, coronal e sagital. A análise semiquantitativa foi realizada através do SUVmax (valor máximo padronizado de captação) considerando como índice de correção a massa corpórea do paciente.(103)

5.4 **Ordem dos exames**

Os testes de função pulmonar e a coleta de sangue foram realizadas no Hospital Universitário Pedro Ernesto (HUPE) na apresentação inicial dos pacientes, assim como os estudos radiológicos. Os testes de função pulmonar e os exames de imagem foram repetidos durante o acompanhamento. Alguns pacientes foram acompanhados desde o momento do diagnóstico, outros já estavam em tratamento e foram incluídos durante o seguimento no ambulatório de doenças intersticiais da Universidade do Estado do Rio de Janeiro (UERJ). A dosagem da CHITO e o PET CT foram realizados em dois momentos.

O processamento das amostras de sangue para dosagem de CHITO, ECA e PCR us foi realizado no Laboratório de Imunopatologia da Faculdade de Ciências Médicas, em parceria com a Fundação Oswaldo Cruz (FIOCRUZ) e a Universidade Federal do Rio de Janeiro (UFRJ).

Figura 1 – Fluxograma dos estudos



5.5 **Definição dos grupos**

5.5.1 Grupo de sarcoidóticos

Pacientes com diagnóstico estabelecido de sarcoidose, realizado pelo conjunto de processo granulomatoso não caseoso de qualquer tecido, associado a exclusão de outras doenças granulomatosas, com quadro radiológico e clínico compatível.(1)

5.5.1.1 Sarcoidóticos em atividade

Pacientes com poliartralgia, poliatrite, eritema nodoso, nódulo ou pápulas cutâneas, sintomas cardiológicos, neurológicos, oftalmológicos associados à sarcoidose, sintomas respiratórios, piora das alterações nos exames de imagem ou nos parâmetros de função pulmonar. (1,104,105)

5.5.1.2 Sarcoidóticos em remissão

Pacientes com diagnóstico de sarcoidose, sem sintomatologia (respiratória, cardíaca, osteomuscular e neurológica) e sem tratamento com corticosteroides. (1,104,105)

5.5.2 Grupo controle

São voluntários saudáveis sem história de doença pulmonar, cardíaca, reumatológica e neurológica, sem histórico de doença crônica ou aguda atual, e que

realizaram exames de sangue em somente um momento, para comparar com o grupo dos pacientes portadores de sarcoidose.

5.6 **Evolução clínica**

Os pacientes foram questionados sobre os sintomas relacionados à sarcoidose apresentados inicialmente, no momento do diagnóstico. Os sintomas respiratórios incluíram: dispneia, dor torácica não anginosa, tosse e sibilos. Os sintomas constitucionais foram: febre, fadiga, perda ponderal, artralgia e sudorese noturna. As palpitações e a angina foram classificadas como sintomas cardiológicos e a paralisia facial e o desequílibrio, sintomas neurológicos.

Posteriormente, após um período mínimo de 24 meses, os pacientes foram classificados de acordo com sua evolução clínica com base na classificação de Baughman et al. (*clinical outcome status* – COS), na qual: COS 1 = doença resolvida sem nunca tratar; COS 2 = doença resolvida sem tratar há mais de 1 ano; COS 3 = doença residual (menos de 25% do máximo de lesão) sem nunca tratar; COS 4 = doença residual sem tratar há mais de 1 ano; COS 5 = doença persistente sem nunca tratar; COS 6 = doença persistente sem tratar há mais de 1 ano; COS 7 = em tratamento e assintomático, sem piora no último ano; COS 8 = em tratamento e sintomático, sem piora no último ano; COS 9 = em tratamento e sintomático, com piora no último ano.(45)

6.0 **RESULTADOS E DISCUSSÃO**

Nesta Tese são apresentados os três estudos como resultados e discussão. O primeiro estudo representa o artigo publicado na revista LUNG, em março de 2019, “Identification of Active Sarcoidosis Using Chitotriosidase and Angiotensin-Converting Enzyme”. O segundo representa o artigo aceito para publicação na revista Medicine, em novembro de 2020, “Defining prognosis in sarcoidosis”. O terceiro estudo “Evaluation of PET/CT and chitotriosidase as predictors of sarcoidosis activity”, já concluído, será apresentado no corpo da tese.

6.1 **Estudo 1**

Identification of Active Sarcoidosis Using Chitotriosidase and Angiotensin-Converting Enzyme (artigo publicado)

Introduction

Sarcoidosis is a multisystem disease, with predominantly pulmonary involvement, no clear etiology, and a variable prevalence throughout the world [1]. Since the 1980s, some markers have been studied to aid the follow-up and treatment of patients and to differentiate between active sarcoidosis and sarcoidosis that is in remission; however, the latter still poses a great challenge [2–5].

Angiotensin-converting enzyme (ACE) has been studied as a biomarker for active sarcoidosis since 1975, but its use is complicated by the fact that other diseases have been also shown to raise the levels of this enzyme [6–9]. The usefulness of ACE for the diagnosis or follow-up of sarcoidosis is controversial, with values of sensitivity and specificity varying between studies [5, 10, 11].

High-sensitivity C-reactive protein (hs-CRP) is a nonspecific acute-phase response biomarker. It is produced by hepatocytes and is used to screen for diseases, monitor therapeutic responses, and detect infections in immunocompromised patients [12]. In sarcoidosis, however, hs-CRP has failed to demonstrate a significant change in most of studies, only being associated with constitutional symptoms, such as fatigue and with Lofgren's syndrome [13, 14].

The diagnosis of sarcoidosis requires histopathological demonstration of non-caseating granulomas composed of activated macrophages [15, 16]. These macrophages express an enzyme called chitotriosidase (CHITO), which is involved in the pathogenesis of sarcoidosis [17].

Chitotriosidase is an enzyme of the chitinase family. It degrades a polymer known as chitin, which is found in the cell walls of fungi and the exoskeletons of insects and crustaceans. Pulmonary neutrophils and macrophages secrete the enzyme after the stimulation of Toll-like receptors by interferon-γ (IFN-γ), tumor

necrosis factor (TNF), and granulocyte/macrophage colony-stimulating factor (GMCSF)[18]. Its activity is also high in other diseases, such as Gaucher disease, malaria, leishmaniasis, beta thalassemia,multiple sclerosis, atherosclerosis, Alzheimer's disease, and tuberculosis [19, 20]. Chitotriosidase is a biomarker that can be measured in both blood and bronchoalveolar lavage fluid samples [21].

The aim of this study was to evaluate the association of serum CHITO activity, ACE levels, and high-sensitivity C-reactive protein (hs-CRP) levels, or a combination of these putative biomarkers, with active sarcoidosis and to construct an algorithm to better differentiate between active sarcoidosis and sarcoidosis that is in remission.

Methods

Study Subjects

A cross-sectional study was performed in sarcoidosis patients and healthy controls at the State University of Rio de Janeiro (UERJ/Brazil) between August 2015 and February 2017. The diagnosis of sarcoidosis was made according to the guidelines of international societies [14]. The active sarcoidosis group consisted of patients with symptoms, but without previous treatment (treatment-naive patients);patients with an established diagnosis, persistent symptoms,and currently under treatment; or patients with symptoms and evidence of disease progression in tomographic images of the chest [11, 12, 15]. The second study group consisted of sarcoidosis patients in remission. These patients had previously been treated for sarcoidosis, but were currently asymptomatic, with demonstrated disease improvement in tomographic images [11, 12, 15]. The third group consisted of healthy, non-smoking individuals, with no prior or current illnesses and not currently taking any medication.

Laboratory Measurements

Peripheral blood was collected from all study subjects and used to measure serum ACE levels, hs-CRP levels, and CHITO activity.

The concentration of hs-CRP in serum samples was determined using a latex-enhanced turbidimetric immunoassay (BioSystems S.A., Barcelona, Spain). Data were expressed as mg/dL.

Serum ACE concentration was quantified using a sandwich enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, USA). Data were expressed as ng/mL.

CHITO activity was determined by a fluorometric method [21], using the Chitinase Assay Kit (catalog number CS1030, Sigma Chemical Co,St Louis, MO, USA). CHITO activity was expressed in U/mL.

Statistical Analysis

Sociodemographic data, clinical data, and laboratory measurements were analyzed among the different groups. For continuous numerical variables, Kruskal–Wallis ANOVA by ranks tests was used to test the hypothesis that the different samples in the comparison were drawn from the same distribution or from distributions with the same median. Similarly, for categorical nominal variables, the Fisher's exact test was used to evaluate frequencies among

the different groups to test the independence between the groups and these variables. Pairwise comparisons of laboratory variable means among the groups of interest were performed by contrasts/differences obtained after both biand multivariate linear models fitted using ordinary least square regressions. To eliminate sample bias, confounding variables were selected by bivariate linear models fitted with ordinary least square regressions by backward elimination and were retained in multivariate models. The cutoff points of the biomarkers for active disease/remission differentiation were calculated from receiver operating characteristic (ROC) curves

using the Youden's index. Additionally, a decision tree classifier (DTC) was built using an implementation of Quinlan's C4.5 algorithm [22]. DTC training parameters included the following: (1) two, as the minimum number of observations that must exist in a node for a split to be attempted; (2) one, as the minimum number of observations in any terminal leaf node; (3) ten,as the maximum depth of any node of the final tree, with the root node counted as depth 0; and (4) Gini impurity as a measure of how often a randomly chosen element from the set would be incorrectly labeled if it were randomly labeled according to the distribution of labels in the subset. Performance of sarcoidosis status differentiation by the biomarkers' cutoff points and by the classification tree was estimated by its leave-one-out cross-validation (LOOCV) accuracy, sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and false positive and negative ratios, with their 95% confidence intervals (CI). All analyses were performed using R software v.3.4.3.

Results

Almost all patients had histopathological evidence of noncaseous granulomatous lesions. Only one patient had a transbronchial biopsy specimen that was insufficient for histological diagnosis. However, bronchoalveolar lavage showed a CD4/CD8 ratio of 8.2 for this patient. Fifty-three patients were selected for the study. Of these, seven were excluded due to severe asthma and corticosteroid use, four were excluded due to autoimmune diseases (two with lupus, one with rheumatoid arthritis, and one with Sjogren's syndrome), and the other two were excluded due to active tuberculosis and leukemia. After exclusions, 46 patients diagnosed with sarcoidosis and 21 healthy individuals were included in the study.

Patients with sarcoidosis were divided into two groups based on whether the disease was active (n = 27) or in remission (n = 19). The active sarcoidosis group consisted of 12 treatment-naïve patients with symptoms; 15 patients with an established diagnosis and persistent symptoms; and 2 patients still under treatment for the maintenance of symptoms, with evidence of disease progression in tomographic images of the chest [11, 12, 15]. The symptoms found in patients currently undergoing treatment for active disease, included cutaneous lesions (n =

12), dyspnea (n = 9), cough (n = 1), and chest pain (n = 1). Of the fifteen patients undergoing treatment, thirteen were using prednisone and two were using hydroxychloroquine. However, eight patients required a second drug (methotrexate or hydroxychloroquine) to optimize their treatment.

The median ages of the patients with sarcoidosis were 46 and 56 years (active and in remission, respectively), with a higher ratio of females, non-Caucasians, and individuals with no history of smoking in the sarcoidosis groups compared with the control group (Table 1). Serum ACE levels, hs-CRP levels, and CHITO activity were measured for all subjects.

The mean (95% CI) serum ACE concentrations were 341.18 ng/mL (269.57–412.79) in the control group, 337.866 ng/mL (262.47–413.26) in the sarcoidosis remission group, and 470.96 ng/mL (407.81–534.09) in the active sarcoidosis group. These values were significantly higher in the active sarcoidosis group compared to the control (P = 0.023) and sarcoidosis remission groups (P = 0.024).

Mean (95% CI) serum chitotriosidase activities were 65.55 U/mL (37.78–168.88) in the control group, 38.096 U/mL (70.54–146.73) in the sarcoidosis remission group, and 297.11 U/mL (205.98–388.24) in the active sarcoidosis group. Again, these values were significantly higher in the active sarcoidosis group compared to the control (P = 0.004) and sarcoidosis remission groups (P = 0.001). There were no significant differences in ACE levels or CHITO activity between the control and sarcoidosis remission groups (Fig. 1). Mean values were adjusted to avoid sample bias by gender in the ACE analysis.

The mean (95% CI) serum hs-CRP concentrations were 0.279 mg/dL (0.18–0.74) in the control group, 0.378 mg/dL (0.11–0.86) in the sarcoidosis remission group, and 1.003 mg/dL (0.6–1.41) in the active sarcoidosis group. We find only nonsignificant trend toward increased serum hs-CRP concentration in the active sarcoidosis group (P = 0.056) compared to the control group (Fig. 1).

For serum ACE concentration, we calculated a cutoff value of 270 ng/mL to identify active sarcoidosis, with an approximate mean sensitivity (95% CI) of 88% (70–97%), a specificity of 47% (24–71%), a PPV of 70% (46–92%), and an NPV of 75% (47–89%). For serum hs-CRP concentration, the cutoff was calculated at 0.4 mg/dL, with an approximate mean sensitivity of 66% (46–83%), a specificity of 68% (43–87%), a PPV of 75% (51–88%), and an NPV of 59% (38–82%). The cutoff value for serum CHITO activity was 120 U/mL, with a mean sensitivity of 55% (35–75%), a

specificity of 100% (82%–∞), a PPV of 100% (78%–∞),and an NPV of 61% (40%–∞) (Fig. 2).

All patients were classified into two subgroups according to their radiological stage, which was categorized from 0 to 4. Higher mean levels (95% CI) of CHITO activity were observed in a combined group of patients with radiological stages of 0, 1, or 2 (447.255 U/mL; 273.61–620.9), than in a combined group of patients with stages 3 and 4 (135.417 U/mL; − 45.51–316.34; P = 0.022). We also observed higher ACE concentrations in stage 0/1/2 patients (532.63 ng/mL; 454.84–610.41) than in stage 3/4 patients (401.553 ng/mL; 320.49–482.62; P = 0.031). There was no significant diferences in hs-CRP levels according to radiological stage (Fig. 3).

