

SECTIONS

EDITORIAL

Penile prosthesis implantation: A solution or a dilemma for the couple.....475

GUIDELINES IN FOCUS

Treatment of bone and soft tissue tumors of the limbs with conformal radiotherapy and intensity-modulated radiotherapy (IMRT).....477

IMAGE IN MEDICINE

Secondary syphilis: The great imitator can't be forgotten.....481

Gastric cancer with lesion extending to spleen and perforation into free peritoneum.....484

Thrombosed aneurysm of saphenous vein coronary artery bypass grafting.....488

ARTICLES

ORIGINAL ARTICLES

Evaluation of medical interns' attitudes towards relevant aspects of medical practice.....492

Concomitant testicular infection by Zika virus and *Schistosoma mansoni* in a Brazilian young boy.....500

Factors associated with burnout syndrome in medical residents of a university hospital.....504

Geographical distribution of medical graduates from a public university.....512

Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: A parallel, case-control study comprising adults and elderly.....521

Mueller-Hillis maneuver and angle of progression: Are they correlated?.....527

Thrombocytopenia as a marker of liver steatosis in a low-endemic area for schistosomiasis mansoni.....532

Analysis of the availability of the resources necessary for urgent and emergency healthcare in São Paulo between 2009-2013.....538

Hospitalization due to exacerbation of COPD: "Real-life" outcomes.....543

REVIEW ARTICLE

Association between physical activity and vitamin D: A narrative literature review.....550



CISBE 2017

CONGRESSO INTERNACIONAL
DE SAÚDE BASEADA EM EVIDÊNCIA AMB

17 A 19 DE AGOSTO

CENTRO DE EVENTOS DO CEARÁ
FORTALEZA - BRASIL



OS TRABALHOS APROVADOS SERÃO
PUBLICADOS NA REVISTA DA AMB

INSCRIÇÕES:

cisbe.amb.org.br

www.amb.org.br

eventos@amb.org.br +55 85 4011-1572

REALIZAÇÃO:



EDITORIAL BOARD
Editor-in-chief

Carlos V. Serrano Jr.

Co-editors

 José Maria Soares Jr.
 Wanderley M. Bernardo

Administrative Co-editor

Paula Jereissati

Managing Editor

César Teixeira

Associated Editors

 Albert Bousso
 Sérgio C. Nahas
 Auro Del Giglio
 Cláudia Leite
 Edna Frasson de S. Montero
 Eduardo F. Borba
 Elias Jirjoss Ilias
 Isabela Giuliano
 José Maria Soares Jr.
 Lucia Pellanda
 Paulo Kassab

Rossana Pulcineli

 V. Francisco
 Werther B. W. de Carvalho
 Linamara Batistella
 Ruy Jorge Cruz Jr.
 Dimas Ikeoki
 Anna Andrei

International Editors

 Frida Leonetti
 Geltrude Mingrone
 Giuseppe Barbaro

Marcelo Marotti

 Walter Ageno
 Michael Farkouh

Junior Editors

Matheus Belloni Torsani

SPECIALTY EDITORS
Acupuncture

 Pedro Cavalcante
 Márcia Lika Yamamura
 João Bosco Guerreiro

Allergy and immunology

 Alexandra Sayuri Watanabe
 Ana Paula Beltran Moschione
 Castro
 Luisa Karla de Paula Arruda

Anesthesiology

 Oscar César Pires
 Rogean Rodrigues Nunes
 Mário José da Conceição
 Maria Angela Tardelli

Angiology and vascular surgery

 Pedro Pablo Komlós
 Vasco Lauria da Fonseca
 Ivan Benaduce Casella
 Winston Bonetti Yoshida
 Fausto Miranda Jr.

Cardiology

 Robson Freitas de Moura
 Amândio Soares Fernandes Jr.
 José Alberto L. Nogueira
 Anna Andrei

Cardiovascular surgery

 Domingo Marcolino Braille
 Rui Almeida
 Fernando Ribeiro Moraes Neto

Citopatology

 Letícia Maria Correia Katz
 Luiz Martins Collaço

Clinical neurophysiology

Carlos Otto Heise

Clinical pathology/laboratory medicine

 Silvana Maria Elói Santos
 Alfredo José Afonso Barbosa
 José Eymard Homem Pittella
 Alvaro Pulchinelli Jr.

Coloproctology

 Fábio G. Campos
 Sergio Nahas

Dermatology

 Andrelou Fralete Ayres Vallarelli
 Denise Steiner

Mário Cezar Pires

Hélio Amante Miot

Digestive endoscopy

Everson Luiz Almeida Artifon

Digestive surgery

 Bruno Zilberstein
 Nelson Andreollo
 Osvaldo Malafaia
 Carlos Eduardo Jacob

Endocrinology and metabolism

 Victória Zeghibi Cochenski Borba
 Alexis Dourado Guedes

Gastroenterology

 André Castro Lyra
 Antonio Carlos da Silva Moares
 João Galizzi Filho
 Raquel Canzi Almada de Souza

General medical clinic

 Fernando Sabia Tallo
 Renan Magalhães M. Jr

Geriatrics and gerontology

Francisca Magalhães Scoralick

Gynecology and obstetrics

 Jurandyr Moreira de Andrade
 Rosiane Mattar
 Edmund C. Baracat
 Paulo Cesar Giraldo

Hand surgery

 Luiz Koiti Kimura
 Giana Silveira Giostrí
 Carlos Henrique Fernandes
 Antonio Carlos da Costa

Head and neck surgery

 Flávio Carneiro Hojajj
 José Guilherme Vartanian
 Leandro Luongo Matos
 Ulyyanov Bezerra Toscano de Mendonça

Hepatology

 Edna Strauss
 Carlos Eduardo Brandão de Mello
 Francisco J. Dutra Souto
 Paulo Lisboa Bittencourt

Homeopathy

Silvia Irene Waisse de Priven

Legal medicine and medical examinations

José Jozafran B. Freite

Nephrology

 João Egidio Romão Jr.
 Marcus Gomes Bastos
 Paulo Novis Rocha

Neurology

 Carlos Alberto Mantovani Guerreiro
 Rubens José Gagliardi

Neurosurgery

 José Marcus Rotta
 Eberval Gadelha Figueiredo
 Guilherme Brasileiro de Aguiar
 Roberto Sérgio Martins

Nuclear medicine

 George Barberio C. Filho
 Ricardo Cavalcante Q. Fonseca
 Bárbara Juarez Amorim
 Sérgio Altino de Almeida

Nutrition

 Vivian Suen
 Ana Lucia dos Anjos Ferreira
 Durval Ribas Filho

Oncology

 Robson Freitas de Moura
 Amândio Soares Fernandes Jr.
 José Alberto L. Nogueira

Ophthalmology

 Renato Ambrósio Jr.
 Mauro Nishi

Orthopedics and traumatology

 Marco Kawamura Demange
 Benno Ejnisman
 Daniel Soares Baumfeld
 Alex Guedes
 Robinson Esteves Santos Pires

Otolaryngology and facial surgery

 Eduardo Macoto Kosugi
 Myriam de Lima Isaac
 Gustavo Korn
 Joel Lavinsky

Parenteral and enteral nutrition

 José Eduardo de Aguiar Siqueira
 do Nascimento
 Jorge M. Curi

Pathology

 Alfredo José Afonso Barbosa
 José Eymard Homem Pittella

Pediatric

Denis Burns

Pediatric surgery

 José Roberto de Souza Baratella
 José Carlos Soares de Fraga
 Antonio Aldo de Melo Filho

Physical medicine and rehabilitation

 Sergio Lianza
 Marcelo Riberto

Psychiatry

 Itiro Shirakawa
 Helena Naria Calil
 João Romildo Bueno
 Sérgio Tamai
 André Ferrer

Pulmonology and thoracic

 Valéria Maria Augusto
 José Antônio Baddini
 Martinez
 Marcelo Basso Gazzana
 Aquiles Assunção Camelier

Radiology and imaging diagnosis

 Dante Luiz Escussato
 Luciana Costa Silva
 Cláudia Leite
 Manoel Rocha
 Carlos N. Piguel

Radiotherapy

 Eduardo Weltman
 Ícaro Thiago de Carvalho
 Gustavo Nader Marta
 Arthur Accioly Rosa

Rheumatology

Paulo Louzada Jr.

Urology

 Marcos Tobias Machado
 Ari Adami Jr.
 Lucas Mendes N. Nogueira
 José Carlos I. Truzzi
 Archimedes Nardoza Filho

Telemedicine

Chao Lung Wen

ASSOCIAÇÃO MÉDICA BRASILEIRA – MANAGEMENT BOARD 2014-2017

President Florentino de Araújo Cardoso Filho	Álvaro Roberto Barros Costa Petrônio Andrade Gomes José Luiz Weffort	2 nd Treasurer Miguel Roberto Jorge	Jorge Carlos Machado Curi (Public Health)
1 st Vice-president Eleuses Vieira de Paiva	Eduardo da Silva Vaz	Directors Giovanni Guido Cerri (Scientific)	Diogo Leite Sampaio (Communications)
2 nd Vice-president Lincoln Lopes Ferreira	Jurandir Marcondes Ribas Filho Aguinel José Bastian Jr.	Antonio Carlos Vieira Lopes (DAP)	Edmund Chada Baracat (Academic)
Vice-presidents Lairson Vilar Rabelo	General Secretary Antônio Jorge Salomão	Jane Maria Cordeiro Lemos (Cultural)	Antonio Carlos Weston (Member Support Service)
Eduardo Francisco de Assis Braga	1 st Secretary Aldemir Humberto Soares	Emilio Cesar Zilli (Professional Defence)	Márcio Silva Fortini (Protection to the Patient)
Cléa Nazaré Carneiro Bichara	1 st Treasurer José Luiz Bonamigo Filho	Nívio Lemos Moreira Jr. (International Relations)	Carmelo Silveira Carneiro Leão Filho (Marketing)
Salustiano José Alves de Moura Jr.		Rafael Klee de Vasconcelos (Medical Economy)	José Luiz Dantas Mestrinho (Parliamentary Subjects)

Associação Médica Brasileira

Address: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal code: 01333-903
Phone: (+55 11) 3178-6800



Editor-in-chief: Carlos V. Serrano Jr.

Managing editor: César Teixeira

E-mail: ramb@amb.org.br

Website: www.ramb.org.br

The norms for publication are available on the website www.ramb.org.br



The Journal of the Brazilian Medical Association is affiliated to the ANATEC and indexed in Medline, SciELO, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.

The Journal of the Brazilian Medical Association is an official publication of the Associação Médica Brasileira (AMB), distributed exclusively to the medical community in Brazil and Latin America.

All rights reserved and protected by Law n. 9.610 – 2/19/1998. No part of this publication may be reproduced without prior written authorization of the AMB, whatever the means employed: electronic, mechanical, photocopying, recording or other.

Manole Publisher

Authorizing editor: Sônia Midori Fujiyoshi

Editor: Cristiana Gonzaga S. Corrêa

Publishing production: Quinta Edições

English version: Graziella Risolia Gallo ME

Reviewers: Folgueira Comunicação and Lia Fugita Editorações

Cover: Rafael Zemantauskas

Graphic design: Sopros Design

Layout: Lira Editorial



The advertisements and opinions published in the Ramb are the sole responsibility of the advertisers and authors. The AMB and Manole Publisher are not responsible for its content.