In the group of patients with active sarcoidosis, there were no significant differences in CHITO activity, ACE levels, or hs-CRP levels between those with or without treatment. The forced vital capacity (FVC), forced expiratory volume-one second (FEV1), FEV1/FVC, and diffusing capacity of the lung for carbon monoxide (DLCO) values were also not significantly different between patients with active sarcoidosis and those in remission.

By training and pruning a DTC for active disease/remission differentiation, we found an algorithm with a mean LOOCV accuracy of 82.61% (74.24–90.97%), LOOCV sensitivity of 77.78% (65.61–89.94%), and LOOCV specificity of 89.47% (78.59–100%). To assemble this algorithm, the following parameters were included: CHITO activity, hs-CRP concentration, and ACE concentration (Fig. 4; Table 2).

Table 1: Clinical aspects of the study population

	Sarcoidosis, active (N=27)	**Sarcoidosis, remission (N=19)**	**Healthy (N=21)**	**P-value***
Age in years	46 [13.5]	56 [18.5]	39 [20]	0.0018
Gender				
Female	19 (28.4)	12 (17.9)	15 (22.4)	0.8516
Male	8 (11.9)	7 (10.4)	6 (9.0)	
Race				
Caucasian	11 (16.4)	4 (6.0)	0	<0.0001
Other	16 (23.9)	15 (22.4)	0	
Unknown	0	0	13 (19.4)	
Smoking status				
Current	1 (1.5)	1 (1.5)	0	0.0157
Never	21 (31.3)	13 (19.4)	0	
Former	5 (7.5)	5 (7.5)	0	
Unknown	0	0	3 (4.5)	
Stage				
1	1 (1.5)	0	0	<0.0001
2	13 (19.4)	0	0	
3	8 (11.9)	0	0	
4	5 (7.5)	0	0	
N.A.	0	19 (28.4)	21 (31.3)	
Treatment				
Untreated	12 (17.9)	0	0	<0.0001
In treatment	15 (22.4)	0	0	
Treated	0	19 (28.4)	0	
N.A.	0	0	21 (31.3)	
FVC (%)	85 (20.5)	88 (17.5)	N.A.	0.554
FEV_1 (%)	82 (24.0)	86 (13)	N.A.	0.3481
FEV_1/FCV	77 (11.0)	78 (11.01)	N.A.	1
DLCO (%)	87 (26.5)	98 (23.75)	N.A.	0.1098
Clinical manifestation				<0.0001
Pulmonary	9 (13.4)	N.A.	N.A.	
Extrapulmonary	9 (13.4)	N.A.	N.A.	
Disseminated	4 (6)	N.A.	N.A.	
Asymptomatic	5 (7.5)	N.A.	N.A.	
Years after diagnosis	1 [6.75]	7 [8]	N.A.	0,0013

Data are given either as median (IQR) or absolute (relative) frequencies for numeric continuous and categorical nominal variables, respectively
N.A. not available; *FVC* forced vital capacity; *FEV1* forced expiratory volume-one second; *DLCO* diffusing capacity of the lung for carbon monoxide
*For categorical nominal variables, *P* values were calculated using Fisher's exact test. For numeric continuous variables, *P* values were calculated using Kruskal–Wallis ANOVA by ranks test. Differences were considered significant with * *P* values < 0.05. *N* = number of individuals
Fonte: A autora, 2020.

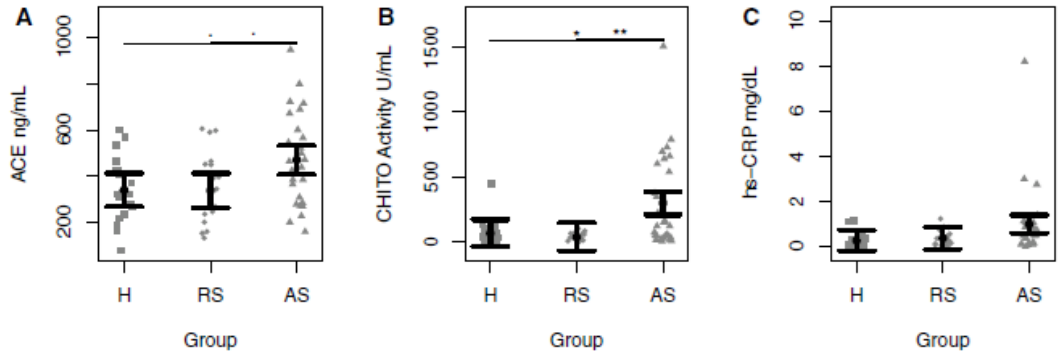


Fig. 1 Biomarker levels according to sarcoidosis status. Patients with sarcoidosis were divided into two groups: those with active disease (n = 27, AS) and those in remission (n = 19, RS). A third group of healthy control individuals was also included (n = 21, H). Serum a ACE levels, b CHITO activity, and c hsCRP levels are represented by gray squares, circles, and triangles, respectively, for groups H, RS, and AS. Black dots and vertical bars represent the linear model estimated adjusted means and 95% confidence intervals (95% CI), respectively. Adjusted means and 95% CI were 341.18 (269.57– 412.79), 337.866 (262.47–413.26), and 470.955 (407.81–534.09) ng/mL for ACE; 65.552 (37.78–168.88), 38.096 (70.54–146.73), and 297.111 (205.98–388.24) U/mL for CHITO activity; and 0.279 (0.18–0.74), 0.378 (0.11–0.86), and 1.003 (0.6–1.41) mg/dL for hs-CRP for groups H, RS, and AS, respectively. Serum ACE levels were adjusted by gender. No confounding variables were selected in bivariate analysis of serum CHITO activity or hs-CRP levels. P values were determined using the Tukey Honest significant difference post hoc method. P < 0.1, *P < 0.05, **P < 0.01.
Fonte: A autora, 2020.

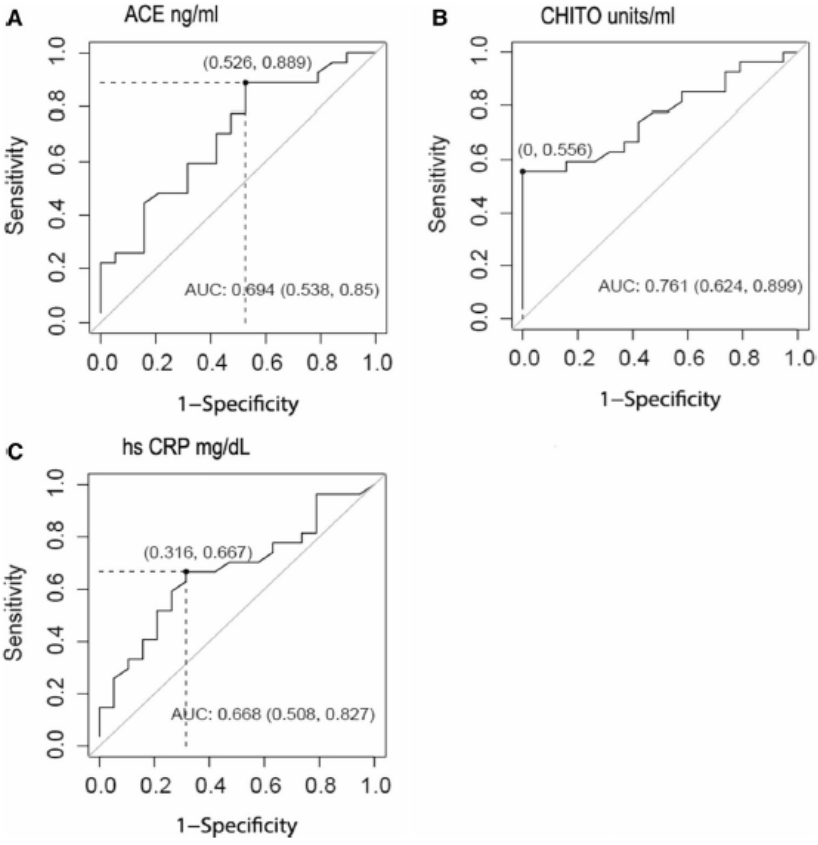


Fig. 2 Selection of optimal discriminant sarcoidosis activity cutoff values calculated from the ROC. ROC curves are represented by solid black lines and optimal sarcoidosis activity discrimination points, as selected by the Youden's index, are represented by solid black dots. Diagonal gray solid lines represent random discrimination. The main results are a ACE concentration: sensitivity of 88% and specificity of 47% for a cutoff value of 270 ng/mL; b CHITO activity: sensitivity of 55% and specificity of 100% for a cutoff value of 120 U/mL; and c hs-CRP concentration: sensitivity of 66% and specificity of 68% for a cutoff value of 0.4 mg/dL. AUC area under the Curve.
Fonte: A autora, 2020.

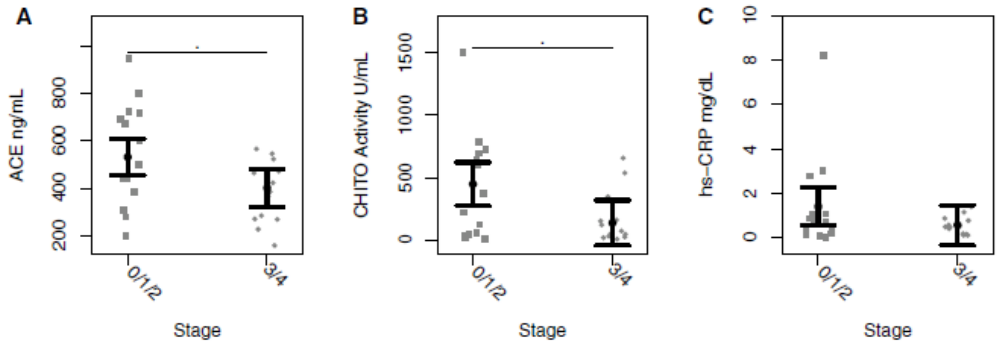


Fig. 3 Biomarker levels in patients with active sarcoidosis according to radiological stage. Patients with active sarcoidosis were divided by radiological stage, as either stage 0/1/2 (n = 14) or stage 3/4 (n = 13). Serum a ACE levels, b CHITO activity, and c hs-CRP levels are represented by gray squares, circles, and triangles, respectively. Black dots and vertical bars represent linear model estimated adjusted means and 95% confidence intervals (95% CI). Adjusted means and 95% CI were 532 ng/mL in stage 0/1/2 and 401 ng/mL in stage 3/4 for ACE concentration; 447 U/mL in stage 0/1/2 and 135 U/mL in stage 3/4 for CHITO activity; and 1.4 mg/dL in stage 0/1/2 and 0.56 mg/dL in stage 3/4 for hs-CRP concentration. Serum ACE levels were adjusted for the confounding variables, gender, clinical manifestation, and treatment. Serum CHITO activity levels were adjusted
for the confounding variables, race, treatment, and time (in years) after sarcoidosis diagnosis. No confounding variables were selected in bivariate analysis of serum hs-CRP levels. P values were calculated using the Tukey Honest Significant Difference post hoc method. P < 0.1, *P < 0.05, **P < 0.01.
Fonte: A autora, 2020.

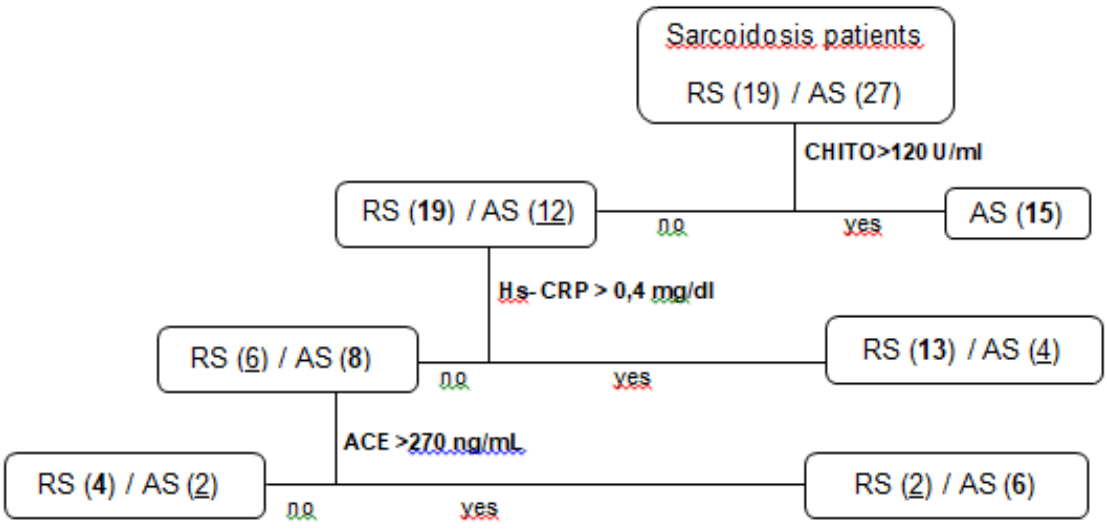


Fig. 4 Graphical representation of decision tree classifier (DTC) for discrimination between active sarcoidosis (n= 27, AS) and sarcoidosis in remission (n = 19, RS). Terminal branches (squares) indicate the class (either AS and RS), and the number inside the branches are their true positive and false positive results (black) and false positive and false negative results (underline). A mean LOOCV accuracy of 82% was found for the determination of patients with active sarcoidosis.
Fonte: A autora, 2020.

Table 2 Assessment of accuracy by the biomarkers and the algorithm to identification of activity or remission sarcoidosis

	CHITO	ECA	PCR us	ALGORITHM
Acc	0.73	0.71	0.67	0.82
Se	0.55	0.88	0.66	0.77
Sp	1.00	0.47	0.68	0.89
PPV	1.00	0.70	0.75	0.91
NPV	0.61	0.75	0.59	0.73
FPR	0.00	0.52	0.31	0.10
FNR	0.44	0.11	0.33	0.22

Performance was estimated by its leave-one-out cross-validation (LOOCV) accuracy (Acc), sensitivity (Se), specificity (Sp), positive(PPV) and negative predictive values (NPV), false positive and negative ratios, with their 95% confidence intervals (CI). Performance evaluation of sarcoidosis activity by the classification tree for activity/remission differentiation combining CHITO activity (> 120 U/mL), hs-CRP (> 0.4 mg/dL), and ACE (> 270 ng/ml) data.The performance was estimated by its leave-one-out cross-validation(LOOCV) accuracy, sensitivity, specificity, positive and negative predictivevalues, false positive and negative ratios, with their 95% confidence intervals (CI).
Fonte: A autora, 2020.

Discussion

One of the major challenges in the management of patients with sarcoidosis is identifying whether they have active disease or are in remission. Treatment of the disease is time dependent and involves progressively smaller doses until it is adequately controlled [14–23]. The purpose of this study was to construct an algorithm, using three recognized biomarkers of sarcoidosis, to allow the differentiation between active disease and remission. In addition, we showed that CHITO activity has discriminatory power when its values are high, with a specificity of 100%. Elevated CHITO activity in peripheral blood has been previously described for sarcoidosis diagnosis and should be investigated when the clinical and epidemiological context is compatible with other clinical conditions [10, 20, 21].

ACE is the most commonly used biomarker for both diagnosis and follow-up [24]. In sarcoidosis patients, the use of corticosteroids and different radiological stages of disease may affect ACE levels. In contrast to other reports, we did not find

a difference in ACE levels between treated and treatment-naïve patients. The highest ACE levels were seen in patients at stages 0, 1, and 2. Some other studies have failed to demonstrate a relationship between serum ACE levels and radiological stages, suggesting that ACE levels may be related to the patient's granuloma burden [4, 5, 7, 10, 25, 26]. ACE levels also depend on genetic variations, such as the I/D polymorphism, where DD genotypes are associated with higher levels, ID with intermediate levels, and II with lower levels[27]. Two published studies have shown mean sensitivity values of 66 and 77% and mean specificity values of 54 and 88% for the differentiation of active sarcoidosis from remission [10, 11]. In our study, ACE levels were higher in patients with active disease than in controls or patients in remission, with a sensitivity of 88% and a specificity of 47%.

CRP is used as a biomarker of inflammation in several diseases. In sarcoidosis, however, only slight elevations in CRP have been reported [14, 28]. We also observed slightly elevated levels of hs-CRP in patients with active sarcoidosis.

Since 2004, studies have shown that CHITO activity is higher in sarcoidosis patients compared to healthy controls and the activity levels increase with the severity and radiological stage of the disease [29]. However, in individuals in remission, CHITO activity is reduced [29,30]. We also found that mean CHITO activity was higher in patients with active disease than in controls or patients in remission. Other studies have also shown a decrease in CHITO levels in sarcoidosis patients, including in those who started treatment with corticosteroids or immunosuppressants [30–32]. In addition, the active sarcoidosis group did not show difference in CHITO activity among treated and untreated patients. This may be due to the fact more than half of the patients undergoing treatment did not have their disease under control and required further optimization of their therapy. CHITO activity may be related to this disease profile. Moreover, we may have found a relationship if we continued to measure CHITO activity during the course of treatment and not only at one time point. However, we did not have the opportunity to do this in these patients. To gain large enough groups to achieve appropriate statistical power, we needed to group the patients into two groups based on radiological stage. Patients classified as stage 0, 1, and 2 had the highest levels of CHITO activity, which is contrary to what has been reported by other authors [10, 30, 33].

A CHITO gene polymorphism has been described, consisting of the duplication of 24 bp in exon 10, which introduces a stop codon that causes the

deletion of 87 nucleotides in the transcribed RNA. This deletion results in decreased production of the enzyme. Lee et al. [34] estimated the allele frequency of this polymorphism in different populations and reported values varying between 7–64%. In Brazil, this variant is present in 30% of the population [35]. Among the patients in our study classified as having active sarcoidosis, we observed a case with a CHITO activity value of 3.58 U/mL, which may be explained by the presence of this variant. However, genotyping was not performed to confirm this hypothesis.

Our work does have some limitations. For example, this was a single-center study, performed over a short time interval, with a limited sample size, and the influence of immunosuppressive therapy on the activity of biomarkers. Furthermore, we did not perform genotyping to detect possible CHITO or ACE variants. Biomarkers were also measured at just one time point, thus not allowing the assessment of their changes during treatment.

Many potential biomarkers of sarcoidosis have been studied in isolation for the diagnosis and follow-up of the disease. However, this is the first study using a combined analysis of more than one biomarker to determine disease activity. We achieved high accuracy and specificity, and therefore, this approach may help in the follow-up of these patients.

References

1. Sharma OP (2008) Sarcoidosis around the world. Clin Chest Med 29:357–363. https ://doi.org/10.1016/j.ccm.2008.03.013

2. Sharma OP (1986) Markers of sarcoidosis activity. Chest 90:471–473

3. Müller-Quernheim J (1998) Serum markers for the staging of disease activity of sarcoidosis and other interstitial lung disease of unknown etiology. Sarcoidosis Vasc Diffuse Lung Dis 15:22–37

4. Miyoshi S, Hamada H, Kadowaki T, Hamaguchi N, Ito R, Irifune K, Higaki J (2010) Comparative evaluation of serum markers in pulmonary sarcoidosis. Chest 137:1391–1397. https ://doi.org/10.1378/chest .09-1975

5. Gungor S, Ozseker F, Yalcinsoy M, Akkaya E, Can G, Eroglu H, Genc NS (2015) Conventional markers in determination of activity of sarcoidosis. Int Immunopharmacol 25:174–179. https ://doi.org/10.1016/j.intim p.2015.01.015

6. Erdös EG (1976) Conversion of angiotensin I to angiotensin II. Am J Med 31:60:749–759

7. Brice EA, Friedlander W, Bateman ED, Kirsch RE (1995) Serum angiotensin-converting enzyme activity, concentration, and specific activity in granulomatous interstitial lung disease, tuberculosis, and COPD. Chest 107:706–710

8. Ryder KW, Jay SJ, Kiblawi SO, Hull MT (1983) Serum angiotensin converting enzyme activity in patients with histoplasmosis.JAMA 249:1888–1889

9. Romer FK (1985) Angiotensin-converting enzyme activity in sarcoidosis and other disorders. Sarcoidosis 2:25–34

10. Popević S, Šumarac Z, Jovanović D, Babić D, Stjepanović M, Jovičić S et al (2016) Verifying sarcoidosis activity: chitotriosidase versus ace in sarcoidosis—a case-control study.J Med Biochem 35:390–400. https ://doi.org/10.1515/jomb-2016-0017

11. Klech H, Kohn H, Kummer F, Mostbeck A (1982) Assessment of activity in Sarcoidosis. Sensitivity and specificity of 67 Gallium scintigraphy, serum ACE levels, chest roentgenography, and blood lymphocyte subpopulations. Chest 82:732–738

12. Pepys MB, Hirschfield GM (2003) C-reactive protein: a critical update. J Clin Invest 111:1805–1812

13. Ziegenhagen MW, Rothe ME, Schlaak M, Muller-Quernheim J (2003) Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. Eur Respir J 21:407–413

14. Drent M, Wirnsberger RM, de Vries J, Van Dieijen-Visser MP, Wouters EF, Schols AM (1999) Association of fatigue with na acute phase response in sarcoidosis. Eur Respir J 13:718–722

15. ATS/ERS/WASOG (1999) Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 160:736–755

16. Hernandez-Pando R, Bornstein QL, Aguilar Leon D, Orozco EH, Madrigal VK, Martinez Cordero E (2000) Inflammatory cytokine production by immunological and foreign body multinucleated giant cells. Immunology 100:352–358.

17. Korolenko TA, Zhanaeva SY, Falameeva OV, Kaledin VI, Filyushina EE, Buzueva II, Paul GA (2000) Chitotriosidase as a marker of macrophage stimulation. Bull Exp Biol Med 130:948–950

18. Cho SJ, Weiden MD, Lee CG (2015) Chitotriosidase in the pathogenesis of inflammation, interstitial lung diseases and COPD. Allergy Asthma Immunol Res 7:14–21

19. Cakır G, Gumus S, Ucar E, Kaya H, Tozkoparan E, Akgul EO, Karaman B, Deniz O, Kurt I, Ozkan M, Bilgic H (2012) Serum chitotriosidase activity in pulmonary tuberculosis: response to treatment and correlations with clinical parameters. Ann Lab Med 32:184–189. https ://doi.org/10.3343/alm.2012.32.3.184

20. Tasci C, Tapan S, Ozkaya S, Demirer E, Deniz O, Balkan A, Ozkan M, Inan I, Kurt I, Bilgic H (2012) Efficacy of serum chitotriosidase activity in early treatment of patients with active tuberculosis and a negative sputum smear. Ther Clin Risk Manag 8:369–372. https ://doi.org/10.2147/TCRM.S3175 2

21. Bargagli E, Margollicci M, Perrone A, Luddi A, Perari MG, Bianchi N, Refini RM, Grosso S, Volterrani L, Rottoli P (2007) Chitotriosidase analysis in bronchoalveolar lavage of patients with sarcoidosis. Sarcoidosis Vasc Diffus Lung Dis 24:59–64

22. Salzberg SL (1994) C4.5: programs for machine learning by J.Ross Quinlan. Morgan Kaufmann Publishers, Inc., 1993. Mach Learning 16:235–240

23. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L,Shigemitsu H, Culver DA, Gelfand J, Valeyre D, Sweiss N,Crouser E, Morgenthau AS, Lower EE, Azuma A, Ishihara M, Morimoto S, Tetsuo Yamaguchi T, Shijubo N, Grutters JC, Rosenbach M, Li HP, Rottoli P, Inoue Y, Prasse A, Baughman RP, Organ Assessment Instrument Investigators TW (2014) The WASOG Sarcoidosis Organ Assessment Instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis 18(1):19–27

24. Lieberman J (1975) Elevation of serum angiotensin converting enzyme (ACE) level in sarcoidosis. Am J Med 59:365–372

25. Ainslie GM, Benatar SR (1985) Serum angiotensin converting enzyme in sarcoidosis: sensitivity and specificity in diagnosis: correlations with disease activity, duration, extra-thoracic involvement, radiographic type and therapy. Q J Med 55:253–270

26. Ungprasert P, Carmona EM, Crowson CS, Matteson EL (2016) Diagnostic utility of angiotensin converting enzyme in sarcoidosis: a population-based study. Lung 194:91–95. https ://doi.org/10.1007/s0040 8-015-9826-3

27. Floe A, Hoffmann HJ, Nissen PH, Moller HJ, Hilberg O (2014) Genotyping increases the yield of angiotensin-converting enzyme in sarcoidosis–a systematic review. Dan Med J 61:A4815

28. Hind CR, Flint KC, Hudspith BN, Felmingham D, Brostoff J, Johnson NM (1987) Serum C-reactive protein concentrations in patients with pulmonary sarcoidosis. Thorax 42:332–335

29. Grosso S, Margollicci MA, Bargagli E, Buccoliero QR, Perrone A, Galimberti D, Morgese G, Balestri P, Rottoli P (2004) Serum levels of chitotriosidase as a marker of disease activity and clinical stage in sarcoidosis. Scand J Clin Lab Invest 64:57–62

30. Bargagli E, Bennett D, Maggiorelli C, Di Sipio P, Margollicci M, Bianchi N, Rottoli P (2013) Human chitotriosidase: a sensitive biomarker of sarcoidosis. J Clin Immunol 33:264–270

31. Boot RG, Hollak CE, Verhoek M, Alberts C, Jonkers RE, Aerts JM (2010) Plasma chitotriosidase and CCL18 as surrogate markers for granulomatous macrophages in sarcoidosis. Clin Chim Acta 411:31–36

32. Tercelj M, Salobir B, Simcic S, Wraber B, Zupancic M, Rylander R (2009) Chitotriosidase activity in sarcoidosis and some other pulmonary diseases. Scand J Clin Lab Invest 69:575–578

33. Bargagli E, Bianchi N, Margollicci M, Olivieri C, Luddi A, Coviello G, Grosso S, Rottoli P (2008) Chitotriosidase and soluble IL-2 receptor: comparison of two markers of sarcoidosis severity.Scand J Clin Lab Invest 68:479–483

34. Lee P, Waalen J, Crain K, Smargon A, Beutler E (2007) Human chitotriosidase polymorphisms G354R and A442V associated with reduced enzyme activity. Blood Cells Mol Dis 39:353–360

35. Rodrigues MD, Muller KB, Pereira VG, Martins AM, D'Almeida V (2010) Chitotriosidase deficiency in Brazil: evaluation of enzyme activity and genotypes. Blood Cells Mol Dis 44:305–306

6.2 **Estudo 2**

Defining prognosis in sarcoidosis (artigo publicado)

1. Introduction

Sarcoidosis is a multi-systemic granulomatous disease whose origin is not yet well established. The sarcoidosis incidence among populations globally varies between 1 and 120 cases per 100,000 people, with the highest and lowest incidences registered among African-Americans and Japanese, respectively.[1-3] In Brazil, the estimated incidence is below 10 per 100,000 people.[4]

Sarcoidosis affects both men and women with a similar frequency, with the main onset occurring between 25 and 45 years of age, and in some regions, with a second onset window between 50 and 60 years of age.[5-9]

There is still no well-defined etiology for sarcoidosis. There is some growing evidence that the sarcoidosis-related immune response may also include an autoimmune response with some reaction to the body's own proteins. However, sarcoidosis is not considered to be a classic autoimmune disease, such as rheumatoid arthritis or systemic lupus erythematosus.