SECTIONS

EDITORIAL

Penile prosthesis implantation: A solution or a dilemma for the couple

THEÓ LERNER, JOSÉ MARIA SOARES JÚNIOR, ANA LÚCIA CAVALCANTI, ELSA PEREYRA GAY, ANA REGINA DOS SANTOS, JOSÉ CURY, MIGUEL SROUGI, EDMUND C. BARACAT 475

GUIDELINES IN FOCUS

Treatment of bone and soft tissue tumors of the limbs with conformal radiotherapy and intensity-modulated radiotherapy (IMRT)

MARCUS SIMÕES CASTILHO, ROBSON FERRIGNO, HELENA BARALDI, PAULO EDUARDO RIBEIRO DOS SANTOS NOVAES 477

IMAGE IN MEDICINE

Secondary syphilis: The great imitator can't be forgotten

CLARISSA PRIETO HERMAN REINEHR, CÉLIA LUIZA PETERSEN VITELLO KALIL, VINÍCIUS PRIETO HERMAN REINEHR 481

Gastric cancer with lesion extending to spleen and perforation into free peritoneum

ROBERTO GONÇALVES, ROBERTO SAAD JR, CARLOS ALBERTO MALHEIROS, PAULO KASSAB, NATHÁLIA LINS PONTES VIEIRA 484

Thrombosed aneurysm of saphenous vein coronary artery bypass grafting

RODOLFO MENDES QUEIROZ, ROGÉRIO NASTRI FILHO, MARCUS ANTÔNIO FERREZ, MAURO JOSÉ BRANDÃO DA COSTA, CLAUDIO BENEDINI LAGUNA, MARCUS VINÍCIUS NASCIMENTO VALENTIN 488

ORIGINAL ARTICLES

Evaluation of medical interns' attitudes towards relevant aspects of medical practice

ÁQUILA TALITA LIMA SANTANA ALVES, FERNANDO VINÍCIUS ALVES, ENALDO VIEIRA MELO, EDMÉA FONTES DE OLIVA-COSTA 492

Concomitant testicular infection by Zika virus and *Schistosoma mansoni* in a Brazilian young boy

LEONARDO SOUZA ALVES, CESAR ESTANISLAU, LUCIO BARRETO, FRANCISCO BATISTA, NIVALDO TOPPA 500

Factors associated with burnout syndrome in medical residents of a university hospital

PEDRO ALVES DA CRUZ GOUVEIA, MARIA HOSANA CHAVES RIBEIRO NETA, CARLOS ALBERTO DE MOURA ASCHOFF, DORIS PIRES GOMES, NADINE ANITA FONSECA DA SILVA, HELTON ALEXSANDRO FIRMINO CAVALCANTI 504

Geographical distribution of medical graduates from a public university

OSCARINA DA SILVA EZEQUIEL, GIANCARLO LUCCHETTI, ALESSANDRA LAMAS GRANERO LUCCHETTI, MARIA HELENA SINGER, LUCAS BRAGA, RAFAEL LACERDA, MARLON FILIPPO, FERNANDO COLUGNATI, DANETTE MCKINLEY, ELIANA AMARAL 512

Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: A parallel, case-control study comprising adults and elderly

BEHROOZ SHOKOUI, KAVEH REZAEI BOOKANI, HOSSEIN GHASEMI, MAHMOUD KHALOUEI, NAGHMEH JAVANSHIR REZAEI, SIMIN MIRAKHOR SAMANI 521

Mueller-Hillis maneuver and angle of progression: Are they correlated?

SOFIA MENDES, RITA SILVA, INÉS MARTINS, SUSANA SANTO, NUNO CLODE 527

Thrombocytopenia as a marker of liver steatosis in a low-endemic area for schistosomiasis mansoni
ALBA OTONI, CARLOS MAURICIO DE FIGUEIREDO ANTUNES, FERNANDA FERREIRA TAVARES, DÉBORA HELOÍSA QUADROS ARAÚJO, THIAGO DE ALMEIDA PEREIRA, LEONARDO CAMPOS DE QUEIROZ, FREDERICO FIGUEIREDO AMÂNCIO, JOSÉ ROBERTO LAMBERTUCCI. **532**

Analysis of the availability of the resources necessary for urgent and emergency healthcare in São Paulo between 2009-2013
SILVANA HEBE COIMBRA, ELIETE DOMINGUEZ LOPEZ CAMANHO, LINDOLFO CARLOS HERINGER, RICARDO VIEIRA BOTELHO, CIDIA VASCONCELLOS **538**

Hospitalization due to exacerbation of COPD: “Real-life” outcomes
LILIA AZZI COLLET DA ROCHA CAMARGO, MARIA VERA OLIVEIRA CASTELLANO, FÁBIO CHECCHIA FERREIRA, FLÁVIO VIEIRA DE FARIA, NELSON CARVAS JR. **543**

REVIEW ARTICLE

Association between physical activity and vitamin D: A narrative literature review
MARCOS RASSI FERNANDES, WALDIVINO DOS REIS BARRETO JUNIOR. **550**

Penile prosthesis implantation: A solution or a dilemma for the couple

IMPLANTE DE PRÓTESE PENIANA: UMA SOLUÇÃO OU UM DILEMA PARA O CASAL

THÉO LERNER¹, JOSÉ MARIA SOARES JÚNIOR¹, ANA LÚCIA CAVALCANTI¹, ELSA PEREYRA GAY¹, ANA REGINA DOS SANTOS², JOSÉ CURY², MIGUEL SROUGI², EDMUND C. BARACAT¹

¹Division of Gynecology, Department of Obstetrics and Gynecology, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP), São Paulo, SP Brazil

²Division of Urology, HC-FMUSP São Paulo, SP Brazil

<http://dx.doi.org/10.1590/1806-9282.63.06.475>

The physical, social and psychological changes resulting from aging have a significant impact on the sexuality of both men and women.¹⁻⁵

Among men, erectile dysfunction (ED) is a common cause of impaired quality of life. In the last decades, an arsenal of alternatives has been developed to deal with this problem. Local drugs such as injectable or intraurethral prostaglandins, systemic agents such as phosphodiesterase inhibitors, and mechanical methods including vacuum constriction devices are among the possibilities of non-surgical intervention. For cases in which vascularization or penile innervation is compromised, surgical treatment of ED is indicated involving placement of a penile implant.⁵ The two types of implants available are semi-rigid and inflatable, differing in cost and functional outcome.

As for women, climacteric corresponds to a period of transition marked by estrogen decline (hypoestrogenism). It is characterized by physical, metabolic and psychological changes with negative repercussions in the psychosocial domain and in sexuality.¹⁻⁴ Culturally, society has stigmatized menopausal women in relation to their sex life. However, with the advent of hormone therapy and career advancement of many women, this perception has changed and sexual interest at this stage of life has once again been accepted.¹⁻⁴ In addition to the urological assessment of the male partner, evaluating the physical changes that occur during perimenopause and which affect the sexuality of women is justified.

The influence of cultural and social factors related to the aging process and the expression of sexuality increases the complexity of treating couples with indication for a penile implant. Assessing the female partner's expectations and degree of satisfaction is critical.

The literature of the 1980s and 1990s dealt with female sexual satisfaction in a generic way and reported satisfaction experienced by most women in relation with their partner's prostheses.^{6,7} Some authors began to ques-

tion the influence of cultural and social factors that prevented this satisfaction from being generalized.⁸ Beliefs related to erection, as an expression of desire (and therefore of love) and fear of infidelity, have generated prejudice against artificially induced erections by a significant proportion of women.⁹ Ultimately, another category of problems began to be observed: women with sexual dysfunctions prior to the treatment of erectile dysfunction, who had become accustomed to the problem of their husbands, began to experience high levels of stress as a result of the new demands and expectations associated with penile implant placement.^{10,11}

Often, the couple's sexual interest disappears completely, being replaced by feelings of friendship and companionship after long years of marital life. The female partner is not always ready to resume sexual activities, which can pose a dilemma for the couple and even break the marital bond.

The prior sexual history of both partners needs to be investigated, including beliefs, fantasies, fears, and expectations related to the procedure. Doubts should be clarified, while conflicts in the relationship can be identified and properly managed.¹²

Couples therapy can be a useful tool for dealing with psychological and behavioral factors that hinder the marital bond and consequently sexual satisfaction.¹⁻⁴ Thorough evaluation and sexuality counseling are fundamental for the prevention of negative impacts of a penile implant on the couple's relationship.

REFERENCES

1. Galhardo CL, Soares JM Jr, Simões RS, Haidar MA, Rodrigues de Lima G, Baracat EC. Estrogen effects on the vaginal pH, flora and cytology in late postmenopause after a long period without hormone therapy. *Clin Exp Obstet Gynecol.* 2006; 33(2):85-9.
2. Favarato MECS, Aldrighi JM. A mulher coronariopata no climatério após a menopausa: implicações na qualidade de vida. *Rev Assoc Med Bras.* 2001; 47(4):339-45.

3. Souza MA, Fonseca AM, Bagnoli VR, Barros N, Neves EM, Moraes SDTA, et al. The expression of the estrogen receptor in obese patients with high breast density (HBD). *Gynecol Endocrinol*. 2014; 30(1):78-80.
4. Fleury HJ, Abdo CHN. Terapia de casal para superar disfunções sexuais. *Diagn Tratamento*. 2016; 21(1):45-8.
5. Gittens P, Moskovic DJ, Avila D Jr, Chandrashekar A, Khera M, Lipshultz LI. Favorable female sexual function is associated with patient satisfaction after inflatable penile prosthesis implantation. *J Sex Med*. 2011; 8(7):1996-2001.
6. McLaren RH, Barrett DM. Patient and partner satisfaction with the AMS 700 penile prosthesis. *J Urol*. 1992; 147(1):62-5.
7. Gerstenberger DL, Osborne D, Furlow WL. Inflatable penile prosthesis: follow-up study of patient-partner satisfaction. *Urology*. 1979; 14(6):583-7.
8. Salama N. Satisfaction with the malleable penile prosthesis among couples from the Middle East: is it different from that reported elsewhere? *Int J Impot Res*. 2004; 16(2):175-80.
9. Montorsi F, Guazzoni G, Bergamaschi F, Rigatti P. Patient-partner satisfaction with semirigid penile prostheses for Peyronie's disease: a 5-year followup study. *J Urol*. 1993; 150(6):1819-21.
10. Vakalopoulos I, Kampantais S, Ioannidis S, Laskaridis L, Dimopoulos P, Toutziaris C, et al. High patient satisfaction after inflatable penile prostheses implantation correlates with female partner satisfaction. *J Sex Med*. 2013; 10(11):2774-81.
11. Hartzell R, King SA, Goldstein I. "Partner Prosthesis Panic": management of female sexual dysfunction in partners of men undergoing penile prosthesis implantation. *J Sex Med*. 2016; 13:S239-62.
12. Pisano F, Falcone M, Abbona A, Oderda M, Soria F, Peraldo F, et al. The importance of psychosexual counselling in the re-establishment of organic and erotic functions after penile prosthesis implantation. *Int J Impot Res*. 2015; 27(5):197-200.

Treatment of bone and soft tissue tumors of the limbs with conformal radiotherapy and intensity-modulated radiotherapy (IMRT)

TRATAMENTO DE TUMORES ÓSSEOS E DE PARTES MOLES DE MEMBROS COM RADIOTERAPIA EXTERNA CONFORMADA E COM INTENSIDADE MODULADA (IMRT)

Authorship: Brazilian Society of Radiotherapy (SBR)

Participants: Marcus Simões Castilho¹, Robson Ferrigno¹, Helena Baraldi¹, Paulo Eduardo Ribeiro dos Santos Novaes¹

¹Sociedade Brasileira de Radioterapia (SBR)

<http://dx.doi.org/10.1590/1806-9282.63.06.477>

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.

The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

GRADES OF RECOMMENDATION AND LEVELS OF EVIDENCE

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Cases reports (non-controlled studies).
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

DESCRIPTION OF EVIDENCE COLLECTION METHOD

Through the elaboration of three relevant clinical questions related to the proposed theme, we sought to present the main evidences regarding safety, toxicity and effectiveness of the presented radiotherapy techniques. The study population consisted of male and female patients of all ages with bone and soft tissue tumors in the upper and lower limbs, regardless of histological type, staging, treatment context (neoadjuvant, radical or adjuvant) or the presence of comorbidities. For this, a systematic review of the literature was carried out in primary scientific databases (MEDLINE – PubMed; Embase – Elsevier; LILACS – BIREME; Cochrane Library – Record of Controlled Trials). All articles available through May 31, 2015 were considered. The search terms used in the research were: (conformal radiotherapies [MeSH Terms]) OR radiotherapies, conformal [MeSH Terms]) OR conformal radiotherapy [MeSH Terms]) OR radiotherapy, intensity-modulated [MeSH Terms]) OR conformal radiotherapy) OR conformal radiotherapies) OR conventional radiotherapy) OR IMRT) OR 3D conformal radiotherapy) OR VMAT)) AND (sarcomas [MeSH Terms]) OR sarcoma, soft tissue [MeSH

Terms]) OR sarcomas, soft tissue [MeSH Terms]) OR soft tissue sarcoma [MeSH Terms]) OR sarcoma) OR sarcomas).

The articles were selected based on critical evaluation using the instruments (scores) proposed by Jadad and Oxford. The references with greater degree of evidence were used. The recommendations were elaborated after discussion with the elaboration group composed by four members of the Brazilian Society of Radiotherapy.

OBJECTIVE

To evaluate the most appropriate technique of radiotherapy for the treatment of patients with bone and soft tissue tumors of the limbs.

INTRODUCTION

The therapeutic strategy of bone and soft tissue tumors of the limbs should be performed through multidisciplinary decision to better associate surgery, radiotherapy and chemotherapy. The decision on the best combination and sequence is based on factors such as tumor type and histological grade, clinical staging, primary tumor location and volume, proposed type of surgery, and general patient conditions. External radiotherapy can be used preoperatively (neoadjuvant) or postoperative (adjuvant) and aims to ensure local control of the primary tumor before or after surgery.