It appears that up to 10% of affected cases can be attributed to some familial predisposition.[10] Some human leukocyte antigen (HLA) class 2 genes have already been identified as being associated with genetic susceptibility, and patients may manifest the disease after some environmental exposure-, occupational-, or infection-related triggers.[11,12]

The course of the disease is quite variable. It can remit spontaneously or with treatment within 2 years, but some patients can progress to a chronic form, requiring treatment including corticosteroid therapy for a long time.[1] Mortality is usually around 1–5%.[13] Some features that have already been studied, such as erythema nodosum, acute arthritis, and bilateral hilar lymphnode enlargement, are related to a better prognosis. However, cardiac and neurological sarcoidosis, lupus pernio, forced

vital capacity < 80%, fibrosis, and pulmonary hypertension are related to the worst prognosis.[14-16]

The main goal of this study was to identify features that are related to prognosis of this disease, and to establish a scoring system that can predict the clinical progression of patients with sarcoidosis.

2. Methods

2.1. Study design and population

The relevant research ethics committee approved this study (protocol No. 1158044). For the study, a cohort of 101 patients was recruited at a single center. Patients were already diagnosed with sarcoidosis at the study inception or were diagnosed within 48 months, with a disease duration ranging from 2 months to 30 years. Sarcoidosis diagnosis was determined according to the American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines on sarcoidosis.

2.2. Data collection

During follow-up, we collected data on the clinical features, pulmonary functional tests, computed tomographic findings, pulmonary artery pressure (estimated by echocardiography),laboratory tests (antinuclear antibodies, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies), early clinical manifestations, and patients' evolution according to treatment. The respiratory clinical manifestations included chest pain, dyspnea, cough, and wheezing. The constitutional symptoms were fever, weight loss, fatigue, arthralgia, and night sweats. Palpitations and angina

were listed as cardiac symptoms. Facial palsy and balance disturbance were considered as neurological symptoms.

Radiological patterns were classified as defined by Scadding,[17] and also according to the computed tomographic findings of ground-glass infiltrate, consolidations, mediastinal and hilar lymph node enlargement, micronodular infiltrates and nodular opacities, traction bronchiectasis, honeycomb and fibrosis, septal thickening, and peribronchovascular thickening.[18] Transthoracic echocardiography was used to estimate pulmonary artery systolic pressure (PASP). PASP > 35mm Hg was considered abnormal.[19]

Pulmonary functional tests were classified as abnormal when at least one of the following criteria were met: forced expiratory volume in 1 second (FEV1) < 80%, forced vital capacity (FVC) < 80%, and FEV1/FVC < 70. Rheumatological markers were considered present if antinuclear antibodies (ANA) titers were ≥ 1:160 and if either rheumatoid factor (RF) or anti-neutrophil cytoplasmic antibodies (ANCA) were detected in blood samples.[1]

We used the clinical outcome status (COS) criterion defined by Baughman et al.[20] to classify the evolution of patients.

2.3. Statistical analysis

Sample calculation revealed that at least 110 patients were required to obtain a 90% confidence level with a standard deviation of 10 and a confidence interval width (2-sided) of 3.

To describe the sociodemographic and clinical characteristics of the study population classified as having either unfavorable, undefined, or favorable clinical evolution, non-parametric Kruskal–Wallis tests were used for continuous variables, and Fisher's exact tests were used for comparison of relative frequencies of categorical variables.

The protection/risk estimation for a favorable clinical evolution as compared to na unfavorable evolution, was calculated as an adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for each variable, using unconditional logistic regression models. To account for selection biases, sociodemographic, clinical, and laboratory

characteristics associated with the outcome of interest at P-values < .2 in the bivariate analysis were included as confounders in multiple unconditional logistic regression models. We developed a scoring system for risk stratification using adjusted parameters of the multiple unconditional logistic regression models with all variables associated with a favorable clinical evolution.[21]

All statistical analyses were performed using R version 3.6.1 (R Core Team, 2019).

3. Results

3.1. Patient characteristics

One hundred and five patients from the State University of Rio de Janeiro (Brazil) diagnosed with sarcoidosis were followed-up between July 2015 and July 2019. Four patients were lost to follow-up, and 11 patients had less than 24 months of follow-up. Ninety individuals were followed-up for at least 24 months, and were classified according to clinical outcome status (COS 1–9) (Table 1). Those with COS 1–4 and COS 5–9 were classified as having favorable and unfavorable outcomes, respectively, while the 11 patients with less than 24 months of follow-up were classified as having undetermined outcomes.

We describe the epidemiological, functional, and radiological characteristics of these 101 individuals in Table 2. The mean age at diagnosis was 44 years. Only 35% of patients were Caucasians. Patients were predominantly women (68%) and were not current or past smokers (72%). Radiological stage 2 was the most prevalent, and twenty one patients (23%) had some positive rheumatological markers (ANA, RF, or ANCA). Moreover, 49% of the patients had some abnormal pulmonary function test results (FEV1 < 80% or FVC < 80%, or FEV1/FVC < 70), with only three patients with estimated PASP > 35 mmHg. The main initial clinical manifestations were respiratory symptoms and skin lesions, as illustrated in Table 3. The most prevalent computed tomographic findings (Table 4) were mediastinal lymph node enlargement (72%), and micronodular infiltrates and/or nodular opacities (59%).

Table 1: Clinical outcome status (COS) classification

Clinical outcome status (COS)	**Definition**	**N = 90 (100%)**
1	Disease resolved, never treated	7 (7)
2	Disease resolved, without treatment for more than 1 year	23 (25)
3	Minimal disease[a], never treated	1 (1)
4	Minimal disease, untreated for more than one year	15 (16)
5	Persistent disease, never treated	3 (3)
6	Persistent disease, untreated for more than 1 year	3 (3)
7	In treatment, without worsening in the last year, asymptomatic	16 (17)
8	In treatment, without worsening in the last year, symptomatic	8 (8)
9	In treatment, worsening[b] in the last year	14 (15)

a Minimal disease = less than 25% of the maximal disease.
b Requiring increase in systemic medication in prior year.

Table 2: Characteristics of 101 patients diagnosed with sarcoidosis.

Feature		Overall N= 101	Unfavorable clinical evolution N= 44	Undefined clinical Evolution N= 11	Favorable clinical Evolution N= 46	p.value
Age(years)		53 (IQR=17)	51.5 (IQR=18.25)	50 (IQR=12.5)	55 (IQR=19.75)	.16
Race (%)	Non white	66 (65.3)	28 (27.7)	6 (5.9)	32 (31.7)	.61
	white	35 (34.7)	16 (15.8)	5 (5)	14 (13.9)	
Sex	female	69 (68.3)	32 (31.7)	6 (5.9)	31 (30.7)	.45
	male	32 (31.7)	12 (11.9)	5 (5)	15 (14.9)	
Tabagism (current or past)	no	72 (72.7)	33 (32.7)	8 (7.9)	31 (30.7)	.73
	yes	27 (27.3)	10 (9.9)	3 (3)	14 (13.9)	
Diagnostic Age (years)		44 (IQR=17)	44.5 (IQR=16.25)	50 (IQR=13)	41.5 (IQR=17.75)	.42
RadiologicalStaging (%)	1	14 (13.9)	4 (4)	0 (0)	10 (9.9)	.26
	2	52 (51.5)	25 (24.8)	7 (6.9)	20 (19.8)	
	3	17 (16.8)	6 (5.9)	1 (1)	10 (9.9)	
	4	18 (17.8)	9 (8.9)	3 (3)	6 (5.9)	
Rheumatological markers - ANA, RF or ANCA (%)	negative	70 (76.9)	27 (26.7)	9 (8.9)	34 (33.7)	.21
	positive	21 (23.1)	13 (12.9)	1 (1)	7 (6.9)	
Pulmonary arterial hypertension	no	92 (96.8)	39 (38.6)	10 (9.9)	43 (42.6)	.72
	yes	3 (3.2)	2 (2)	0 (0)	1 (1)	
FEV1		83 (IQR=23.5)	75 (IQR=25.5)	84 (IQR=24)	86 (IQR=15.75)	.002
FEV1/FVC		80.5 (IQR=11)	80 (IQR=10)	82 (IQR=6.5)	80 (IQR=11.75)	.82
FVC		83.5 (IQR=24.25)	79 (IQR=20.5)	81 (IQR=16)	93.5 (IQR=19.5)	.001
Pulmonary tests [a]	Normal	51 (51)	15 (14.9)	5 (5)	31 (30.7)	.007
	Impared	49 (49)	28 (27.7)	6 (5.9)	15 (14.9)	

Data are given either as median (interquartile range - IQR) or absolute (relative) frequencies for numeric continuous and categorical nominal variables, respectively.
a Pulmonary function tests were considered normal when FEV1 and FVC ≥ 80% and FEV1 / FVC ≥ 70, impared when FEV1 or FVC <80% or FEV1 / FVC <70
Fonte: A autora, 2020.

Table 3: Clinical manifestations reported as initial symptoms by patients.

Early clinical manifestations	**N (%)**
Respiratory[a]	62 (61)
Skin	46 (45)
Constitutional symptoms[b]	23 (22)
Asymptomatic	11 (10)
Ophthalmologic	10 (9)
Cardiology[c]	6 (6)
Peripheral lymphnode enlargement	3 (3)
Parotid gland	2 (2)
Neurology[d]	2 (2)
Queilitis	1 (1)
Nephrotic syndrome	1 (1)

a Thoracic pain, cough, dyspnea, wheezes
b Fever,weight loss, fatigue, night sweating, arthralgia
c Angina, palpitation
d Unbalance, facial palsy
Fonte: A autora, 2020.

Table 4: Prevalence of tomographic patterns in sarcoidosis patients.

Tomographic patterns	**N (%)**
Lymphnode enlargement	72 (71)
Micronodular infiltrate and /or nodular opacities	59 (59)
Septal thickening	32 (32)
Ground glass	25 (25)
Traction bronchiectasis and/or honeycombing and/or fibrosis	17 (17)
PeribronchovascularThickening	15 (15)
Consolidation	12 (12)

Fonte: A autora, 2020.

Ninety patients were followed for at least 24 months, and 48% developed a chronic form of the disease (COS 5, 6, 7, 8, or 9).

Unconditional logistic analyses were performed to define which variables were related to the more favorable outcome (Table 5). For these analyses, only the 90 patients with at least 24 months of follow-up were included.

Table 5: Variables related to the outcome in sarcoidosis.

Feature		**Unfavorable evolution**	**Favorable evolution**	**Adjusted Model**	**p.value**
Race	Non white	28 (63.64)	32 (69.57)	0.93 (0.33-2.62)	.88
	white	16 (36.36)	14 (30.43)		
Sex	female	32 (72.73)	31 (67.39)	0.95 (0.33-2.7)	.92
	male	12 (27.27)	15 (32.61)		
Tabagism	no	33 (76.74)	31 (68.89)	1.91 (0.6-6.05)	.27
	yes		14 (31.11)		
Radiological stage	2	10 (23.26)	20 (43.48)		
	1	4 (9.09)	10 (21.74)	3.39 (0.66-17.42)	.14
	3	6 (13.64)	10 (21.74)	1.54 (0.42-5.66)	.51
	4	9 (20.45)	6 (13.04)	0.65 (0.18-2.36)	.51
Rheumatologic markers	negative	27 (67.5)	34 (82.93)		
	positive	13 (32.5)	7 (17.07)	0.19 (0.05-0.76)	.01
Pulmonary tests	impared	28 (65.12)	15 (32.61)	4.42 (1.59-12.3)	.004
	normal	15 (34.88)	31 (67.39)		
Pulmonary arterial hypertension	no	39 (95.12)	43 (97.73)	0.4 (0.03-5.56)	.49
	yes	2 (4.88)	1 (2.27)		
Initial respiratory clinical manifestations	yes	23 (52.27)	34 (73.91)	0.22 (0.07 – 0.65)	.006
	no	21 (47.73)	12 (26.09)		

Fonte: a autora, 2020.

We then developed a scoring system to help predict the likelihood of a patient having a favorable or unfavorable outcome. Of our patients, 48% developed a chronic form of the disease (COS 5–9). Three clinical features were predictive of prognosis in sarcoidosis. We built a scorebased model where the absence of rheumatological markers (1 point), normal pulmonary functions (2 points), and the presence of early respiratory symptoms manifestations (2 points) were associated with favorable prognosis. We predicted that a patient with a score of 5 would have na 86% (95% CI 74–98%) probability of having a favorable prognosis, while those with

scores of 4, 3, 2, 1, and 0 had probabilities of 72% (95% CI 59–85%), 52% (95% CI 40–63%), 31% (95% CI 17–44%), 15% (95% CI 2–28%), and 7% (95% CI 0–16%) of having a favorable prognosis, respectively (Table 6).

Table 6: Probability score of favorable outcome in sarcoidosis

Score	**Probability of favorable outcomes (CI 95%)**
0	0.07 (-0.01- 0.16)
1	0.15 (0.02-0.28)
2	0.31 (0.17-0.44)
3	0.52 (0.40-0.63)
4	0.72 (0.59-0.85)
5	0.86 (0.74-0.98)

Score = rheumatological marker + lung function test + initial respiratory manifestation
Rheumatological marker positive= 0, negative = 1; lung function test changed = 0, normal = 2; initial respiratory manifestations absent = 0, present = 2.
Fonte: A autora, 2020.

Discussion

Sarcoidosis is a disease with variable presentation and course. Several characteristics that influence the patient's prognosis have already been identified. In addition to describing the clinical, epidemiological, functional, and radiological characteristics of the 101 patients in our study, we aimed to establish a scoring system based on easily identifiable factors that could predict the clinical evolution of patients and help in the management of each case.

The mean age at diagnosis of our patients was 44 years, similar to that previously published, although we did not find a relationship between age and prognosis.[22] Smoking was identified as a protective factor against sarcoidosis in other studies, but this was not confirmed by our results.[23,24]

Moreover, Kobak et al.[25] showed the presence of rheumatological markers in sarcoidosis, with positive ANA testing in 28% and RF in 16% of patients. We observed that 23% of our patients tested positive for one of the rheumatological markers.

In three large study cohorts (ACCESS, MUSC, and TTS), the lung was the organ most affected by sarcoidosis (95%, 89%, and 99%, respectively), followed by the skin, eyes, and peripheral lymph nodes.[21,26-28] All our patients had pulmonary involvement, although only 61% had respiratory symptoms. In our study too, the second most-affected site was the skin.

Pulmonary function tests can present restrictive or obstructive disorders in sarcoidosis, but generally, lung function is not greatly altered, as demonstrated in our population, which presented mean values of FVC, FEV1, and FEV1/FVC within normal ranges. However, 49% of the patients presented some change in these variables.[29] We also found little change in lung function, as described in other studies.[21] Echocardiographic signs of pulmonary hypertension were presented in only 3% of patients in our study, whereas other cohorts found a prevalence ranging from 5% to 28%.[30-34]

In 2009, the WASOG organized a task force to provide a better definition of clinical outcome status in sarcoidosis by examining patients 2 or 5 years after diagnosis.[20] Authors disagreed on the ideal follow-up time for defining the disease as chronic. Neville et al.[14] and Judson et al.[35] used a 2-year cut-off point, while Baughman et al.[20] found more reliable results after 5 years of follow-up. Our patients were followed for at least 2 years after diagnosis.

Studies have already shown risk factors associated with poor sarcoidosis prognosis, e.g., Afro-American ethnicity,[16,36-38] older age,[16,21,37] changes in pulmonary function tests, and radiological stage 3.[39] Pulmonary hypertension and pulmonary fibrosis are clinical features that have already been shown to be independent predictors of mortality among sarcoidosis patients.[16,40,41] However, very few studies have developed scores, including multiple variables to define prognosis.

Walsh et al.[42] constructed an algorithm combining pulmonary function tests using the composite physiologic index (CPI) with computed tomography evaluation of the presence and extent of fibrosis, and the ratio of the main pulmonary artery diameter to the ascending aorta diameter, to categorize cases as good or poor prognosis, with consideration to mortality as the primary outcome.[43] The study included 251 patients from a single center over a 10-year period and concluded that this score was a better predictor of mortality than any individual variable alone.

In another study, Drent et al.[44] showed that a score of radiological tomographic findings (thickening of the bronchovascular bundle, parenchymal consolidation, intra-parenchymal nodules, septal and nonseptal lines, focal pleural thickening, and enlargement of the lymph nodes) was related to lung function, i.e., a higher total score predicted respiratory functional impairment and a worse prognosis.[45]

The gender, age, and physiology (GAP) index, initially created as a predictor of mortality in idiopathic pulmonary fibrosis, has also been evaluated in sarcoidosis, and was shown to be related to a higher risk of death in stages 2 or 3, with age as the most important variable.[16,46]

Since mortality in sarcoidosis is usually low, particularly outside reference centers, we decided to establish a scoring system to assess prognosis, using COS instead of mortality, similar to that reported by Walsh et al.[42] Using this system, we were able to predict patients who would develop chronic disease based on three clinical variables (respiratory symptoms, rheumatological markers, and pulmonary function tests).

The limitations of the study include the small number of patients; sample derived from a single center; a follow-up time of only 2 years; and the uniqueness of our sample. All patients were under clinical follow-up at a university hospital where cases of greater complexity are treated, usually using second-line medications, due to previous therapeutic failure.

Conclusion

Based on a simple algorithm derived from clinical, laboratory, and lung functional data, we were able to estimate the probability of the clinical evolution of patients with sarcoidosis, thus facilitating their management, which often requires more than one drug for treatment, and multiple follow-ups at reference centers.

References:

1. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16(2): 149-73.

2. Sharma OP. Sarcoidosis Around the World. Clin Chest Med 2008;29(3):3 57-363.

3. Deubelbeiss U, Gemperli A, Schindler C, Baty F, Brutsche MH. Prevalence of sarcoidosis in Switzerland is associated with environmental factors. Eur Respir J. 2010;35(5): 1088-1097.

4. Bethlem NM. Epidemiology of sarcoidosis in Brazil. Sarcoidosis. 1985;2: 162.

5. Hillerdal G, Nou E, Osterman K, Schmekel B. Sarcoidosis: epidemiology and prognosis. A 15-year European study. Am Rev Respir Dis.1984;130(1): 29-32.

6. Morimoto T, Azuma A, Abe S, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J.2008;31(2): 372-379.

7. Silva VL, Araújo PB, Lopes C, Rufino R, Costa CH. Epidemiological characteristics of sarcoidosis patients in the city of Rio de Janeiro, Brazil. J Bras Pneumol. 2011;37(4): 438-445.

8. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol.1997;145(3): 234-241.

9. Pietinalho A, Hiraga Y, Hosoda Y, Lofroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan: a comparative epidemiological study. Sarcoidosis.1995;12(1): 61-67.

10. Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis. A casecontrol etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med. 2001;164(11): 2085-2091.

11. Semenzato G. ACCESS: A Case Control Etiologic Study of Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(2): 83-6.

12. Fisher A, Grunewald J, Spagnolo P, Nebel A, Schreiber S, Muller-Quernheim J. Genetics of sarcoidosis. Semin Respir Care Med. 2014;35(3): 296-306.

13. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21): 2153-2165.

14. E. Neville, A. N. Walker, D. Geraint James. Prognostic Factors Predicting the Outcome of Sarcoidosis: An Analysis of 818 Patients. Q J Med. 1983;52(208): 525-533.

15. Baughman RP, Lower EE. Features of sarcoidosis associated with chronic disease. SarcoidosisVasc Diffuse Lung Dis. 2015;31(4): 275-281.

16. Kirkil G, Lower EE, Baughman RP. Predictors of Mortality in Pulmonary Sarcoidosis. Chest.2018;153(1): 105-113.

17. Scadding JG. Prognosis of intrathoracic sarcoidosis in England: a review of 136 cases after five years' observation. BMJ 1961;(2): 1165-1172.

18. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society:glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

19. Patel MB, Mor-Avi V, Murtagh G, et al. Right Heart Involvement in Patients with Sarcoidosis.Echocardiography. 2016;33(5): 734-741.

20. Baughman RP, Nagai S, Balter M, et al. Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG Task Force. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28(1): 56-64.

21. Zhang Z, Zhang H, Khanal MK. Development of Scoring System for Risk Stratification in Clinical Medicine: A Step-By-Step Tutorial. Ann Transl Med. 2017; 5(21):436.

22. Mañá J, Rubio-Rivas M, Villalba N, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis: Cohort study of a 40-year clinical experience at a tertiary referral center in Barcelona, Spain. Medicine (Baltimore). 2017;96(29):e7595.

23. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. Respir Med. 2016;120: 87-90.

24. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis:environmental and occupational risk factors. Am J Respir Crit Care Med. 2004 15;170(12):1324-1330.

25. Kobak S, Yilmaz H, Sever F, Duran A, Sen N, Karaarslan A. The prevalence of antinuclear antibodies in patients with sarcoidosis. Autoimmune Dis. 2014;2014: 351852.

26. Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation,diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffuse Lung Dis. 2012; 29 (2):119–127.

27. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10): 1885-1889.

28. Okumus G, Musellim B, Cetinkaya E, et al. Extrapulmonary involvement in patients with sarcoidosis in Turkey. Respirology. 2011;16(3): 446-450.

29. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clin Rev Allergy Immunol. 2015;49(1): 63-78.

30. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. Chest. 2006;129(5): 1246-1252.

31. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis.Eur Respir J. 2008;32(2): 296-302.

32. Maimon N, Salz L, Shershevsky Y, Matveychuk A, Guber A, Shitrit D. Sarcoidosis-associated pulmonary hypertension in patients with near-normal lung function. Int J Tuberc Lung Dis.2013;17(3): 406–411.

33. Hu X, Carmona EM, Yi ES, Pellikka PA, Ryu J. Causes of death in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Oct 7;33(3): 275-280.

34. Nardi A, Brillet PY, Letoumelin P, et al. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respir J. 2011;38(6): 1368-1373.

35. Judson MA, Baughman RP, Thompson BW, et al. Two-year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis 2003; 20 (3): 204-211.

36. Mirsaeidi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. Chest. 2015;147(2): 438-449.

37. Gerke AK, Yang M, Tang F, Cavanaugh JE, Polgreen PM. Increased hospitalizations among sarcoidosis patients from 1998 to 2008: a population-based cohort study. BMC Pulm Med. 2012;12:19.

38. Foreman MG, Mannino DM, Kamugisha L, Westney GE. Hospitalization for patients with sarcoidosis: 1979-2000. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23(2): 124-129.

39. Viskum K, Vestbo J. Vital prognosis in intrathoracic sarcoidosis wit special reference to pulmonary function and radiological stage. Eur Respir J. 1993;6(3): 349-353.

40. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest. 2003;124(3): 922-928.

41. Baughman RP, Engel PJ, Taylor L, Lower EE. Survival in sarcoidosis associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest. 2010;138(5): 1078-1085.

42. Walsh SL, Wells AU, Sverzellati N, et al. An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med. 2014;2(2): 123-130.

43. Wells AU, Desai SR, Rubens MB, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med. 2003;167(7): 962-969.

44. Drent M, De Vries J, Lenters M, et al. Sarcoidosis: assessment of disease severity using HRCT. Eur Radiol. 2003 Nov;13(11):2462-2471.

45. Oberstein A, Zitzewitz H von, Scweden F, Muller-Quernheim J. Non invasive evaluation of the inflammatory activity in sarcoidosis with high-resolution computed tomography. Sarcoidosis Vasc asc Diffuse Lung Dis. 1997 Mar;14(1):65-72.

46. Ley B, Ryerson CJ, Vittinghoff E, et al.A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012 May;156(10):684-691.

6.3 **Estudo 3**

Evaluation of PET/CT and chitotriosidase as predictors of sarcoidosis activity

Sarcoidosis is a multisystemic granulomatous disease that affects the lungs in most patients but can be identified in several organs. A major challenge for monitoring these patients is the therapeutic management through the diagnosis of disease activity and progression. (1)

The Positron Emission Tomography Computed Tomography (PET/CT) scanning proved to be a tool with excellent sensitivity in detecting pulmonary and extrapulmonary sites of active sarcoidosis. (2)

Several biomarkers have also been studied to help identify disease activity, among them chitotriosidase (CHITO), an enzyme of the chitinase family secreted through macrophages and pulmonary neutrophils. (3,4)

The aim of this work was to evaluate the PET/CT and serum chitotriosidase as predictors of the clinical progression in patients with sarcoidosis.

Patients diagnosed with sarcoidosis were evaluated at two times, with an average interval of 29 months (21-40 months) by the same physician. The testing was divided into clinical, metabolic, and laboratory. The clinical investigation included the symptoms reported by the patient and physical examination. The metabolic assessment was done through the PET/CT scan of the whole body using the radiopharmaceutical 18 F-fluorodeoxyglucose (FDG) with tomography and PET images acquired after 60 minutes of tracer infusion with semi-quantitative analysis using the maximum standardized uptake value (SUVmax). Chitotriosidase serum levels were dosed by a fluorimetric method using the Chitinase Assay Kit (catalog number CS1030, Sigma Chemical Co.). This project was approved by the research ethics committee (Protocol No. 1158044).

We included 23 patients with a confirmed sarcoidosis diagnosis, who underwent PET CT and CHITO measurements in 2 moments and were followed up in this interval by medical consultations. The patients were divided into good or bad clinical evolution according to the clinical outcome status (COS) proposed by Baughman et al (5). Those under treatment, worsening in the last year (COS 9) were

considered to have a poor outcome. Asymptomatic or symptomatic patients, but without worsening in the last year, were considered to have a good evolution. (COS 1-8) The good metabolic progression was determined by reducing more than 25% in the SUVmax of the second PET compared to the first investigation (6). For chitotriosidase activity, a good progression was considered when there was a drop of more than 50% in the serum level between investigations.(7)

To describe the sociodemographic and clinical characteristics of the study population classified accordingly to the clinical evolution, non-parametric Kruskal–Wallis tests were used for continuous variables, and Fishers exact tests were used for comparison of relative frequencies of categorical variables. Kappa index was used in agreement analyzes among clinical, metabolic (PET/CT scan), and laboratory (CHITO) predictions of sarcoidosis progression. Performances of PET/CT scan and CHITO in comparison with the gold-standard clinical progression were estimated by its leave-one-out cross-validation (LOOCV) accuracy (Acc), sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive values (NPV), and false-positive and negative ratios and their 95% CI. All analysis was performed in software R v. 3.6.3.

In total, 46 PET/CT scans were performed, of which 23 showed tracer uptake with SUVmax ranged from 1.9 to 16.1. (Table 1)

Clinical deterioration was observed in 5 patients in the period between the two analyzes. Metabolic worsening occurred in 9 patients and laboratory worsening in 10 patients. (Table 1)

PET/CT scan showed 65% mean accuracy in determining sarcoidosis activity progression with 60% mean sensitivity, and 66% mean specificity. CHITO had a mean accuracy of 60 %, a mean sensitivity of 60 %, and a mean specificity of 61 % (Table 2).

Defining disease activity progression in sarcoidosis is very relevant in the therapeutic management of patients, including drug choice, change of treatment, and assessment of the patient's response to the proposed therapy. To date, there is not a gold standard for this definition.

The association between sarcoidosis activity and elevated CHITO serum levels and CHITO serum reduction after treatment have already been reported.(3,4)

PET/CT had gained relevance in sarcoidosis since the publication of Lewis et al. (1994), reporting their experience with two cases of sarcoidosis tracer uptake at

various sites by PET/CT. (8) Since then, new studies have shown that PET/CT is an exam with good sensitivity in determining disease activity, allowing the identification of sites for biopsy, defining patients who still benefit from immunosuppressive therapy even in stage IV, besides being useful in the follow-up of these individuals to control the therapeutic response and progression.(9-12).