Although there are no viscera or vital organs in the limbs, the joints and soft tissues are susceptible to severe complications of radiotherapy, such as lymphedema, joint stiffness, soft tissue fibrosis, and necrosis of bones and soft tissues. If an irradiated bone fractures, there is no consolidation of this fracture due to changes in the mi-

crovasculature caused by irradiation. These sequelae may lead to limitation of limb functions, such as articulation and movement, and consequent impairment of quality of life. In some situations, sequelae may leave the patients disabled and, depending on their profession, drive them out of the job market.

Therefore, the radiation dose should be directed as concentrated as possible to the area at risk of local recurrence after surgery or in the primary tumor prior to surgery, also minimizing or avoiding the therapy in areas at risk that do not need to be treated, such as those with soft tissues, bones, tendons, vessels, nerves, muscles and joints.

In recent years, the technical development of radiotherapy has allowed the planning of the radiation deposit to be made using imaging tests, which is not performed with conventional radiotherapy, but with conforming techniques and IMRT.

Conventional radiotherapy is performed from simple radiographs of the affected limb, on which the area to be irradiated is drawn in two dimensions. Dose calculation is done manually taking into account the size of the field and the thickness of the limb. This technique can not estimate the amount of dose released in areas that do not require treatment. Because of these characteristics, conventional radiotherapy has been abandoned for several years in developed countries and is not recommended by the Brazilian Society of Radiotherapy for the treatment of limb tumors.¹ (D)

Conformal radiotherapy was developed so that the planning would be performed with imaging tests such as computed tomography, and the calculation of the dose with computerized systems that evidence the dose distribution in three dimensions. With this, it is possible to estimate if the dose distribution is adequate and safe. The planning system allows various combinations of radiation input fields to be modified in their incidence and size, in order to focus the radiation only where it is needed. Thus, radiotherapy has become potentially safer and more effective for patients with bone and soft tissue tumors of the limbs.

IMRT radiotherapy was developed from conformal radiotherapy with the addition of a planning system that can place radiation filters in the front of the beam so that the homogeneity of dose is greater, avoiding excessive doses and bypassing risk structures more efficiently.

Based on these premises, this guideline aims to show the benefits of the most modern techniques of radiotherapy in the management of patients with bone and soft tissue tumors of the limbs, with the support of published dosimetric and clinical evidence.

To that end, three questions were elaborated to answer the main points.

1. IS THERE A DOSIMETRIC SUPERIORITY IN THE IRRADIATION OF SOFT TISSUE AREAS WITH CONFORMAL RADIOTHERAPY OR INTENSITY-MODULATED RADIATION BEAM (IMRT) COMPARED TO CONVENTIONAL RADIOTHERAPY?

Although limb neoplasms are rare diseases, which makes it difficult to conduct prospective and randomized studies for a dosimetric comparison between radiotherapy techniques, there are some experimental or observational studies of better consistency showing that both IMRT and conformal radiotherapy are superior to radiotherapy as they allow the evaluation of irradiated treatment volumes and doses in normal structures of interest such as bones, surgical wound, graft flaps and skin bands, in both adults and children with indication of pre- or postoperative radiotherapy. Six studies have shown that the dose of radiation in areas of risk is greatly reduced when IMRT or conformal technique are used compared to conventional radiotherapy.²⁻⁷ (C)

Three more recent studies have demonstrated superiority of the IMRT technique compared to conformal radiotherapy. All of them found greater conformity and dose homogeneity in treatment volumes and dose reduction for risk structures.⁸⁻¹⁰ (C)

Robinson et al. compared the dosimetric plans of 11 patients with endometrial tumors between conventional radiotherapy and conformal radiotherapy. The volume of treatment with conformal radiotherapy was reduced in all patients. Normal muscle volume was reduced by 30% in thigh tumors. Likewise, the volumes of femur, tibia/fibula and ileum were reduced by 38%, 18% and 14%.² (C) Stewart et al. updated these results by analyzing ten patients submitted to adjuvant radiotherapy after limb-preserving surgical resection due to thigh sarcomas, comparing conformal radiotherapy and IMRT. For all patients, the IMRT plans showed better conformity than those of conformal radiotherapy. IMRT allowed the release of a lower dose in the femur and normal tissue. In patients with lesions extending into the pelvis, bladder, rectum and bowel doses were also minimized. For the other parameters, there was no difference between techniques.⁶ (C)

Sladowska et al. also presented the comparative results between IMRT and conformal radiotherapy in ten patients with thigh sarcomas. IMRT demonstrated better dose conformity in the target volume, especially when concave dose distribution was required. It also promoted a decrease

of 31% in the maximum and average doses released in the femur, in all patients.¹⁰ (C)

Due to the dosimetric data published in the literature, IMRT, when available, is the most recommended technique for the treatment of soft tissue tumors in the limbs, while conformal radiotherapy should be the least recommended technique.

2. IS THERE LESS TOXICITY IN THE USE OF CONFORMAL RADIOTHERAPY OR IMRT COMPARED TO CONVENTIONAL RADIOTHERAPY FOR SOFT TISSUE TUMORS IN THE LIMBS?

Alektiar et al.¹¹ (B) analyzed the impact of IMRT on 41 adult patients with end-stage sarcomas treated at the Memorial Sloan-Kettering Cancer Center in New York between February 2002 and May 2005. The risk of complications was encouraging low, even including 25% of patients considered to be at high risk for the development of bone fractures after undergoing periosteal stripping or bone resection during surgery. Only two patients (4.8%) developed grade 1 and 2 fractures and did not require surgical intervention for repair. Other complications such as edema and joint stiffness were also favorable when compared to conformal radiotherapy. Folker et al.¹² (B), from the same institution, analyzed 319 patients with end-stage sarcomas treated with conservative limb surgery and adjuvant radiotherapy from 1996 to 2010. Of these, 154 were treated with conformal radiotherapy and 165 with IMRT technique. Acute grade ≥ 2 radiodermatitis was more frequent in patients treated with conformal radiotherapy (48.7% versus 31.5%; $p=0.002$). Grade ≥ 2 chronic edema was also more frequent in patients who received conformal radiotherapy (14.9% versus 7.9%; $p=0.05$). There was no difference in the incidence of pathological fracture, neuritis and joint stiffness between the two techniques. During the study period, no patient was treated with conventional radiotherapy.

O'Sullivan et al.¹³ (B) published the results of a phase 2 study involving 59 patients with end-stage sarcoma treated preoperatively with IMRT. The incidence of surgical wound complications was 30.5%, less than the findings of the National Cancer Institute Canada study, which was 43% with conventional radiotherapy.

Clinical results with IMRT are still short-term and patients treated by different institutions require longer follow-up to consolidate results, but it can be inferred that these will not be inferior to those of conformal radiotherapy. The use of a conformal technique should constitute the minimum standard (least recommended) of radiotherapy for bone and soft tissue tumors of the limbs.

3. IS THERE A DIFFERENCE IN EFFICACY BETWEEN CONFORMAL OR IMRT AND CONVENTIONAL RADIOTHERAPY?

There are no randomized studies comparing the three planning and application techniques of radiotherapy. Due to the rarity of the disease and the multiplicity of possible presentations of limb tumors, it is unlikely that randomized trials for this evaluation will be performed.

In the American institution with the longest tradition in treating limb tumors (Memorial Sloan Kettering Cancer Center), from 1996 to 2010, 395 soft tissue sarcoma patients were treated with limb-preserving surgery and radiotherapy.¹² (B) All patients after 2002 were treated with IMRT. Their study is the largest existing and compares the conformal and IMRT techniques. Conventional radiotherapy was not used in this period. In the study, the first 154 patients received adjuvant conformal radiotherapy and the following 165 received IMRT. Analysis of patient and tumor characteristics showed that the IMRT group had significantly more risk factors for recurrence (greater percentage of surgeries with positive or low margins and higher percentage of high-grade tumors). Patients treated with IMRT had fewer local recurrences (8% versus 15%, $p=0.05$). In a detailed multivariate analysis, IMRT remained a protective factor of independent recurrence (HR=0.458; CI 0.235-0.891).

A Canadian study compared a group of patients treated with IMRT in a phase 2 protocol with another group previously treated with conformal radiotherapy in a randomized study from the same institution.¹⁴ (B) The analysis showed 5-year recurrence-free survival of 88% in the IMRT-treated group and 89% of the historical control with conformal radiotherapy.

A study in children with rhabdomyosarcoma treated in a prospective protocol from the American Children's Oncology Group showed improvement in target volume coverage with IMRT. However, this did not translate into improvement of disease control results compared to conformal radiotherapy.¹⁴ (C)

There is therefore no evidence of good quality that demonstrates greater efficacy between IMRT and conforming techniques, making it impossible at this moment to recommend one over another. Regarding conventional radiotherapy, despite the absence of evidence of good quality, we recommend whenever possible that this technique not be used, due to its inability to allow evaluation of risk structures. In addition, there is a great risk of geographic error of the target to be irradiated due to the complex tissue irradiation needs in limb tumors.

CONCLUSION

Bone and soft tissue tumors of the limbs are diseases with very variable presentation (histology, stage, volume of disease and location). Surgery is the treatment of choice and, because of the highly variable locations, it may not be feasible in many cases or it may be performed with minimally recommendable oncological principles.

The disease is a challenge for treatment and it is highly unlikely that randomized trials testing radiotherapy techniques will be performed anywhere in the world. There will probably never be high quality level 1 evidence for a decision on the radiotherapy technique and, thus, other criteria should be used for recommendations.

Conventional technique does not allow the physician to properly view the region being treated, nor the organs at risk. It does not allow international and national recommendations for doses in organs at risk because it is not possible to assess distribution. It is also subject to gross target location errors due to rotations of the limb that will be irradiated, which places the muscle bundle in an unconventional position. In any service that has the possibility of guiding the treatment using CT scans, we strongly recommend that the conventional technique be definitively abandoned as it has been for many years in developed countries.

If available, IMRT is superior to the others and potentially has a greater ability to control disease with lower toxicity. Due to a lack of clinical evidence, the minimally recommended radiotherapy technique to preserve the safety of patients with soft tissue tumors of the limbs is the conformal one.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Almeida CE, Haddad CK, Ferrigno R. A evolução técnica da radioterapia externa. In: Sociedade Brasileira de Radioterapia. Radioterapia Baseada em Evidências. Recomendações da Sociedade Brasileira de Radioterapia. 1. ed. São Paulo: SBRT; 2010. Chapter 2. p. 21-6.
- Robinson MH, Bidmed AM, Harmer CL. Value of conformal planning in the radiotherapy of soft tissue sarcoma. *Clin Oncol (R Coll Radiol)*. 1992; 4(5):290-3.
- Verhey LJ. Comparison of three-dimensional conformal radiation therapy and intensity-modulated radiation therapy systems. *Semin Radiat Oncol*. 1999; 9(1):78-98.
- Patel S, DeLaney TF. Advanced-technology radiation therapy for bone sarcomas. *Cancer Control*. 2008; 15(1):21-37.
- DeLaney TF, Trofimov AV, Engelsman M, Suit HD. Advanced-technology radiation therapy in the management of bone and soft tissue sarcomas. *Cancer Control*. 2005; 12(1):27-35.
- Stewart AJ, Lee YK, Saran FH. Comparison of conventional radiotherapy and intensity-modulated radiotherapy for post-operative radiotherapy for primary extremity soft tissue sarcoma. *Radiother Oncol*. 2009; 93(1):125-30.
- Hua C, Gray JM, Merchant TE, Kun LE, Krasin MJ. Treatment planning and delivery of external beam radiotherapy for pediatric sarcoma. *Int J Radiat Oncol Biol Phys*. 2008; 70(5):1598-606.
- Chan MF, Chui CS, Schupak K, Amols H, Burman C, Ling CC. The treatment of large extraskelatal chondrosarcoma of the leg: comparison of IMRT and conformal radiotherapy techniques. *J Appl Clin Med Phys*. 2001; 2(1):3-8.
- Griffin AM, Euler CI, Sharpe MB, Ferguson PC, Wunder JS, Bell RS, et al. Radiation planning comparison for superficial tissue avoidance in radiotherapy for soft tissue sarcoma of the lower extremity. *Int J Radiat Oncol Biol Phys*. 2007; 67(3):847-56.
- Śladowska A, Hetnal M, Dymek P, Kabat D, Kisielewicz K, Wawrzak M, et al. Application of IMRT in adjuvant treatment of soft tissue sarcomas of the thigh - Preliminary results. *Rep Pract Oncol Radiother*. 2011; 16(3):110-4.
- Alektiar KM, Brennan MF, Healey JH, Singer S. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol*. 2008; 26(20):2440-4.
- Folkert MR, Singer S, Brennan MF, Kuk D, Qin LX, Kobayashi WK, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol*. 2014; 32(29):3236-42.
- O'Sullivan B, Griffin AM, Dickie CI, Sharpe MB, Chung PW, Catton CN, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer*. 2013; 119(10):1878-84.
- Lin C, Donaldson SS, Meza JL, Anderson JR, Lyden ER, Brown CK, et al. Effect of radiotherapy techniques (IMRT vs. 3D-CRT) on outcome in patients with intermediate-risk rhabdomyosarcoma enrolled in COG D9803—A report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2012; 82(5):1764-70.

Secondary syphilis: The great imitator can't be forgotten

CLARISSA PRIETO HERMAN REINEHR^{1*}, CÉLIA LUIZA PETERSEN VITELLO KALIL², VINÍCIUS PRIETO HERMAN REINEHR³

¹MD, Dermatologist, Member of the Brazilian Society of Dermatology, Master's Student at the Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

²Dermatologist, Member of the Brazilian Society of Dermatology, Porto Alegre, RS, Brazil

³MD, General Practitioner, Porto Alegre, RS, Brazil

SUMMARY

Syphilis is an infection caused by *Treponema pallidum*, mainly transmitted by sexual contact. Since 2001, primary and secondary syphilis rates started to rise, with an epidemic resurgence. The authors describe an exuberant case of secondary syphilis, presenting with annular and lichen planus-like lesions, as well as one mucocutaneous lesion. Physicians must be aware of syphilis in daily practice, since the vast spectrum of its cutaneous manifestations is rising worldwide.

Keywords: cutaneous syphilis, sexually transmitted disease, benzathine penicillin G, *Treponema pallidum*.

Study conducted at Clínica Dermatológica
Célia Kalil, Porto Alegre, RS, Brazil

Article received: 11/7/2016

Accepted for publication: 12/4/2016

*Correspondence:

Address: Rua Félix da Cunha, 1.009,
conj. 401
Porto Alegre, RS – Brazil
Postal code: 90570-001
cla.reinehr@gmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.481>

INTRODUCTION

Syphilis is an infection caused by *Treponema pallidum*, a spirochete bacterium transmitted mostly by sexual contact. Spirochetes penetrate skin or mucosa in areas of micro-trauma and disseminate systemically within 24 hours.¹

The incidence of syphilis started to rise again in 2001, with epidemic resurgence especially among men who have sex with men and HIV-infected patients.² More specifically, the incidence of syphilis has tripled in the last 10 years.³ The authors describe an exuberant case of secondary syphilis.

CASE REPORT

A previously healthy 63-year-old man presented with cutaneous asymptomatic lesions that appeared approximately three months before, first on the hands and wrists, and later affecting feet, thighs and lips. During the clinical examination, sharply demarcated hyperkeratotic, violaceous scaly plaques on his hands and feet, including annular and well-circumscribed lesions on the palms and soles were observed (Figure 1); also, the patient showed a papule located at the right angle of the upper lip (Figure 2). First hypotheses included lichen planus and secondary syphilis. He denied previous genital ulceration, but reported unprotected sex in the past. Laboratory tests revealed a venereal disease research laboratory test (VDRL) titer of 1:32 (normal value < 1:2) and positive tests for syphilis-specific IgM and IgG antibodies. Serology was negative for human immunodeficiency virus and hepatitis B and C. A diagnosis of secondary syphilis was con-

firmed and the patient was treated with three weekly intramuscular injections of benzathine penicillin G 2.4×10⁶ IU.⁴ The patient was advised to contact his sexual partners so that they could seek medical evaluation. One month after treatment, the lesions resolved (Figure 3).

DISCUSSION

Secondary syphilis, the most florid stage of the disease, called “the great imitator,” has a variety of cutaneous manifestations.⁵ The onset of secondary syphilis varies but typically occurs two to eight weeks after the disappearance of the primary chancre. This stage can present with systemic symptoms and painless generalized adenopathy. If left untreated, secondary syphilis tends to progress to a latent stage, but clinical manifestations can recur for up to five years if not treated.¹

The first cutaneous manifestation of secondary syphilis is a macular nonpruritic rash, composed of small and well-defined erythematous and/or hyperpigmented lesions (roseola syphilitica) that spontaneously resolve in 20 to 40 days.⁶ Some time after that, the classic exanthema of secondary syphilis occurs: a diffuse nonpruritic maculopapular rash that frequently involves palms, soles and scrotum. Variants of classic secondary syphilis rash include annular, pustular, nodular, nodulo-ulcerative, berry-like, corymbiform, photosensitive systemic lupus erythematosus-like, lues maligna, leukoderma and chancriform presentations.⁶

The classic maculopapular rash can mimic lichen planus, with violaceous flat-topped papules on the wrists, lower legs and acral sites, as observed in our case.⁷ The



FIGURE 1 Sharply demarcated hyperkeratotic, violaceous, scaly plaques on the hands and feet, including annular and well-circumscribed lesions on the palms and soles.



FIGURE 2 Papule located at the right angle of the upper lip.



FIGURE 3 Regression of lesions one month after treatment.

main difference between these two diseases is that syphilitic lesions are usually nonpruritic and they tend to affect palms and soles.⁵

Our patient also had annular lesions with well-defined scaly borders on the palms and soles, a well-described feature of secondary syphilis;⁶ some of these lesions were thicker than others and also displayed a violaceous hue. This finding should remind dermatologists of a variety of conditions in the differential diagnosis, including lichen planus, subacute lupus erythematosus, sarcoidosis, mycobacterial infection, granuloma annulare, erythema annulare centrifugum and dermatophytosis.⁶

Mucous plaques and split papules at the angle of the lips are other findings of secondary syphilis; the latter was observed in our patient.¹

Secondary syphilis diagnosis in daily practice includes clinical suspicion due to the presence of characteristic skin and mucous lesions and confirmation by serologic tests that measure nontreponemal and treponemal antigens.⁸ Treatment of choice remains benzathine penicillin G, and quantitative titers of VDRL are used to verify treatment success together with the clearance of lesions.⁹ In addition, sexual partners must be examined and tested for syphilis.³

To conclude, physicians must be aware of syphilis: the spectrum of cutaneous manifestations is vast and rates of this infection keep rising worldwide.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Sífilis secundária: a grande imitadora não pode ser esquecida

A sífilis é uma infecção causada pela espiroqueta *Treponema pallidum*, transmitida principalmente por contato sexual. Desde 2001, houve o ressurgimento dessa epidemia, com aumento das taxas de sífilis primária e secundária. Os autores descrevem um caso exuberante de sífilis secundária apresentando lesões cutâneas anulares e lesões que lembram líquen plano, além de uma lesão mucocutânea. Médicos de todas as especialidades devem estar cientes das diversas apresentações de sífilis: o vasto espectro de manifestações cutâneas da sífilis secundária e as crescentes taxas dessa patologia representam um desafio.

Palavras-chave: sífilis cutânea, doenças sexualmente transmissíveis, penicilina G benzatina, *Treponema pallidum*.

REFERENCES

1. Cohen SE, Klausner JD, Engelman J, Philip S. Syphilis in the Modern Era. *Infect Dis Clin North Am*. 2013; 27(4):705-22.
2. Buchacz K, Klausner JD, Kerndt PR, Shouse RL, Onorato I, McElroy PD, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004 to 2005. *J Acquir Immune Defic Syndr*. 2008; 47(2):234-40.
3. Morales-Múnera EC, Fuentes-Finkelstein PA, Vall Mayans M. Update on the diagnosis and treatment of syphilis. *Dermosifiliogr minutes*. 2015; 106:68-9.
4. 2015 STD (Sexually Transmitted Diseases) Treatment Guidelines [Internet]. Available from: <http://www.cdc.gov/std/tg2015/syphilis.htm>.
5. Ivars Lleó M, Clavo Escibano P, Menéndez Prieto B. Manifestaciones cutáneas atípicas en la sífilis. *Actas Dermo-Sifiliográficas*. 2016; 107(4):275-83.
6. Balagula Y, Mattei PL, Wisco OJ, Erdag G, Chien AL. The great imitator revisited: the spectrum of atypical cutaneous manifestations of secondary syphilis. *Int J Dermatol*. 2014; 53(12):1434-41.
7. Nazzaro G, Boneschi V, Coggi A, Gianotti R. Syphilis with a lichen planus-like pattern (hypertrophic syphilis): Letter to the Editor. *J Cutan Pathol*. 2012; 39(8):805-7.
8. Farhi D, Dupin N. Origins of syphilis and management in the immunocompetent patient: facts and controversies. *Clin Dermatol*. 2010; 28(5):533-8.
9. Morales-Múnera CE, Fuentes-Finkelstein PA, Vall Mayans M. Update on the diagnosis and treatment of syphilis. *Actas Dermo-Sifiliográficas*. 2015; 106:68-9.

Gastric cancer with lesion extending to spleen and perforation into free peritoneum

ROBERTO GONÇALVES^{1*}, ROBERTO SAAD JR², CARLOS ALBERTO MALHEIROS², PAULO KASSAB², NATHÁLIA LINS PONTES VIEIRA³

¹MD, MSc. Department of Surgery, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil

²MD, PhD. Department of Surgery, FCMSCSP São Paulo, SP, Brazil

³MD. General Surgery Resident, Department of Surgery, FCMSCSP São Paulo, SP, Brazil

Study conducted at the Department of Surgery, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil

Article received: 11/8/2016

Accepted for publication: 12/4/2016

*Correspondence:

Address: Rua Dr. Cesário Mota Júnior, 61
São Paulo, SP – Brazil
Postal code: 01221-020
rgtorax@yahoo.com.br

<http://dx.doi.org/10.1590/1806-9282.63.06.484>

SUMMARY

Perforated gastric carcinoma is a rare condition that is hard to diagnose preoperatively. It is associated with advanced cancer stages and has a high mortality, particularly in cases presenting preoperative shock. Few studies have investigated the presentation and adequate management of these carcinomas. In addition, there are no reports in the literature on perforations extending to the spleen, as described in this case, making the management of these lesions challenging. Our article reports a case of gastric tumor perforation extending to the spleen, which presented as a perforated acute abdomen. The patient was treated with total gastrectomy and D2 lymph node resection with splenectomy and progressed well with current survival of one year at disease stage IV.

Keywords: acute abdomen, hemoperitoneum, stomach neoplasms.

INTRODUCTION

Perforation of gastric cancer is a rare condition occurring in only 1% of gastric tumors and accounting for 10 to 16% of all perforations to this organ, with a mortality rate of up to 82%. Cancer is generally not suspected in these cases because the majority of patients seeking emergency services have a picture consistent with acute perforated abdomen and diffuse peritoneal irritation. Intraoperative diagnosis remains challenging especially in services without freezing techniques for anatomopathological analysis.¹⁻³

Given the low incidence of cases and consequent scant studies, the optimal surgical treatment in these situations is not yet well defined. Full oncological resection can be hampered by the absence of pre or intraoperative diagnosis of the tumor.

CASE REPORT

A 54-year-old male patient with history of significant weight loss of 10 kg over the past two months presented to emergency services with intense abdominal pain and fainting 1 hour before. Physical examination revealed the patient to be thin, pale (++)/+++ and dehydrated (++)/+++). The abdomen was flat, painful on palpation, tympanic on percussion in the right hypochondrium (Jobert's Sign) and there were signs of peritoneal irritation (abdominal muscular rigidity). This patient was diagnosed with a

suspected acute perforated abdomen, and exploratory laparotomy was indicated.

The intraoperative finding was a tumor of the gastric floor with blockage and perforation of the spleen, and this also perforated the free peritoneum (Figures 1-3). A total gastrectomy including the spleen, large omentum and regional lymph nodes was performed. Reconstruction was achieved by Roux-en-Y jejunoesophageal anastomosis.

The anatomopathological exams revealed a moderately differentiated gastric adenocarcinoma contiguous to the hilar face of the spleen, affecting 7 of the 13 lymph nodes studied. Since no distal metastases were found, the patient was classified as stage IV. He was discharged on day 15 of the hospital stay and has been undergoing outpatient follow-up for one year.