Teirstein et al. (2007) described 137 sarcoidosis patients who underwent PET/CT and observed tracer uptake mainly in mediastinal, extrathoracic lymph nodes, and lungs with SUVmax ranging from 2.0 to 15.8 (12), which was similar to our results (SUVmax ranging from 1.9 to 16.1). In their sample, 15% of the tests with PET/CT tracer uptake did not correspond to clinical examination or other imaging tests. A similar situation was observed by Guleria et al (2014) in 22% of patients with complete clinical response and evidence of uptake in PET/CT, showing moderate agreement between clinical and metabolic expression. (11).

In our study, six asymptomatic patients had pulmonary and extrapulmonary PET CT uptake sites, as well as six asymptomatic patients also had high CHITO values (> 120 U/ml). (3) The finding of 18 FDG uptake sites in PET CT and increased CHITO levels will not always be decisive to treat, as we observed in our patients with bone and splenic disease elucidated in PET, as well as in a patient who presented high CHITO values without correspondence with the clinic status and activity at PET CT.

Despite the tests showing accuracy> 60% in the clinical evolution of sarcoidosis, we must consider the viability of each one.PET CT has high cost and scarce availability in treatment centers. Its use to detect sarcoidosis activity in individuals with fibrosing disease seems to be interesting, as it can change the therapeutic plan as it did with two patients in this study. CHITO can be considered in the follow-up of patients, as it is na accessible and low cost diagnostic instrument.

The evolution of patients with sarcoidosis must be treated in specialized centers by a professional trained to identify the clinical signs of disease activity, using PET CT and CHITO in selected cases, increasing the arsenal for monitoring sarcoidosis.

Table 1 Characteristics of the study population.

Feature	Levels	Overall n=23	A n=18	B n=5	p.value
Age		50 (IQR=12)	51 (IQR=14.5)	50 (IQR=5)	0.8229
Sex	female	18 (78.3)	14 (60.9)	4 (17.4)	1
	male	5 (21.7)	4 (17.4)	1 (4.3)	
Race	non white	14 (60.9)	10 (43.5)	4 (17.4)	0.6106
	white	9 (39.1)	8 (34.8)	1 (4.3)	
ClinicalActivity t1	asymptomatic	11 (47.8)	9 (39.1)	2 (8.7)	0.7911
	pulmonary	4 (17.4)	3 (13)	1 (4.3)	
	extrapulmonary	6 (26.1)	5 (21.7)	1 (4.3)	
	pulmonary+extrapulmonary	2 (8.7)	1 (4.3)	1 (4.3)	
Treatment t1	untreated	4 (17.4)	4 (17.4)	0 (0)	0.7842
	intreatment	14 (60.9)	10 (43.5)	4 (17.4)	
	treated	5 (21.7)	4 (17.4)	1 (4.3)	
PETactivity t1	active	10 (43.5)	9 (39.1)	1 (4.3)	0.3394
	unactive	13 (56.5)	9 (39.1)	4 (17.4)	
PET site activity t1	none	13 (56.5)	9 (39.1)	4 (17.4)	0.8446
	pulmonary	3 (13)	3 (13)	0 (0)	
	extrapulmonary	1 (4.3)	1 (4.3)	0 (0)	
	pulmonary+extrapulmonary	6 (26.1)	5 (21.7)	1 (4.3)	
SUVmax t1		9.05 (IQR=5.28)	8.4 (IQR=5.3)	13 (IQR=0)	0.4
CHITO t1		56 (IQR=262.05)	54.5 (IQR=171.5)	72 (IQR=341.1)	0.9703
ClinicalActivity t2	asymptomatic	12 (52.2)	12 (52.2)	0 (0)	0.0088
	pulmonary	3 (13)	2 (8.7)	1 (4.3)	
	extrapulmonary	4 (17.4)	3 (13)	1 (4.3)	
	pulmonary+extrapulmonary	4 (17.4)	1 (4.3)	3 (13)	
Treatment t2	untreated	1 (4.3)	1 (4.3)	0 (0)	0.496
	intreatment	13 (56.5)	9 (39.1)	4 (17.4)	
	treated	9 (39.1)	8 (34.8)	1 (4.3)	
PETactivity t2	active	13 (56.5)	10 (43.5)	3 (13)	1
	unactive	10 (43.5)	8 (34.8)	2 (8.7)	
PET site activity t2	none	10 (43.5)	8 (34.8)	2 (8.7)	0.6694
	pulmonary	4 (17.4)	4 (17.4)	0 (0)	
	extrapulmonary	3 (13)	2 (8.7)	1 (4.3)	
	pulmonary+extrapulmonary	6 (26.1)	4 (17.4)	2 (8.7)	
SUVmax t2	SUVmax.t2	6.5 (IQR=3.6)	6.55 (IQR=3.9)	6.5 (IQR=3.15)	0.8112
CHITO t2	CHITO.t2	73 (IQR=54.5)	76 (IQR=51.75)	64 (IQR=44)	0.8815
CHITO evolution	A	13 (56.5)	11 (47.8)	2 (8.7)	0.6175
	B	10 (43.5)	7 (30.4)	3 (13)	
PET evolution	A	14 (60.9)	12 (52.2)	2 (8.7)	0.3428
	B	9 (39.1)	6 (26.1)	3 (13)	

Fonte: A autora, 2020.

A – good clinical evolution
B – bad clinical evolution
T1 – first moment
T2 - second moment

Table 2 Classifiers related to sarcoidosis clinical evolution.

	PET CT	CHITO
Acc	0.65 (0,47;0,82)	0,60 (0,42; 0,78)
Sens	0,6 (0,13;1)	0,6 (0,13;1)
Spec	0,66 (0,46;0,86)	0,61 (0,40; 0,81)
Ppv	0,33 (0,03;0,63)	0,3 (0,02; 0,57)
Npv	0,85 (0,68; 1)	0,84 (0,66;1)
Fpr	0,33 (0,13; 0,53)	0,38 (0,18;0,59)
Fnr	0,4 (0; 0,86)	0,4 (0; 0,86)

Fonte: A autora, 2020.

Acc: accuracy, Sens:sensitivity, Spec: specificity, Ppv: positive predictive values, Npv: Negative predictive values, Fpr: False positive ratio, Fnr: False negative ratio.

References

1. Dominique Valeyre, Antje Prasse, Hilario Nunes, Yurdagul Uzunhan, Pierre-Yves Brillet, Joachim Müller-Quernheim. Sarcoidosis. Lancet 2014; 383: 1155–1167

2. Ruth G M Keijsers , Jan C Grutters . In Which Patients with Sarcoidosis Is FDG PET/CT Indicated? J Clin Med 2020 Mar 24;9(3):890.

3. Lopes MC, Amadeu TP, Ribeiro-Alves M, da Costa CH, Rodrigues LS, Bessa EJC, Bruno LP, Lopes AJ, Rufino R. Identification of Active Sarcoidosis Using Chitotriosidase and Angiotensin-Converting Enzyme. Lung. 2019 Jun;197(3):295-302.

4. Bargagli E, Bennett D, Maggiorelli C, Di Sipio P, Margollicci M, Bianchi N, Rottoli P. Human chitotriosidase: a sensitive biomarker of sarcoidosis. J Clin Immunol. 2013; 33(1):264–270.

5. Baughman RP, Nagai S, Balter M, et al. Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG Task Force. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28(1): 56-64.

6. Harlander M, Salobir B, Zupančič M, Dolenšek M, Vodovnik TB, Terčelj M. Serial chitotriosidase measurements in sarcoidosis - Two to five year follow-up study. Respir Med 2014;108:775-782.

7. Chen H, Jin R, Wang Y, Li L, Li K, He Y. The utility of 18F-FDG PET/CT for Monitoring response and predicting prognosis after glucocorticoids therapy for sarcoidosis. Biomed Res Int 2018;2018:1823710.

8. P J Lewis, A Salama. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J. Nucl. Med. 1994; 35(10): 1647–1649.

9. D. Sobic-Saranovic, I. Grozdic, J. Videnovic-Ivanov, V. Vucini-Mihailovic, V. Artiko, D. Saranovic, A. Djuric-Stefanovic, D. Masulovic, S. Odalovic, A. Ilic-Dudvarski, S. Popevic, S. pavlovic, V. Obradovic. The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in patients with active chronic sarcoidosis. J Nucl Med. 2012; 53 (10): 1543–1549.

10. Hengyi Chen , Rongbing Jin , Yubo Wang , Li Li , Kunlin Li , Yong He. The Utility of 18F-FDG PET/CT for Monitoring Response and Predicting Prognosis after Glucocorticoids Therapy for Sarcoidosis. Biomed Res Int. 2018;2018:1823710.

11. Randeep Guleria, Amudhan Jyothidasan, Karan Madan, Anant Mohan, Rakesh Kumar, Ashu Seith Bhalla, Arun Malhotra. Utility of FDG–PET–CT scanning in assessing the extent of disease activity and response to treatment in sarcoidosis. Lung India 2014 Oct;31(4):323-330.

12. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC. Results of 188 whole-body fluorodeoxyglucose pósitron emission tomography scans in 137 patients with sarcoidosis. Chest 2007;132(6):1949-1953.

CONCLUSÕES

Estudo 1

1. CHITO e ECA mostraram elevação significativa nos pacientes com sarcoidose, em atividade, quando comparados com os em remissão e com o grupo controle;

2. Foram definidos pontos de corte para CHITO = 120,U/ml ECA = 270 ng/ml, PCR = 0,4 mg/dl;

3. Combinando os valores de CHITO com PCR e ECA foi construído um algoritmo diagnóstico para atividade da sarcoidose com acurácia superior aos biomarcadores isoladamente;

4. Os estágios radiológicos 0,1 e 2 apresentaram níveis de ECA e CHITO mais elevados em relação aos estágios 3 e 4.

Estudo 2

1. Os principais sintomas na apresentação inicial dos pacientes foram os respiratórios, seguido dos cutâneos;

2.Os marcadores reumatológicos estão presentes em 23% dos pacientes;

3. Quarenta e nove por cento dos pacientes têm alteração de função pulmonar;

4.Quarenta e oito por cento dos pacientes evoluíram com a forma crônica da sarcoidose;

5 Três variáveis se relacionaram com prognóstico na evolução clínica: marcadores reumatológicos, sintomas respiratórios na apresentação inicial da doença e parâmetros funcionais pulmonares;

6. Por meio de um escore, identificamos a probabilidade de desfecho favorável do paciente com sarcoidose.

Estudo 3

1.PET CT e CHITO apresentam acurácia superior a 60% para detecção de melhora ou piora evolutiva na sarcoidose.

2.Pacientes assintomáticos com sítios de atividade evidenciados no PET CT ou níveis elevados de CHITO devem ser estudados individualmente para definir a necessidade de tratamento;

3.Por se tratar de um exame de alto custo, pouca disponibilidade e nem sempre ser utilizado para definir o tratamento, o PET CT não deve ser utilizado de rotina.

REFERÊNCIAS

1. HUNNINGHAKE, G.W. et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16(2): 149-73.

2. BETHLEM, N.M. Epidemiology of sarcoidosis in Brazil. Sarcoidosis. 1985;2:162.

3. ROSEN, Y. Sarcoidosis. In: Hammer DHD and SP, editor. Pulmonary Pathology. 2nd ed. New York: Springer-Verlag; 1994. p. 13–645.

4. SHEFFIELD, E.A. Pathology of sarcoidosis. Clin Chest Med. 1997 Dec;18(4):741-54.

5. BAUGHMAN, R.P., LOWER, E.E. Features of sarcoidosis associated with chronic disease. SarcoidosisVasc Diffuse Lung Dis. 2015;31(4): 275-281.

6. KIRKIL, G., LOWER, E.E., BAUGHMAN, R.P.. Predictors of Mortality in Pulmonary Sarcoidosis. Chest.2018;153(1): 105-113.

7. RAMOS-CASALS, M. et al. Clinically-useful serum biomarkers for diagnosis and prognosis of sarcoidosis Expert Rev Clin Immunol. 2019 Apr;15(4):391-405.

8. CHEN, H. et al. The utility of 18F-FDG PET/CT for Monitoring response and predicting prognosis after glucocorticoids therapy for sarcoidosis. Biomed Res Int 2018;2018:1823710.

9. ROSEN, Y. Pathology of sarcoidosis. Semin Respir Crit Care Med. 2007;28(1):36–52.

10. PIETINALHO, A. et al. The frequency of sarcoidosis in Finland and Hokkaido, Japan: a comparative epidemiological study. Sarcoidosis. 1995;12(1):61–67.

11. SWIGRIS J.J. et al. Sarcoidosis-related mortality in the United States from 1988 to 2007. Am J Respir Crit Care Med. 2011;183:1524–30.

12. HUANG, C.T. et al. Mortality in sarcoidosis. A changing pattern of the causes of death. Eur J Respir Dis. 1981;62:231–8.

13. ARCASOY, S.M. et al. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest. 2001;120:873–80.

14. RYBICKI, B.A. et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997;145:234–41.

15. RYBICKI, B.A. et al.Photocopier exposure and risk of sarcoidosis in African-American sibs. Sarcoidosis Vasc Diffus Lung Dis. 2004;21:49–55.

16. NEWMAN, L.S. et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med. 2004 15;170(12):1324-1330.

17. COSTA, C.H. et al. HLA in a cohort of Brazilian patients with sarcoidosis. Hum Immunol. 2013;74(10):1326-1332.

18. FISHER, A. et al. Genetics of sarcoidosis. Semin Respir Care Med. 2014;35(3): 296-306.

19. DE VUYST, P. et al. Sarcoidlike lung granulomatosis induced hy aluminum dusts. Am Rev Respir Dis. 1987;135(2):493–497.

20. SKELTON, H.G. et al. Zirconium granuloma resulting from an aluminum zirconium complex: a previously unrecognized agent in the development of hypersensitivity granulomas. J Am Acad Dermatol. 1993;28:874–876.