DISCUSSION

Perforation of gastric adenocarcinomas is rare. The patient in this case, akin to the majority of other cases described in the literature, presented at our emergency service with signs of perforated acute abdomen and no prior diagnosis of gastric neoplasia. The most commonly described signs and symptoms include abdominal pain and peritoneal irritation, which was the case of our patient. Recent studies have shown that only 15 to 30% of patients are diagnosed with neoplasia at a preoperative stage.^{1,2} The

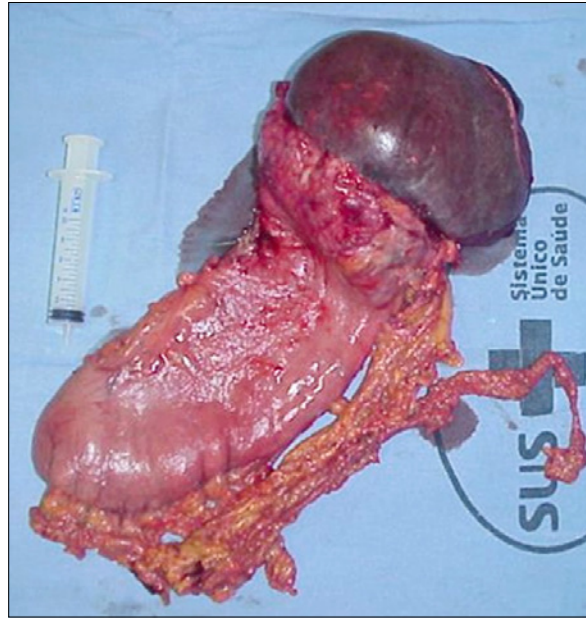


FIGURE 1 Surgical specimen of stomach and spleen, anterior view.

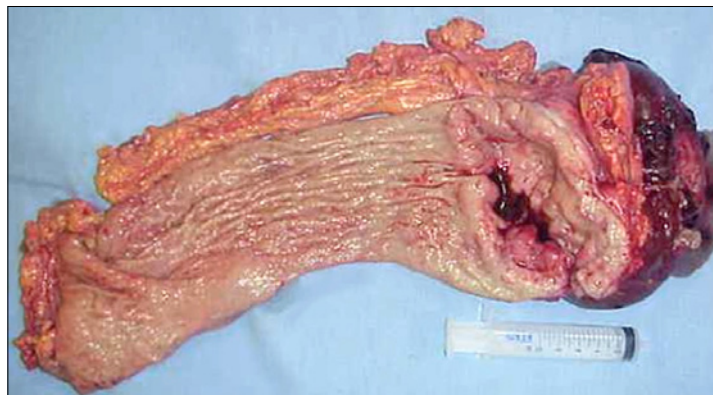


FIGURE 2 Surgical specimen of stomach and spleen, sagittal section.

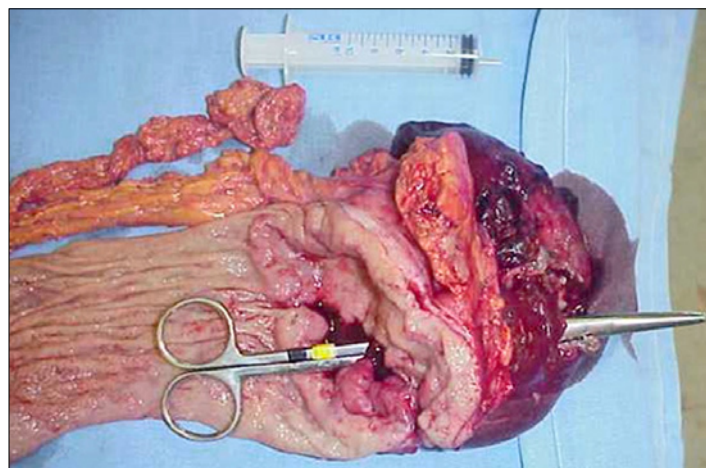


FIGURE 3 Surgical specimen of stomach and spleen, sagittal section showing gastric perforation contiguous to splenic perforation.

only factor indicating suspected cancer is the patient's advanced age, which was not applicable to our case, diagnosed intraoperatively based on presentation suggestive of cancer with perforated lesion.¹

Similarly to most studies in the literature, the reported case presented an advanced tumor with severe invasion and lymph node metastasis.^{1,2} However, there are no previous reports of a gastric perforation by adenocarcinoma progressing with splenic perforation. A literature search of the PubMed and Lilacs databases spanning 20 years with search words, gastric cancer, splenic perforation and perforated gastric cancer, found no case reports similar to that outlined above.

The spleen has a close relation with the stomach. The stomach floor, and the part proximal to its body, interfaces laterally with the spleen, increasing the likelihood of an extended lesion.⁴ However, the site of this patient's lesion, which was the gastric floor, is atypical according to the literature that reports that 50 to 80% of gastric perforations by cancer invade the distal third of the stomach.^{1-3,5}

The optimal management of neoplastic lesions of the stomach complicated by perforation is not yet well-defined. The surgeon must be able to refrain the deleterious effects of the perforation, such as diffuse peritonitis and bleeding, and to provide curative correction or correction with a good prognosis for the patient. Given that the diagnosis of cancer is typically confirmed at the postoperative stage, full neoplastic resection is hampered. Moreover, most of the cases of perforation occur in advanced cancers with peritoneal dissemination.⁵ The most debated issue is whether the surgical treatment should comprise one or two operations, i.e. full resection in a single operation, or correction of the lesion in a first operation followed by oncological resection in a second. The current trend is to surgically manage these cases using two separate operations.^{1,2,5} In the present case, however, the patient underwent radical resection in a single surgical procedure, because neoplasia was suspected intraoperatively.

Another common debate regarding gastric cancers revolves around lymph node resection. Various Western and Japanese studies have sought to compare effectiveness in terms of mortality and morbidity among patients submitted to D1 (neoplastic tumor of up to 3 cm) or D2 (up to 6 cm) lymph node resection, the latter done without splenectomy or pancreatectomy. The result of these studies favors D2 resection, with splenectomy and pancreatectomy elected only in certain cases.⁶⁻⁸ In our patient, in addition to total gastrectomy and D2 lymph node resection, splenectomy was also carried out due to the organ's

perforation. The patient presented N2 staging and the operation seems to have been curative.

The prognosis of patients with gastric tumor perforation depends on several factors but outcomes are poor in most cases. A study reviewing factors that contribute to poor prognosis showed that mortality is linked to advanced cancer stages.⁹ In very advanced cases, however, the only possible approach is that of simple suturing of the perforation, although patients undergoing this procedure have a higher mortality than those submitted to gastrectomy.¹⁰ There is no relation between perforation site and chances of survival. However, the study showed that preoperative shock and time until resolution of perforation were directly linked to mortality.⁹ Patients with advanced cancer are less able to deal with the complications of gastric perforation such as peritonitis and hemorrhage. Despite presenting advanced neoplasia in addition to the association with a splenic lesion, which may have led to bleeding and resultant shock, the patient progressed well, with current survival at one year. According to the literature, the 5-year survival rate is 40% for emergency cases treated with total resection, which was the procedure performed in our patient.²

CONCLUSION

Exclusive perforated gastric carcinoma is *per se* a rare condition, and its association with splenic perforation has not yet been reported in the literature. The stage of the disease, presence of preoperative shock and time to surgical intervention are the main prognostic factors. Association with splenic lesion can aggravate bleeding, leading to shock and a poor outcome. Optimal management of this condition remains unclear and depends on surgeon skill and experience for a successful outcome.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Neoplasia gástrica perfurada com extensão da lesão para o baço

A neoplasia gástrica perfurada é uma condição incomum e de difícil diagnóstico pré-operatório, estando relacionada a estágios avançados e com alta mortalidade, principalmente na presença de choque pré-operatório. Poucos estudos foram feitos quanto a sua forma de apresentação e ao tratamento adequado. Além disso, não há nenhum relato em literatura quanto à extensão da perfuração para

o baço, como é descrito neste caso, tornando mais difícil a conduta. Este artigo relata um caso de perfuração de neoplasia gástrica com extensão para o baço, que se apresentou como abdome agudo perfurativo. Submetido a gastrectomia total e ressecção linfonodal D2 com esplenectomia, apresentou boa evolução e sobrevida atual de 1 ano, em um estadiamento IV da doença.

Palavras-chave: abdome agudo, hemoperitônio, neoplasias gástricas.

REFERENCES

1. Roviello F, Rossi S, Marrelli D, Manzoni G, Pedrazzani C, Morgagni P, et al. Perforated gastric carcinoma: a report of 10 cases and review of the literature. *World J Surg Oncol.* 2006; 4:19.
2. Kotan C, Sumer A, Baser M, Kızıltan R, Carparlar MA. An analysis of 13 patients with perforated gastric carcinoma: A surgeon's nightmare? *World J Emerg Surg.* 2008; 3:17.
3. Ergul E, Gozetlik EO. Emergency spontaneous gastric perforations: ulcer versus cancer. *Langenbecks Arch Surg.* 2009; 394(4):643-6.
4. Soybel DI. Anatomy and physiology of the stomach. *Surg Clin North Am.* 2005; 85(5):875-94.
5. Kasakura Y, Ajani JA, Fujii M, Mochizuki F, Takayama T. Management of perforated gastric carcinoma: a report of 16 cases and review of world literature. *Am Surg.* 2002; 68(5):434-40.
6. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of MRC randomised surgical trial. *Surgical Co-operative Group. Br J Cancer.* 1999; 79(9-10):1522-30.
7. Ilias EJ, Malheiros CA, Kassab P, Castro OAP. Linfadenectomia no adenocarcinoma gástrico. *Rev Assoc Med Bras.* 2006; 52(4):270-4.
8. Toneto MG, Hoffmann A, Conte AF, Schambeck JPL, Ernani V, Souza HP. Linfadenectomia ampliada (D2) no tratamento do carcinoma gástrico: análise das complicações pós-operatórias. *Rev Col Bras Cir.* 2008; 35(4):229-34.
9. Ozmen MM, Zulfikaroglu B, Kece C, Aslar AK, Ozalp N, Koc M. Factors influencing mortality in spontaneous gastric tumour perforations. *J Int Med Res.* 2002; 30(2):180-4.
10. Gertsch P, Yip SKH, Chow LWC, Lauder IJ. Free perforation of gastric carcinoma. Results of surgical treatment. *Arch Surg.* 1995; 130(2):177-81.

Thrombosed aneurysm of saphenous vein coronary artery bypass grafting

RODOLFO MENDES QUEIROZ^{1*}, ROGÉRIO NASTRI FILHO¹, MARCUS ANTÔNIO FERREZ^{1,2}, MAURO JOSÉ BRANDÃO DA COSTA¹,
CLAUDIO BENEDINI LAGUNA¹, MARCUS VINÍCIUS NASCIMENTO VALENTIN¹

¹Radiology and Imaging Diagnosis Department, Documenta – Hospital São Francisco, Ribeirão Preto, SP, Brazil

²Intensive Care Center Department, Hospital São Francisco, Ribeirão Preto, SP, Brazil

Study conducted at Documenta –
Centro Avançado de Diagnóstico
por Imagem, Hospital São Francisco,
Ribeirão Preto, SP, Brazil

Article received: 11/25/2016
Accepted for publication: 12/1/2016

*Correspondence:
Address: Rua Bernardino
de Campos, 980
Ribeirão Preto, SP – Brazil
Postal code: 14015-130
rod_queiroz@hotmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.488>

SUMMARY

We describe the case of a male patient, aged 76 years, referred for cardiac investigation due to retrosternal chest pain and dyspnea. He had a history of acute myocardial infarction and angioplasties in the last 30 years, including a saphenous vein coronary artery bypass grafting (SVCABG). Echocardiogram showed hypoechoic oval formation near the right ventricle, suggesting a pericardial cyst. Computed angiogram revealed a predominantly fusiform and thrombosed aneurysmal dilation of the SVCABG to the right coronary artery. SVCABG aneurysms are very rare and potentially fatal. They usually appear in the late post-operative period, and patients are often asymptomatic. On radiography, it is frequently presented as enlargement of the mediastinum, with echocardiography, computed tomography and magnetic resonance imaging being very useful for diagnosis. Coronary angiography is the gold standard to detect these cases. Our report illustrates a rare situation arising late from a relatively common surgery. Due to its severity, proper recognition in the routine assessment of patients with a similar history is essential.

Keywords: aneurysm, bypass, coronary, saphenous, myocardium.

CASE REPORT

Male patient, 76 years old, underwent complementary investigation through imaging examinations due to complaints of retrosternal chest pain and mild dyspnea several months ago. The patient reported hospitalization and clinical treatment of acute myocardial infarction one month before. The patient had hypertension, dyslipidemia, was a former smoker and had a history of two other acute myocardial infarctions prior to 2010. The patient's history included saphenous vein coronary artery bypass grafting (SVCABG) for about 30 years, two percutaneous transluminal coronary angioplasty procedures, one with stenting to clear the SVCABG, and surgical repair of abdominal aortic aneurysm with endoprosthesis for approximately 4 years. Reports of catheterizations prior to 2015 described new SVCABG occlusion.

A chest radiograph showed only a metallic sternal suture and a small stent near the cardiac silhouette (Figure 1A and B).

The echocardiogram showed a hypoechoic, elongated oval image, adjacent to the right cardiac chambers,

causing a slight extrinsic compression on diastole (Figure 2A and B), apparently without flow according to color Doppler investigation. The diagnostic possibility of pericardial cyst was raised.

Computed tomography of the thorax showed a large, oval and elongated hypoattenuating (approximately 45 HU) mediastinal mass with lobulated contours, located in close contact with the right heart chambers, presenting peripheral parietal calcifications with a maximum caliber of 4.9 cm and measuring approximately 10.0 cm in length (Figure 3A-C), not enhanced after the injection of intravenous contrast medium (Figure 3D-F). The mass could be seen from the emergence of the ascending aorta, with the small stent evident in its interior, extending even to the lower cardiac wall. Such findings were compatible with thrombosed SVCABG aneurysm in the right coronary artery.

Due to the high surgical risk, as well as clinical and electrocardiographic stability of the patient, we opted for conservative management and clinical therapy for general support with periodic follow-up.

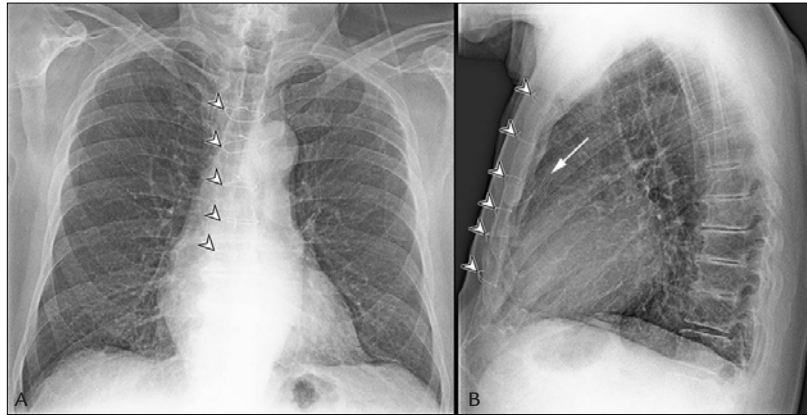


FIGURE 1 Chest X-ray in posteroanterior (A) and profile (B) views, showing mainly the metallic sternotomy (arrow heads) and the small stent along the cardiac silhouette (small arrow).

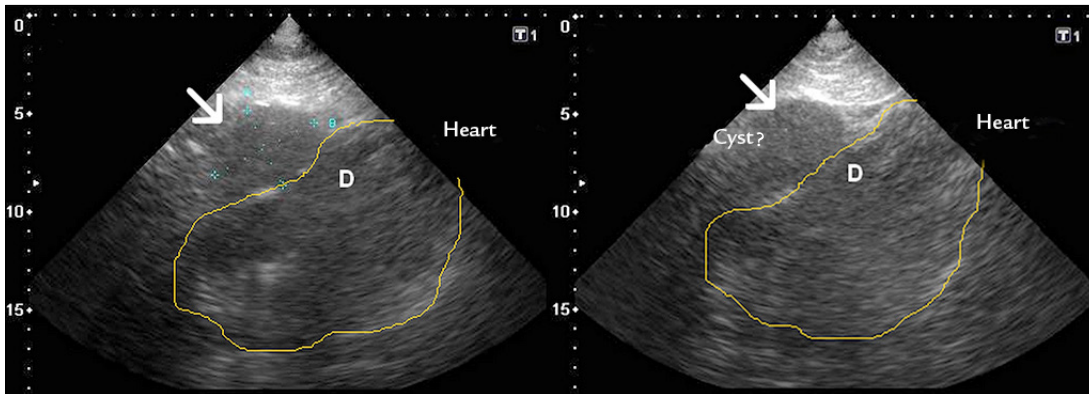


FIGURE 2 A and B. Echocardiogram showing a hypoechoic oval image (thin arrow) adjacent to the right cardiac chambers that causes slight compression in the latter.

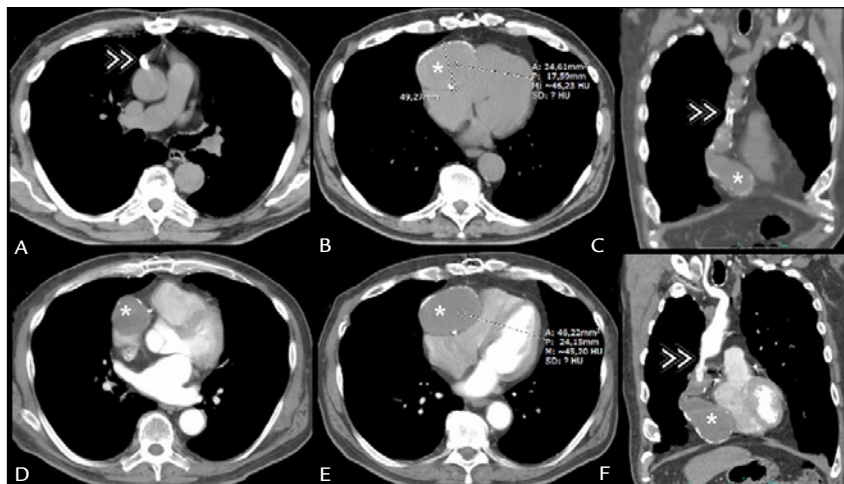


FIGURE 3 Computed tomography of the chest, images acquired before (A, B, C) and after (D, E, F) the administration of intravenous contrast medium, showing aneurysms of aortocoronary saphenous vein bypass grafts to the right coronary artery (*) and the small stent in its implantation surgical ostium (thin double arrowheads). The aneurysm is characterized by a large oval and elongated formation in the middle mediastinum, hypoattenuating, with lobulated contours and in close contact with the right heart chambers. It presents peripheral parietal calcifications, without enhancement after intravenous iodine contrast.

DISCUSSION

Aneurysmal formations, also known as “saphenous bridges,” are rare in SVCABG. These cases should be differentiated from ectasia, which does not exceed 1.5 times the normal vessel size and is observed in about 14% of patients 5-7 years after surgery.¹⁻⁴

They can be divided into pseudoaneurysms and true aneurysms. Pseudoaneurysms do not involve all the usual layers of the vascular wall. They occur earlier and usually close to anastomoses, often related to trauma, surgical technique problems, infections and the preparation of the vein.¹ True aneurysms usually occur later, consisting of true distended walls, often associated with atherosclerosis, hyperlipidemia, endothelium weakness, and smoking.¹ Aneurysms are commonly diagnosed 10 years after revascularization (69%).⁵

The incidence of aneurysmal formations in SVCABG varies between 0.07 and 2%,^{6,7} with the most common being true aneurysms (61-86%).^{3,5,7,8} The two types of aneurysm predominate in men (76-86%) between 50-75 years.^{3,5,7,8} Approximately 45-66% of the patients have symptoms, especially chest pain, angina and dyspnea.⁵

The discovery of aneurysmal formations often occurs incidentally due to mediastinal enlargement identified on chest radiography performed for other reasons.^{4,6,9} The golden standard of diagnosis is coronary angiography,¹ but echocardiography, computed tomography and magnetic resonance imaging can also be used.¹ The latter two evaluate size, permeability and the relationship with neighboring structures.⁹

The most-affected SVCABGs are those directed to the right coronary arteries (38%) and the left anterior descending artery (25%).⁵ They can become quite large,^{4,7} with a mean diameter between 6.0 and 7.0 cm, often with internal thrombi or thrombosed (61%).⁵

Approximately 36% of cases develop with complications such as rupture with consequent hemothorax and hemopericardium,^{1,6,9} thromboembolism, fistulas, acute myocardial infarction, heart failure and compression of adjacent structures,^{1,4,7,9}

Surgical treatment with new revascularization is recommended even in asymptomatic patients, due to the high mortality rate in case of rupture. Conservative therapy such as the use of polytetrafluoroethylene-coated stents, hemodynamic embolization with coils or amplatzer vascular plug is advised in individuals with a very high surgical risk, followed by imaging tests.¹⁻⁹

Our report illustrates a rare situation arising late from a relatively common surgery. Due to its severity, proper recognition in the routine assessment of patients with a similar history is essential.

RESUMO

Aneurisma trombosado de *bypass* aortocoronariano de veia safena

Descrevemos o caso de paciente do sexo masculino, 76 anos, em avaliação cardiológica em razão de dor torácica retroesternal e dispneia. Antecedente de infartos agudos do miocárdio e angioplastias nos últimos 30 anos, incluindo um *bypass* aortocoronário de veia safena (BACVS) ou “ponte de safena”. Em ecocardiograma, observou-se formação ovalada alongada hipocóica junto ao ventrículo direito, podendo sugerir um cisto pericárdico. Angiotomografia computadorizada do tórax evidenciou uma dilatação aneurismática predominantemente fusiforme e trombosada de “ponte de safena” para artéria coronária direita. Aneurismas de BACVS são raríssimos e potencialmente fatais. Geralmente, surgem em um período tardio pós-cirúrgico, sendo seus portadores muitas vezes assintomáticos. Na radiografia, frequentemente se apresentam como alargamento do mediastino, sendo a ecocardiografia, a tomografia computadorizada e a ressonância magnética muito úteis no diagnóstico. A angiografia coronariana é o padrão-ouro na detecção. Este relato ilustra uma situação rara decorrente tardiamente de uma cirurgia relativamente comum, e por causa de sua gravidade torna-se essencial o seu reconhecimento na rotina de avaliação de pacientes com antecedentes semelhantes.

Palavras-chave: aneurisma, *bypass*, coronária, safena, miocárdio.

REFERENCES

1. Albuquerque MG, Farran JA, Pereira CAP, Romano ER, Brotto INM, Romano MLP. Giant aneurysm of saphenous vein bypass for right coronary after angioplasty. *Arq Bras Cardiol.* 2012; 99(2):125-7.
2. Frazier AA, Qureshi F, Read KM, Gilkeson RC, Poston RS, White CS. Coronary artery bypass grafts: assessment with multidetector CT in the early and late postoperative settings. *Radiographics.* 2005; 25(4):881-96.
3. Kalimi R, Palazzo RS, Graver LM. Giant aneurysm of saphenous vein graft to coronary artery compressing the right atrium. *Ann Thorac Surg.* 1999; 68(4):1433-7.
4. Memon AQ, Huang RI, Marcus F, Xavier L, Alpert J. Saphenous vein graft aneurysm: case report and review. *Cardiol Rev.* 2003; 11(1):26-34.

5. Ramirez FD, Hibbert B, Simard T, Pourdjabbar A, Wilson KR, Hibbert R, et al. Natural history and management of aortocoronary saphenous vein graft aneurysms: a systematic review of published cases. *Circulation*. 2012; 126(18):2248-56.
6. Fukui T, Suehiro S, Shibata T, Sasaki Y, Minamimura H, Kinoshita H. Aortocoronary saphenous vein graft aneurysm in redo coronary artery bypass grafting: report of a case. *Surg Today*. 1998; 28(3):321-4.
7. Dieter RS, Patel AK, Yandow D, Pacanowski-Jr JP, Bhattacharya A, Gimelli G, et al. Conservative vs. invasive treatment of aortocoronary saphenous vein graft aneurysms: Treatment algorithm based upon a large series. *Cardiovasc Surg*. 2003; 11(6):507-13.
8. Almanaseer Y, Rosman HS, Kazmouz G, Giraldo AA, Martin J. Severe dilatation of saphenous vein grafts: A late complication of coronary surgery in which the diagnosis is suggested by chest X-ray. *Cardiology*. 2005; 104(3):150-5.
9. Távora FR, Jeudy J, Burke AP. Multiple aneurysms of aortocoronary saphenous vein grafts with fatal rupture. *Arq Bras Cardiol*. 2007; 88(5):107-10.

Evaluation of medical interns' attitudes towards relevant aspects of medical practice

ÁQUILA TALITA LIMA SANTANA ALVES^{1*}, FERNANDO VINICIUS ALVES¹, ENALDO VIEIRA MELO², EDMÉA FONTES DE OLIVA-COSTA²

¹Medical Student, Department of Medicine, Universidade Federal de Sergipe (UFS), Aracaju, SE, Brazil

²PhD, Adjunct Professor, Department of Medicine, UFS, Aracaju, SE, Brazil

SUMMARY

Introduction: In traditional medical school curriculum, sixth-year is the moment in which students experience medical practice more intensively. Attitudes can be considered predictors of behaviors and actions. Evaluating them contributes to improve medical training.