21. AGOSTINI, C., ADAMI, F., SEMENZATO, G. New pathogenetic insights into the sarcoid granuloma. Curr Opin Rheumatol. 2000;12:71–6.

22. SHORR, A.F., DAVIES, D.B., NATHAN, S.D. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest. 2003;124(3): 922-928.

23. BAUGHMAN, R.P. et al. Survival in sarcoidosis associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest. 2010;138(5): 1078-1085.

24. BAUGHMAN, R.P. et al. Defining the clinical outcome status (COS) in sarcoidosis: results of WASOG Task Force. Sarcoidosis Vasc Diffus Lung Dis. 2011;28:56–64.

25. WANAT, KA., ROSENBACH, M. Cutaneous Sarcoidosis. Clin Chest Med. 2015 Dec;36(4):685-702.

26. PASADHIKA, S., ROSENBAUM, J.T. Ocular Sarcoidosis. Clin Chest Med. 2015 Dec;36(4):669-83.

27. TEIRSTEIN AS et al.Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest. 2007;132:1949–53.

28. KUMAR, M., HERRERA, J.L. Sarcoidosis and the Liver. Clin Liver Dis. 2019 May;23(2):331-343.

29. CORREIA, F.A.S.C., MARCHINI, G.S., TORRICELLI, F.C., et al. Renal manifestations of sarcoidosis: from accurate diagnosis to specific treatment. Int Braz J Urol. 2020;46(1):15-25.

30. BIRNIE, D.H. et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Hear Rhythm. 2014;11:1305–24.

31. HULTEN, E. et al. Cardiac sarcoidosis—state of the art review. Cardiovasc Diagn Ther. 2016 Feb; 6(1): 50–63.

32. SCHWENDIMANN, R.N., HARRIS, M.K., ELLIOTT, D.G., et al. Neurosarcoidosis: clinical features, diagnosis, and management. Am J Ther. 2013 May-Jun;20(3):292-9.

33. VOORTMAN, M., DRENT, M., BAUGHMAN, R.P. Management of neurosarcoidosis: a clinical challenge. Curr Opin Neurol. 2019 Jun;32(3):475-483.

34. JUDSON, M.A. The diagnosis of sarcoidosis. Clin Chest Med. 2008;29:415–27.

35. COSTABEL, U. Sensitivity and specificity of BAL findings in sarcoidosis. Sarcoidosis. 1992;211–4.

36. JENY, F., BERNAUDIN, J.F., COHEN AUBART, F., et al. Diagnosis issues in sarcoidosis. Respir Med Res. 2020 Mar;77:37-45.

37. SPAGNOLO, P. et al. Pulmonary sarcoidosis. Lancet Respir Med.2018 May;6(5): 389-402.

38. SCADDING, J.G. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br Med J.1961 Nov 4;2(5261):1165-72

39. IANNUZZI,M.C., BENJAMIN,A.R, TEIRSTEIN,A.S. Sarcoidosis. N Engl J Med. 2007;357:2153–65.

40. DEREMEE, RA. The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. Chest. 1983;83:128–33.

41. HAWTIN, K.E. et al. Pulmonary sarcoidosis: the “Great Pretender.” Clin Radiol. 2010;65:642–50.

42. KALKANIS, A., JUDSON, M.A. Distinguishing asthma from sarcoidosis: an approach to a problem that is not always solvable. JAsthma. 2013;50:1–6.

43. BAYDUR, A. et al.. Respiratory muscle strength, lung function, and dyspnea in patients with sarcoidosis. Chest. 2001;120:102–8.

44. JUDSON, M.A., BOAN, A.D., LACKLAND, D.T. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large White and black cohort in the United States. Sarcoidosis Vasc Diffus Lung Dis. 2012;29:119–27.

45. BAUGHMAN, R.P. et al. Survival in sarcoidosis-associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest. 2010;138:1078–85.

46. WALSH, S.L. et al. An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study. Lancet Respir Med. 2014;2(2): 123-130.

47. Crouser, E.D. et al. Diagnosis and Detection of Sarcoidosis: An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. Apr. 15, 2020; 201(8): e26–e51.

48. MCKINZIE, B.P, et al. Efficacy of short-course, low-dose corticosteroid therapy for acute pulmonary sarcoidosis exacerbations. Am J Med Sci. 2010;339:1–4.

49. BAUGHMAN, R.P., LOWER, E.E. Treatment of Sarcoidosis. Clin Rev Allergy Immunol. 2015 Aug;49(1):79-92.

50. SAHOO, D.H. et al. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. Eur Respir J. 2011;38:1145–50.

51. VORSELAARS, A.D.M.. et al.Methotrexate vs Azathioprine in Second-line Therapy of Sarcoidosis. Chest. 2013 Sep;144(3):805-812.

52. BAUGHMAN,R.P., GRUTTERS, J.C. New treatment strategies for pulmonary sarcoidosis: antimetabolites, biological drugs, and other treatment approaches. Lancet Respir Med.2015 Oct;3(10):813-22.

53. Third WASOG meeting, 1994, Los Angeles. *Activity of sarcoidosis*. Eur Respir J; 1994. p. 624–7.

54. POPEVIĆ, S. et al. Verifying sarcoidosis activity: chitotriosidase versus ace in sarcoidosis—a case-control study. J Med Biochem. 2016 Oct; 35(4): 390–400.

55. ROTHKRANTZ-KOS, S. et al. Potential Usefulness of Inflammatory Markers to Monitor Respiratory Functional Impairment in Sarcoidosis.Clin Chem. 2003 Sep;49(9):1510-7.

56. LEWIS, P.J., SALAMA, A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J. Nucl.Med 1994;35(10):1647–1649.

57. SOBIC-SARANOVIC, D. et al. The utility of 18F-FDG PET/CT for diagnosis and adjustment of therapy in patients with active chronic sarcoidosis. J Nucl Med 2012;53:1543–1549

58. GULERIA, R.,The utility of FDG–PET–CT scanning in assessing the extent of disease activity and response to treatment in sarcoidosis. Lung India 2014;31:323-330.

59. TEIRSTEIN, A.S. et al. Results of 188 whole-body fluorodeoxyglucose pósitron emission tomography scans in 137 patients with sarcoidosis. Chest 2007;132:1949-1953.

60. CHO, S.J.,WEIDEN, M.D., LEE, C.G. Chitotriosidase in the Pathogenesis of Inflammation, Interstitial Lung Diseases and COPD. Allergy Asthma Immunol Res. 2015 Jan; 7(1): 14–21..

61. CAKIR, G. et al. Serum chitotriosidase activity in pulmonary tuberculosis: response to treatment and correlations with clinical parameters. Ann Lab Med. 2012;32(3):184–9.

62. TASCI, C. et al. Efficacy of serum chitotriosidase activity in early treatment of patients with active tuberculosis and a negative sputum smear. Ther Clin Risk Manag. 2012;8:369–72.

63. MICHELAKAKIS, H., DIMITRIOU, E., LABADARIDIS,I. The expanding spectrum of disorders with elevated plasma chitotriosidase activity: an update. J Inherit Metab Dis. 2004;27(5):705-6.

64. VAN EIJK, M. et al. Characterization of human phagocyte-derived chitotriosidase, a component of innate immunity. Int Immunol. 2005;17(11):1502–12.

65. MALAGUARNERA, L. et al. A 24-bp duplication in exon 10 of human chitotriosidase gene from the sub-Saharan to the Mediterranean area: role of parasitic diseases and environmental conditions. Genes Immun. 2003;4:570–4.

66. CHOI, E.H. et al. Genetic polymorphisms in molecules of innate immunity and susceptibility to infection with Wuchereria bancrofti in South India. Genes Immun. 2001;2:248–53.

67. LABADARIDIS, I. et al., Chitotriosidase in neonates with fungal and bacterial infections. Arch Dis Child Fetal Neonatal. 2005;90(6):531–2
.
68. GROSSO, S. et al. Serum levels of chitotriosidase as a marker of disease activity and clinical stage in sarcoidosis. Scand J Clin Lab Invest. 2004;64(1):57–62.

69. BARGAGLI, E. et al. Chitotriosidase analysis in bronchoalveolar lavage of patients with sarcoidosis. Sarcoidosis Vasc Diffus Lung Dis. 2007;24(1):59–64.

70. BARGAGLI, E. et al. Human chitotriosidase: a sensitive biomarker of sarcoidosis. J Clin Immunol. 2013;33(1):264–70.

71. BOOT, R.G. et al. Plasma chitotriosidase and CCL18 as surrogate markers for granulomatous macrophages in sarcoidosis. Clin Chim Acta 411(2010):31–36

72. BOOT, R.G. et al. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem. 1998;273(40):25680–5.

73. RODRIGUES, M.D. et al. Chitotriosidase deficiency in Brazil: evaluation of enzyme activity and genotypes. Blood Cells Mol Dis 44(2010):305–306

74. COATES, D. The angiotensin converting enzyme (ACE). Biochem Cell Biol. 2003;35:769–73.

75. LIEBERMAN, J. Elevation of Serum Angiotensin converting enzyme (ACE) level in sarcoidosis. Am J Med. 1975;59(3):365–72.

76. PETER, R. et al. Biochemical findings in sarcoidosis. J Clin Pathol. 1980;33(6):528–33.

77. NOSAL, A et al. Angiotensin-Iconverting enzyme and galium scan in noninvasive evaluation of sarcoidosis. Ann Int Med. 1979;90:328–31.

78. ROHRBACH, M.S., DEREMEE, R.A. Serum angiotensin converting enzyme activity in sarcoidosis as measured by a simple radiochemical assay. Am Rev Respir Dis. 1979;119:761–7.

79. ROHATGI, P.K., RYAN, J.W. Simple radioassay for measuring serum activity of angiotensin converting enzyme in sarcoidosis. Chest. 1980;78:69–75.

80. BUNTING, P.S., SZALAI, J.P., KATIC, M. Diagnostic aspects of angiotensin converting enzyme in pulmonary sarcoidosis. Clin Biochem. 1987;20:213–9.

81. THELIER, N. et al. Osteoarticular involvement in a series of 100 patients with sarcoidosis referred to rheumatology departments. J. Rheumatol. 2008;35:1622– 1628.

82. KHAN, AH. et al. Role of serum angiotensin converting enzyme in sarcoidosis. J. Pak. Med. Assoc.1998;48:131–133.

83. RIGAT, B. et al. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest. 1990 Oct; 86(4): 1343–1346.

84. LIEBERMAN, J. et al., Serum angiotensin converting enzyme for diagnosis and therapeutic evaluation of sarcoidosis. Am Rev Respir Dis. 1979;120:329–35.

85. HIND, C.R.K. ,PEPYS, M.B. Acute phase proteins. In: Lessof, MH, Lee TH KD, editors. Allergy. 2nd ed. Chicester: Wiley; 1987. p. 237–53.

86. PEPYS, M.B., LANHAM, J.G., DE BEER, F.C. C reactive protein in SLE. Clin Rheum Dis. 1982;8:91–103.

87. HIND, C.R. Serum C reactive protein measurement in the detection of intercurrent infection in Oriental patients with systemic lupus erythematosus. Ann Rheum Dis. 1985;44:260–1.

88. WHICHER, J.T., MARTIN, M.F.R., DIEPPE, P.A. Absence of prostaglandin stimulated increase in acute phase proteins in systemic sclerosis. Lancet. 1980;2:1187–8.

89. FAGAN, E.A. et al. Serum levels of CRP in Crohn's disease and ulcerative colitis. Eur J Clin Invest. 1982;12:351–9.

90. HAAS, R.H. et al. CRP in childhood dermatomyositis. Ann Rheum Dis. 1982;41:483–5.

91. KEOGH, B.A. et al. The alveolitis of pulmonary sarcoidosis: evaluation of natural history and alveolitis-dependent changes in lung function. Am Rev Respir Dis. 1983;128:256–65.

92. WINTERBAUER, R.H., HUTCHINSON, J.F. Use of pulmonary function tests in the management of sarcoidosis. Chest. 1980;78:640–7.

93. ZIEGENHAGEN, MW. et al. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. Eur Respir J 21(2003):407–413

94. DRENT, M. et al. Association of fatigue with na acute phase response in sarcoidosis. Eur Respir J 13(1999):718–722

95. MCDONNEL, M.J. et al. Predictive value of C-reactive protein and clinically relevant baseline variables in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Dec 23;33(4):331-340.

96. SWEISS, N.J. ET al. C-reactive protein predicts response to infliximab in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010 Jul;27(1):49-56.

97. SU, R. et al. Interferon-inducible chemokines reflect severity and progression in sarcoidosis. Respir. Res. 2013;14:121.

98. MILLER, MR. et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–338.

99. HANSELL, DM. et al. Fleischner Society:glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722.

100. BARGAGLI, E. et al. Chitotriosidase activity in patients with interstitial lung diseases. Respir Med. 2007 Oct;101(10):2176-81.

101. ARAÚJO, LS. et al. Obstructive sleep apnea is independently associated with inflammation and insulin resistance, but not with blood pressure, plasma catecholamines, and endothelial function in obese subjects. Nutrition. 2015 Nov-Dec;31(11-12):1351-7.

102. UYSAL, P. et al. YKL-40, Soluble IL-2 Receptor, Angiotensin Converting Enzyme and C-Reactive Protein: Comparison of Markers of Sarcoidosis Activity. Biomolecules. 2018 Aug 28;8(3):84.

103. SCHIRMER, MR. et al. Fluorine-18-fluorodeoxyglucose PET/CT in hematopoietic stem cell transplant patients with fusariosis: initial findings of a case series review. Nucl Med Commun. 2018 Jun;39(6):545-552.