Objective: To evaluate attitudes during medical internship considering medical practice and associated factors in a Brazilian public university.

Method: Cross-sectional study that included 69 students, based on a structured questionnaire and an attitude scale (Colares, 2002). We used descriptive statistics, with classification of the attitude tendency, clusters analysis and F-statistics.

Results: The average age of the participants was 25.1 ± 1.9 , and 56.5% of them were male. Students presented positive attitudes to emotional aspects in organic diseases, primary health care, the medical contribution to the scientific advancement of medicine, and other aspects of medical activity and health politics; there were conflicting attitudes concerning mental illness and negative attitudes concerning death.

Conclusion: Results show the need for interventions in order to reduce the identified conflicting and negative attitudes.

Keywords: medical students, attitude, medical education, doctor-patient relationship.

Study conducted at Universidade Federal de Sergipe, Aracaju, SE, Brazil

Article received: 12/9/2016

Accepted for publication: 12/19/2016

*Correspondence:

Address: Rua José Deodoro Santos, Repleto, bloco Alegria, 406 Aracaju, SE – Brazil
Postal code: 49048-390
aquilalima2@yahoo.com.br

<http://dx.doi.org/10.1590/1806-9282.63.06.492>

INTRODUCTION

Medical education and practice have undergone transformations throughout history. Scientific developments and key therapeutic advances have emerged, but medicine has become fragmented, focusing more on disease than on the patients, affecting the doctor-patient relationship.¹

Traditional medical training focuses on technical performance. The traditional medical curriculum conveys, in its teaching methods, the impression of fragmented learning, knowledge hierarchization and disintegration, and resistance to “de-hospitalization.” In the last decades, the traditional model of medical training has been criticized and the importance of preparing a professional sensitive to human needs has gained space.² Educators recognized the importance of patient-centered training, but the culture of medical education focused primarily on illnesses may represent an obstacle to the development of student attitudes in this regard.³

One of the meanings of the word attitude, according to the monolingual Brazilian Portuguese dictionary by

Aurélio Buarque de Holanda, is “reaction or way of being, in relation to people and objects.”⁴ In general, attitudes are behaviors that determine how individuals position themselves before people and events.⁵

In recent years, the focus has been on developing positive attitudes toward aspects common to all medical students. One of the goals of medical training has been to develop these attitudes. For this, there is a search for measurement instruments and interventionist measures.^{3,5-7} Assessing the attitudes of medical students has been the subject of studies by several authors.⁸⁻¹⁵

Medical undergraduate courses promote experiences that enable the acquisition of attitudes, values and behavior patterns as a consequence of the contact with several players, including instructors/professors, other students, patients and members of the health team.¹⁶ In medical courses that follow a traditional curriculum, internship is the time when students experience medical practice more intensively. In this period, the student ex-

periences the transition from a theoretical basis to active practice, starts discussing cases and treating patients under the guidance of physicians, working on aspects such as the doctor-patient relationship. This is the moment when a professional builds his or her identity, adopting a posture that will reflect their practice. Based on the assumption that attitudes can be considered as predictors of behaviors and actions, evaluating students' attitudes to relevant situations in medical practice contributes to the improvement of the training of future physicians.^{2,5}

Medical training should include technical preparation, ethics, ability to develop an empathic doctor-patient relationship, and social responsibility, that is, biopsychosocial training. Thus, the future medical professional is expected to assume a differentiated posture that, together with his or her knowledge and scientific development, projects positive attitudes towards aspects of medical practice. Thus, our study aims to evaluate students' attitudes during medical internship at a public university in the Northeast of Brazil, facing relevant situations in medical practice, and assessing whether their attitudes differ according to sociodemographic variables, personal aspects and process educational.

METHOD

Study site

The Health Campus of a public university in northeastern Brazil was the site of this study. This medical course is based on the traditional model of medical education, with 12 semesters divided as follows: from the 1st to the 4th semester (Basic Sciences Cycle), from the 5th to the 9th semester (Preclinical Cycle) and from the 10th to the 12th semester (Internship / Clinical Cycle). At the time of data collection, the Internship course had 100 students.

Target population and study population

All 100 internship students were invited to participate, but only 69 accepted.

Study design and data collection

This is an observational cross-sectional analytical study. Data collection was performed on a single occasion in March 2015. Only those who refused to participate in the survey were excluded.

Student privacy was respected during data collection. Secrecy of identity was also guaranteed, so that when the students returned their questionnaires, the free and informed consent form was placed in a separate unidentified envelope, and then inserted in a sealed urn.

Instruments

Two instruments were used for data collection: 1) A structured questionnaire elaborated by the authors on sociodemographic characteristics, personal aspects and educational process; 2) A Medical Students Attitude Scale (validated by Maria de Fátima Colares et al. in the study "Building an Instrument for Assessing the Attitudes of Medical Students to Relevant Aspects of Medical Practice"). This is a Likert-type scale, with a high degree of internal consistency, expressed by a Cronbach's alpha coefficient with a high reliability value ($\alpha=0.86$). The instrument contains 52 items, with five options of answer (1: totally agree; 2: partially agree; 3: not sure; 4: partially disagree; 5: totally disagree). The scale items are divided into favorable and unfavorable statements against the following aspects, which represent the factors of the scale:

- Factor 1. Psychological and emotional aspects in organic and mental diseases. This factor is composed of 11 items and evaluates the importance attributed by the students to the role of the emotional state in the course of the diseases.
- Factor 2. Management of death-related situations. This factor has eight items that aim to show the degree of difficulty of students in situations related to death.
- Factor 3. Primary health care. This factor has 11 items on the importance of the general practitioner, and the practice of preventive medicine by any medical specialist.
- Factor 4. Aspects related to mental illness. This factor is constituted by eight items and analyzes the feelings and difficulties of the student regarding patients with mental disorder.
- Factor 5. Contribution of the doctor to the scientific advancement of medicine. This aims, through six items, to know what students think about the importance of research in their medical careers.
- Factor 6. Other aspects related to medical practice and health policies. Composed of eight items, this factor analyzes the students' attitudes regarding various aspects related to medical practice, and some issues focusing on mental health policies.

Data analysis

For each item on the scale, there were five options for answers and the interns should choose the one that expressed their opinion about each statement. From the completed questionnaires, elaborated so that the answers were already codified, a database was built on a statistical program.

The analysis was performed using descriptive statistics to describe the profile of the population studied and then the responses to the items expressing favorable attitudes were awarded 1 to 5 points for the five options, according to the intensity of agreement expressed by the subjects surveyed. Likewise, responses to items expressing negative attitudes received a score of 1 to 5 points, in reverse, according to the intensity of the discordance contained in the response. Thus, for each student a point score was determined relative to the items of each of the six factors. To categorize the students' attitudinal trend, a mean (M) of the scores was calculated for each factor studied. The results were interpreted as follows:

- $M < 3$: predominantly negative attitudes;
- M between 3 and 3.9: conflicting or indefinite attitudes;
- $M > 4$: predominantly positive attitudes.

Multivariate cluster analysis was used to evaluate the variables with the greatest discrimination capacity among

individuals, making it possible to classify them into three subgroups. F statistic was used to determine the discrimination capacity of the variables.

Ethical considerations

The study was presented to the institution's Ethics Committee on Research in Humans and approved according to CAAE 38995814.1.0000.5546. Participants signed a free and informed consent form. All proposed and approved ethical procedures were rigorously followed by the research team.

RESULTS

Sixty-nine (69) students participated in the study. The distribution of sociodemographic, personal and academic variables is presented in Tables 1 and 2, respectively.

We observed that students had a higher percentage of predominantly positive attitudes in four of the six aspects evaluated, and a higher percentage of predominantly negative attitudes in the case of Factor 2 (Table 3).

TABLE 1 Distribution of medical interns from a public university according to sociodemographic variables, Aracaju (Sergipe, Brazil), 2015.

Variables	N	%	Mean
Total	69	100	
Age (years)			25.1±1.9
Sex			
Female	30	43.5	
Male	39	56.5	
Religion			
Yes	42	60.9	
No	27	39.1	
Marital status			
Single	65	94.2	
Married	3	4.3	
Separated/divorced	1	1.4	
Place of origin			
State capital	48	69.6	
Other locations within the state	11	15.9	
Other states	10	14.5	
Income			
1 to 10 minimum wages	29	42	
11 to 20 minimum wages	29	42	
Over 20 minimum wages	11	15.9	
Lives with			
Relatives	58	84.1	
Friends or classmates	2	2.9	
Alone	9	13	

TABLE 2 Distribution of medical interns from a public university according to personal aspects and academic variables, Aracaju (Sergipe, Brazil), 2015.

Variables	N	%
Total	69	100
Has a doctor in the family		
Yes	36	52.2
No	33	47.8
Previously diagnosed mental disorder		
Yes	5	7.2
No	64	92.8
Use of psychoactive medication		
Yes	10	14.5
No	59	85.5
Experienced severe illnesses		
Yes	35	50.7
No	34	49.3
Satisfaction concerning teaching strategies		
Yes	6	8.7
No	63	91.3
Has emotional support in the context of medical training		
Yes	10	14.5
No	59	85.5
Expectations for the course		
Meets my expectations	33	47.8
Does not meet my expectations	36	52.2
Academic performance		
Satisfactory	48	69.6
Unsatisfactory	21	30.4

TABLE 3 Classification of the attitudes of medical interns from a public university regarding relevant aspects of medical practice, Aracaju (Sergipe, Brazil), 2015.

Factors	N	%
Total	69	100
Factor 1. Emotional aspects in organic diseases		
Predominantly positive	59	85.5
Conflicting	10	14.5
Factor 2. Death-related situations		
Predominantly positive	2	2.9
Conflicting	33	47.8
Predominantly negative	34	49.3
Factor 3. Primary health care		
Predominantly positive	50	72.5
Conflicting	19	27.5
Factor 4. Aspects related to mental illness		
Predominantly positive	11	15.9

(Continues)

TABLE 3 (Cont.) Classification of the attitudes of medical interns from a public university regarding relevant aspects of medical practice, Aracaju (Sergipe, Brazil), 2015.

Factors	N	%
Conflicting	36	52.2
Predominantly negative	22	31.9
Factor 5. Contribution of the doctor to the scientific advancement of medicine		
Predominantly positive	39	56.5
Conflicting	23	33.3
Predominantly negative	7	10.1
Factor 6. Other aspects related to medical practice in the community		
Predominantly positive	50	72.5
Conflicting	17	24.6
Predominantly negative	2	2.9

In the multivariate group analysis, seven variables allowed students to be divided into three subgroups (Table 4).

Group III corresponds to individuals with a lower average age among the three groups, a lower frequency of students who consider their performance unsatisfactory and a higher percentage of individuals with unmet expectations. In addition, it presents the lowest frequency of positive attitudes regarding Factors 5, 4, 3 and 1 (Table 4).

Group II presents the highest mean age, higher frequency of students who consider their performance unsatisfactory and greater frequency of expectations about the course met than group III. There was also a high percentage of positive attitudes for Factors 1 and 3, a low value for Factor 4 and intermediate values for Factors 5 and 6 (Table 4).

Group I presented mean age similar to group III (younger), a high percentage of satisfaction with academic performance, higher expectations regarding the course attended, high percentage of positive attitudes to Factors 1, 3, 5 and 6, and higher frequency of positive attitudes for Factor 4 (Table 4).

DISCUSSION

The population studied has interesting demographic, personal and educational characteristics. Participants included young individuals, most of whom were single, practiced a religion, lived with relatives, had experience with serious illnesses, had medical doctors in their families, had never been diagnosed with a mental disorder by a psychiatrist, were unhappy with the teaching strategies used, believed that they did not receive the emotional support they need, and claimed that the medical course did not meet their expectations. However, they point out that they have a good academic performance. This leads us to assume that having doctors in their families encourages them to continue the course even in situations of dissatisfaction.

Previous research with a similar population has demonstrated a high prevalence of common mental disorder, depressive symptoms and burnout syndrome among medical students. However, in these surveys, participants also said that they had never been diagnosed with any mental disorder by a psychiatrist.^{17,18} This reinforces the need for more research on the mental health of students for early identification of psychopathological symptoms and planning of appropriate preventive measures, thus avoiding the worsening of such symptoms.

An earlier study in the same institution estimating the prevalence of common mental disorders (CMD) among medical students throughout the course demonstrated there was a progressive increase of CMD, from 12.5% among freshmen to 54% during internship. After adjusting for the final logistic regression model, the authors identified that the main associated factors were related to the teaching-learning process and the psycho-emotional aspects.¹⁸ Thus, it is possible that characteristics peculiar to internship, namely growing pressure and concern to prepare students to enter the labor market or a medical residency, not only affect the students' mental health but also possibly compromise their attitudes regarding relevant aspects of medical practice.