104. KLECH, H. et al. Assessment of activity in Sarcoidosis. Sensitivity and specificity of 67 Gallium scintigraphy, serum ACE levels, chest roentgenography, and blood lymphocyte subpopulations. Chest 1982; 82:732–738

105. PEPYS, MB, HIRSCHFIELD, GM. C-reactive protein: a critical update. J Clin Invest 2003; 111:1805–1812

APÊNDICE A – Termo de consentimento

Consentimento Livre e Esclarecimento

Título do projeto: Uso da Quitriosidase como instrumento de identificação de atividade da Sarcoidose

Nome do pesquisadores responsáveis: Dr. Rogério Lopes Rufino Alves e Dra. Cláudia Henrique da Costa, Dra. Thais Porto Amadeu

Nome dos médicos responsáveis: Dr. Rogério Rufino, Dra. Mariana Carneiro Lopes

Nomes e telefones de contato para questões e problemas: Dra. Mariana Carneiro Lopes: 21-2868-8248

Financiador do projeto: Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ)

Você está sendo convidado(a) a participar deste projeto, que está em acompanhamento nos ambulatório de pneumologia.

Todos os pacientes com sarcoidose, tuberculose e fibrose pulmonar idiopática precisam fazer vários exames de sangue e de imagem (radiografia ou tomografia computadorizada de tórax), para verificar se a doença está sendo controlada com o uso de medicamentos. Essa avaliação é feita de forma rotineira nos ambulatórios.

O principal objetivo deste projeto é identificar se um exame de sangue pode ser um método de acompanhamento da doença chamada de sarcoidose. Essa doença acomete os pulmões e outros locais do corpo, levando a cansaço, falta de ar, dores articulares, inchaço nas articulações, tosse, dor no peito, emagrecimento. Algumas doenças como a fibrose pulmonar idiopática ou a tuberculose podem ter sintomas muito parecidos, o que dificulta o médico a estabelecer o diagnóstico e o tratamento da sarcoidose.

Procedimentos e riscos

Coleta de sangue: Um profissional bem treinado neste procedimento fará a punção da veia do seu antebraço. O procedimento toma de 5 a 10 minutos, e é idêntico aquele usado quando se tira sangue para exame.

Desconfortos e riscos: Os possíveis desconfortos e riscos, se ocorrerem, são aqueles relacionados com a retirada de sangue, como dor local e/ou hematoma (mancha roxa) no local, e infecção (muito raramente). A quantidade de sangue necessária para o estudo é muito pequena, e não causará nenhuma complicação. Os pacientes com sarcoidose, fibrose pulmonar idiopática, tuberculose e os indivíduos saudáveis (sem doença conhecida) farão o exame de sangue.

Prova de Função Respiratória: É o exame de sopro, para medir o volume de ar que os pulmões possuem. Esse exame só será realizado para esse projeto nos pacientes com sarcoidose. Ele pode provocar, tosse, chiado, falta de ar, dor no peito e desmaios. Somente os pacientes com sarcoidose farão esse exame para o estudo.

Os pacientes com fibrose pulmonar idiopática, tuberculose e os indivíduos saudáveis (sem doença conhecida) não farão esse exame.

Benefícios: Os exames realizados neste estudo poderão contribuir para o tratamento de casos com sarcoidose. Os voluntários do estudo têm sarcoidose, tuberculose pulmonar, fibrose pulmonar idiopática ou pessoas saudáveis (sem doença conhecida). Esse estudo beneficiará futuramente os pacientes com sarcoidose.

Ressarcimento de Despesas

Não haverá nenhum tipo de compensação financeira para os participantes da pesquisa. Por outro lado todos os exames serão feitos no Hospital Universitário Pedro Ernesto e não serão cobrados.

Confiabilidade: As pessoas que vão puncionar o seu sangue e os pesquisadores que estão coordenando este estudo irão tratar sua identidade com padrões profissionais de confiabilidade. Nas amostras não constará o seu nome, e ninguém (exceto os pesquisadores envolvidos no estudo) será capaz de identificar você como doador desta amostra.

Responsabilidade: A comissão de Ética responsabilizará o coordenador pelo estudo por qualquer transtorno que aconteça durante o mesmo.

Declaração

O médico da equipe de pesquisa colocou-me a par destas informações, estando à disposição para responder minhas perguntas sempre que eu tiver novas dúvidas. Também tenho toda liberdade para contatar os pesquisadores responsáveis: Dra. Mariana Carneiro Lopes e Dr. Rogério Rufino

Participação Voluntária/Retirada:

Sua participação neste estudo é completamente voluntária. Cabe ao Sr.(a) decidir se quer participar ou não. Mesmo se decidir participar, o Sr.(a) é livre para desistir do estudo a qualquer momento sem dar um motivo ou explicação. Isto não afetará seu cuidado médico futuro de qualquer forma.

Anuência para fazer parte do Estudo

Assinando este documento você concorda que:

1- Você teve uma chance para fazer perguntas.

2- Você é voluntário(a) para participar deste estudo.

Nome: _____Data:_____

Assinatura_____

Pesquisador supervisor da assinatura do termo de consentimento:

Nome:_____Data:_____

Assinatura_____

APÊNDICE B – Publicação: Identification of Active Sarcoidosis Using Chitotriosidase and Angiotensin-Converting Enzyme

Lung
https://doi.org/10.1007/s00408-019-00219-2

INTERSTITIAL LUNG DISEASE

Identification of Active Sarcoidosis Using Chitotriosidase and Angiotensin-Converting Enzyme

Mariana Carneiro Lopes[1] · Thaís Porto Amadeu[1] · Marcelo Ribeiro-Alves[2] · Claudia Henrique da Costa[1] · Luciana Silva Rodrigues[1] · Elisabeth Jauhar Cardoso Bessa[1] · Leonardo Palermo Bruno[1] · Agnaldo José Lopes[1] · Rogerio Rufino[1]

Received: 13 October 2018 / Accepted: 13 March 2019

Abstract

Purpose Activity/remission differentiation is a great challenge in the follow-up and treatment of sarcoidosis patients. Angiotensin-converting enzyme (ACE) and high sensitivity C-reactive protein (hs-CRP) were proposed as sarcoidosis biomarkers. More recently, chitotriosidase (CHITO) has been described as a better alternative. This study has the aim to evaluate the association of CHITO activity, ACE, hs-CRP or a combination of these biomarkers and to construct a clinical algorithm to differentiate between sarcoidosis activity/remission status.

Methods Forty-six patients with either active sarcoidosis or sarcoidosis in remission and 21 healthy individuals were included. ACE, hs-CRP, and CHITO were evaluated in serum samples. Comparisons of the laboratory variable means among groups were performed by linear models. The cutoff points of the biomarkers for activity/remission differentiation were calculated using the Youden's index. Biomarker cutoff points and decision tree classifier (DTC) performance were estimated by their leave-one-out cross-validation (LOOCV) accuracy (Acc), sensitivity (Se), and specificity (Sp).

Results A 55% mean Se and a 100% mean Sp were found for CHITO, while an 88% Se and a 47% Sp were found for ACE, and a 66% Se and a 68% Sp for hs-CRP cutoff points for activity/remission differentiation. The DTC algorithm with CHITO, hs-CRP, and ACE information had an LOOCV mean Acc of 82%, Se of 78%, and Sp of 89% for sarcoidosis activity/remission differentiation.

Conclusions The algorithm involving CHITO, hs-CRP, and ACE could be a suitable strategy for differentiation between sarcoidosis activity/remission status.

Keywords Sarcoidosis · Activity · Biomarkers · Chitotriosidase · Angiotensin-converting enzyme

Introduction

Sarcoidosis is a multisystem disease, with predominantly pulmonary involvement, no clear etiology, and a variable prevalence throughout the world [1]. Since the 1980s, some markers have been studied to aid the follow-up and treatment of patients and to differentiate between active sarcoidosis and sarcoidosis that is in remission; however, the latter still poses a great challenge [2–5].

Angiotensin-converting enzyme (ACE) has been studied as a biomarker for active sarcoidosis since 1975, but its use is complicated by the fact that other diseases have been also shown to raise the levels of this enzyme [6–9]. The usefulness of ACE for the diagnosis or follow-up of sarcoidosis is controversial, with values of sensitivity and specificity varying between studies [5, 10, 11].

High-sensitivity C-reactive protein (hs-CRP) is a non-specific acute-phase response biomarker. It is produced by hepatocytes and is used to screen for diseases, monitor therapeutic responses, and detect infections in immunocompromised patients [12]. In sarcoidosis, however, hs-CRP has failed to demonstrate a significant change in most of studies,

✉ Rogerio Rufino
rrufino.uerj@gmail.com

[1] State University of Rio de Janeiro, Boulevard 28 de Setembro, 77 – Vila Isabel, 2nd floor - Pulmonology Service, Rio de Janeiro, RJ 20551-030, Brazil

[2] National Institute of Infectiology Evandro Chagas, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Published online: 19 March 2019

APÊNDICE C – Publicação:Defining prognosis in sarcoidosis.

Observational Study

Medicine

OPEN

Defining prognosis in sarcoidosis

Mariana Carneiro Lopes, MD[a], Thaís Porto Amadeu, PhD[b], Marcelo Ribeiro-Alves, PhD[c], Claudia Henrique da Costa, PhD[a], Bruno Rangel Antunes Silva, PhD[a], Luciana Silva Rodrigues, PhD[b], Elisabeth Jauhar Cardoso Bessa, MD[a], Leonardo Palermo Bruno, MD[a], Agnaldo José Lopes, PhD[a], Rogerio Rufino, PhD[a,*]

Abstract

Sarcoidosis is a multi-systemic granulomatous disease. Affected individuals can show spontaneous healing, develop remission with drug treatment within 2 years, or become chronically ill. Our main goal was to identify features that are related to prognosis.

The study consisted of 101 patients, recruited at a single center, who were already diagnosed with sarcoidosis at the start of the study or were diagnosed within 48 months. Ninety individuals were followed-up for at least 24 months and were classified according to clinical outcome status (COS 1 to 9). Those with COS 1–4 and COS 5–9 were classified as having favorable and unfavorable outcomes, respectively. Unconditional logistic regression analyses were conducted to define which variables were associated with sarcoidosis outcomes. Subsequently, we established a scoring system to help predict the likelihood of a favorable or unfavorable outcome.

Of our patients, 48% developed a chronic form of the disease (COS 5–9). Three clinical features were predictive of prognosis in sarcoidosis. We built a score-based model where the absence of rheumatological markers (1 point), normal pulmonary functions (2 points), and the presence of early respiratory symptoms manifestations (2 points) were associated with a favorable prognosis. We predicted that a patient with a score of 5 had an 86% (95% confidence interval [CI] 74%–98%) probability of having a favorable prognosis, while those with scores of 4, 3, 2, 1, and 0 had probabilities of 72% (95% CI 59–85%), 52% (95% CI 40–63%), 31% (95% CI 17–44%), 15% (95% CI 2–28%), and 7% (95% CI 0–16%) of having a favorable prognosis, respectively. Thus, our easy-to-compute algorithm can help to predict prognosis of sarcoidosis patients, facilitating their management.

Abbreviations: ANA = antinuclear antibodies, ANCA = anti-neutrophil cytoplasmic antibodies, aOR = adjusted odds ratio, COS = clinical outcome status, CPI = composite physiologic index, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GAP = gender, age, physiology, HLA = human leukocyte antigen, PASP = pulmonary artery systolic pressure, RF = rheumatoid factor.

Keywords: prognosis, sarcoidosis, score-based predictive model

ANEXO - Parecer do Comitê de Ética em Pesquisa

HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Uso da Quitriosidase como instrumento de identificação de atividade da Sarcoidose

Pesquisador: Rogério Lopes Rufino Alves
Área Temática:
Versão: 1
CAAE: 46767915.8.0000.5259
Instituição Proponente: Hospital Universitário Pedro Ernesto/UERJ
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.158.044
Data da Relatoria: 08/07/2015

Apresentação do Projeto:
Projeto com apresentação adequada.

Objetivo da Pesquisa:
Avaliar a quitriosidase sérica de pacientes com sarcoidose pulmonar em atividade e em remissão.

Avaliação dos Riscos e Benefícios:
Os participantes do estudo colherão exame de sangue venoso periférico, o que pode levar a hematoma, equimose e dor. Os pacientes com sarcoidose farão também a prova de função respiratória. Este exame pode levar a tosse, falta de ar, dispneia e lipotimias. O grupo controle não fará o exame de função pulmonar.

Comentários e Considerações sobre a Pesquisa:
Estudo transversal, sem riscos evidentes. A pesquisa está bem estruturada e o referencial teórico e metodológico estão explicitados, demonstrando aprofundamento e conhecimento necessários para sua realização. As referências estão adequadas e a pesquisa é exequível.

Considerações sobre os Termos de apresentação obrigatória:
Termos de apresentação obrigatória estão de acordo com a legislação pertinente e devidamente assinados pelos responsáveis. TCLE adequado

Endereço: Avenida 28 de Setembro 77 - Térreo
Bairro: Vila Isabel **CEP:** 20.551-030
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)2868-8253 **Fax:** (21)2264-0853 **E-mail:** cep-hupe@uerj.br

HOSPITAL UNIVERSITÁRIO PEDRO ERNESTO/ UNIVERSIDADE DO ESTADO

Continuação do Parecer: 1.158.844

Conclusões ou Pendências e Lista de Inadequações:

Projeto com objetivos claros, procedimentos bem detalhados sem riscos elevados. O trabalho pode ser realizado da fora como está apresentado. Diante do exposto e à luz da Resolução CNS nº466/2012, o projeto pode ser enquadrado na categoria – APROVADO.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente, o CEP recomenda ao Pesquisador: 1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas. 2. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes. 3. O Comitê de Ética solicita a V. Sª., que encaminhe relatórios parciais e anuais referentes ao andamento da pesquisa ao término da pesquisa encaminhe a esta comissão um sumário dos resultados do projeto.

RIO DE JANEIRO, 23 de Julho de 2015

Assinado por:
MICHELLE QUARTI MACHADO DA ROSA
(Coordenador)

Endereço: Avenida 28 de Setembro 77 - Terreo
Bairro: Vila Isabel **CEP:** 20.551-030
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)2868-8253 **Fax:** (21)2264-0853 **E-mail:** cep-hupe@uerj.br