Positive attitudes predominated against four of the six aspects evaluated: Factor 1 (psychological and emotional aspects in organic and mental diseases); Factor 3 (primary health care); Factor 5 (contribution of the doctor to the scientific advancement of medicine); and Factor 6 (other aspects related to medical practice and health policies). Studies in other Brazilian public universities show similar results.^{12,13}

This similarity of positive attitudes towards the same aspects in different studies corroborates the importance of evaluating the way students face everyday situations of

TABLE 4 Distribution of medical interns from a public university in the state of Sergipe according to the multivariate cluster analysis, Aracaju (Sergipe, Brazil), 2015.

Variables	Group I N	Group II N	Group III N
Age (years)	24.3±1.0*	27.8±1.0*	23.9±1.9*
Academic performance			
Unsatisfactory	7 (21.9%)	10 (55.6%)	4 (21.1%)
Satisfactory	25 (78.1%)	8 (44.4%)	15 (78.9%)
Expectations for the course			
Meets my expectations	21 (65.6%)	8 (44.4%)	4 (21.15%)
Does not meet my expectations	11 (34.4%)	10 (55.6%)	15 (78.9%)
Factor 1. Emotional aspects in organic diseases			
Positive attitudes	31 (96.9%)	15 (83.3%)	13 (68.4%)
Conflicting attitudes	1 (3.1%)	3 (16.7%)	6 (31.6%)
Factor 3. Primary health care			
Positive attitudes	28 (87.5%)	15 (83.3%)	7 (36.8%)
Conflicting attitudes	4 (12.5%)	3 (16.7%)	12 (63.2%)
Factor 4. Aspects related to mental illness			
Positive attitudes	11 (34.4%)	0	0
Conflicting attitudes	19 (59.4%)	7 (38.9%)	10 (52.6%)
Negative attitudes	2 (6.3%)	11 (61.1%)	9 (47.4%)
Factor 5. Contribution of the doctor to the scientific advancement of medicine			
Positive attitudes	26 (81.3%)	11 (61.1%)	2 (10.5%)
Conflicting attitudes	6 (18.8%)	7 (38.9%)	10 (52.6%)
Negative attitudes	0	0	7 (36.8%)
Factor 6. Other aspects related to medical practice in the community			
Positive attitudes	29 (90.6%)	12 (66.7%)	9 (47.4%)
Conflicting attitudes	3 (9.4%)	6 (33.3%)	8 (42.1%)
Negative attitudes	0	0	2 (10.5%)

*Mean

medical practice and, in addition, elucidates two axes discussed in medical education: vocation and skill acquisition.

Evaluating by the scope of the medical vocation, these positive attitudes are intrinsic to the student, and relate to the personal characteristics of those who choose the medical career.¹⁹ As for skill acquisition, medical courses promote experiences that enable the development of attitudes, values and behavior patterns as a consequence of the contact with several players, namely instructors/professors, other students, patients and members of the health team.¹⁶

It is important to note that the results found in our study were, in part, similar to those obtained in the pioneering study by Troncon et al.³ However, while our study showed a predominance of positive attitudes regarding Factor 5 (contribution of the doctor to the scientific advancement of medicine) and negative attitudes regarding Factor 2 (management of death-related situations), the research carried out by Troncon et al.³ revealed a predominance of conflicting attitudes for these two factors.

This fact deserves more research and reflection, since the study was performed at a major research center in Brazil.

With regard to attitudes towards mental illness (Factor 4), our study showed that the students presented predominantly conflicting attitudes. Considering that studies indicate that 30 to 50% of hospitalized patients present psychiatric symptoms,²⁰ the result of this factor is worrisome, since it analyzes the student's feelings and difficulties in treating patients with mental disorders. We must consider that the emotional aspect is often neglected in medical student training, leading to deficiency in physician rapport with the human being in front of him or her.²¹

The prevalence of negative attitudes towards Factor 2 (management of situations related to death) in our study and in similar works^{12,13} is well explained by the idea that death motivates emotional difficulties among all health-care professionals, and is often perceived as medical failure, generating anxiety in the doctors themselves.²² Moreover, in Brazil, thanatology is not adequately addressed in un-

dergraduate courses, it is up to the students to seek knowledge or deny the difficulty, which leads to failures in communicating bad news to patients and their families.²³

A qualitative study with students of the fourth and sixth year of the Botucatu Medical School – Unesp described that both fourth- and sixth-year students considered death a taboo because it is a subject little discussed in medical training.²⁴ We emphasize that, in addition to scientific technical knowledge, interpersonal skills are important for medical training.

A study carried out in a Brazilian university hospital aimed to determine the profile of students, physicians and medical instructors/professors before death and terminally ill patients. The authors observed that the vast majority of respondents were interested in the subject, but had difficulties approaching it.²⁵ Another study using the Attitude Scale⁵ showed that second- and sixth-year medical students had a predominantly negative attitude in death-related situations.¹³ These data indicate that physicians must have great emotional balance to deal with such demands and suffer less from each death they witness. The importance of preparing the future doctor in this respect cannot be underestimated.

As for the contribution of the doctor to the scientific advancement of medicine (Factor 5), students demonstrated predominantly positive attitudes, meaning they consider scientific research as part of the medical career and think the physician's work contributes to the advancement of medicine. This may be a consequence of the opportunities in scientific initiation projects offered by the country's public institutions. There are authors who have demonstrated the growing interest of medical students in participating in this type of project during their undergraduate course.^{26,27}

Our study has limitations that should be considered in the analysis. The number of students enrolled in the internship at the time of data collection was reduced due to a delay in the semester caused by a strike. In addition, it is possible that the few students who refused to participate were precisely those who were more committed to their attitudes, which could worsen the results. Besides, we can not attribute causality to the associations found, since our study is transversal and, thus, outcome and exposure are analyzed simultaneously. In spite of this, the findings of our study are useful to promote a deeper contemplation about the teaching-learning process in medicine and to subsidize preventive strategies to the psychological suffering of the student, also contributing to the planning of the pedagogical model of the course with a view to changing the conflicting attitudes and negative

aspects of students in relation to relevant aspects of medical practice. We thus believe that more studies on the subject are necessary, especially with longitudinal and qualitative design, which will contribute to verify the consistency of the results obtained in our study.

CONCLUSION

In this sample of interns, the results showed predominantly positive attitudes towards some relevant aspects of the medical practice, indicating that the medical training is in line with the educational objectives. However, in relation to other aspects, such as those related to mental illness and death, the attitudes were respectively conflicting and negative, evidencing the need for specific educational interventions. Cluster analysis allowed us to infer that attitudes differ according to academic variables.

RESUMO

Avaliação de atitudes de internos de medicina frente a aspectos relevantes da prática médica

Introdução: No curso de medicina com currículo tradicional, o internato é o momento em que o estudante vivencia as experiências da prática médica de forma mais intensa. Atitudes podem ser consideradas preditoras de comportamentos e ações, e avaliá-las contribui para aperfeiçoar a formação desses futuros médicos.

Objetivo: Avaliar atitudes dos internos de medicina frente à prática médica e a fatores associados em uma universidade pública brasileira.

Método: Estudo transversal com 69 alunos, por meio de questionário estruturado e da Escala de Atitude (Colares, 2002). Foram realizados estatística descritiva, categorização da tendência atitudinal, análise de agrupamentos (*clusters*) e estatística F.

Resultados: Média de idade foi 25,1±1,9 anos e 56,5% eram do sexo masculino. Os estudantes apresentaram atitudes positivas frente aos aspectos emocionais nas doenças orgânicas, atenção primária à saúde, contribuição do médico ao avanço científico da medicina e outros aspectos relacionados à atuação médica e às políticas de saúde, e apresentaram atitudes conflitantes frente à doença mental e negativas frente à morte.

Conclusão: Os resultados mostram a necessidade de intervenções que visem a reduzir as atitudes conflitantes e negativas identificadas.

Palavras-chave: estudantes de medicina, atitude, formação médica, relação médico-paciente.

REFERENCES

- Miranda SM. A educação médica: uma análise da relação da sessão tutorial e o desenvolvimento de atitudes, voltada a uma avaliação global na formação do médico na Universidade do extremo sul catarinense - Santa Catarina [monografia]. Criciúma: Universidade do Extremo Sul Catarinense; 2003.
- Perez E. A propósito da educação médica. *Rev Bras Saúde Matern Infant*. 2004; 4(1):9-13.
- Troncon LEA, Colares MFA, Figueiredo JFC, Cianflone ARL, Rodrigues MLV, Piccinato CE, et al. Atitudes de graduandos em Medicina em relação a aspectos relevantes da prática médica. *Rev Bras Educ Med*. 2003; 27(1):20-7.
- Holanda AB. Aurélio: o mini dicionário da língua portuguesa. 4. ed. Rio de Janeiro: Nova Fronteira; 2002.
- Colares MFA, Troncon LEA, Figueiredo JFC, Cianflone ARL, Rodrigues MLV, Piccinato CE, et al. Construção de um instrumento para avaliação das atitudes de estudantes de Medicina frente a aspectos relevantes da prática médica. *Rev Bras Educ Med*. 2002; 26(3):194-203.
- Goldie J, Schwartz L, McConnachie A, Morrison J. Students' attitudes and potential behaviour with regard to whistle blowing as they pass through a modern medical curriculum. *Med Educ*. 2003; 37(4):368-75.
- Masson N, Lester H. The attitudes of medical students towards homeless people: does medical school make a difference? *Med Educ*. 2003; 37(10):869-72.
- Todres M, Tsimtsiou Z, Sidhu K, Stephenson A, Jones R. Medical students' perceptions of the factors influencing their academic performance: an exploratory interview study with high-achieving and re-sitting medical students. *Med Teach*. 2012; 34(5):e325-31.
- Tsimtsiou Z, Kerasidou O, Efsthathiou N, Papaharitou S, Hatzimouratidis K, Hatzichristou D. Medical students' attitudes toward patient-centred care: a longitudinal survey. *Med Educ*. 2007; 41(2):146-53.
- Peixoto JM, Ribeiro MMF, Amaral CFS. Atitude do estudante de Medicina a respeito da relação médico-paciente x modelo pedagógico. *Rev Bras Educ Med*. 2011; 35(2):229-36.
- Miranda SM, Pires MMDS, Nassar SM, Silva CAJD. Construção de uma escala para avaliar atitudes de estudantes de Medicina. *Rev Bras Educ Med*. 2009; 33(1):104-10.
- Andrade SC, Deus JAD, Barbosa ECH, Trindade EMV. Avaliação do desenvolvimento de atitudes humanísticas na graduação médica. *Rev Bras Educ Med*. 2011; 35(4):517-25.
- Mascia ARSFB, Lucchese AC, Marco MAD, Martins MCFN, Martins LAN. Atitudes frente a aspectos relevantes da prática médica: estudo transversal randomizado com alunos de segundo e sexto anos. *Rev Bras Educ Med*. 2009; 33(1):40-8.
- Parlow J, Rothman A. Attitudes towards social issues in medicine of five health science faculties. *Soc Sci Med*. 1974; 8(6):351-8.
- Goldie J, Schwartz L, Morrison J. Students' attitudes and potential behaviour to a competent patient's request for withdrawal of treatment as they pass through a modern medical curriculum. *J Med Ethics*. 2004; 30(4):371-6.
- Ferreira RA, Peret Filho LA, Goulart EM, Valadao MM. [Undergraduate students of "Universidade Federal de Minas Gerais": profile and trends]. *Rev Assoc Med Bras*. 2000; 46(3):224-31.
- Costa EF, Santana YS, Santos AT, Martins LA, Melo EV, Andrade TM. [Depressive symptoms among medical intern students in a Brazilian public university]. *Rev Assoc Med Bras*. 2012; 58(1):53-9.
- Costa EF, Andrade TM, Silvany Neto AM, Melo EV, Rosa AC, Alencar MA, et al. Common mental disorders among medical students at Universidade Federal de Sergipe: a cross-sectional study. *Rev Bras Psiquiatr*. 2010; 32(1):11-9.
- Millan L. Vocaç o m dica, uma opç o precoce. *Revista Ser M dico*. 2006; 36. Available from: <http://www.cremesp.org.br/?siteAcao=Revista&id=258>.
- Gullich I, Ramos AB, Zan TR , Scherer C, Mendoza-Sassi RA. [Prevalence of anxiety in patients admitted to a university hospital in southern Brazil and associated factors]. *Rev Bras Epidemiol*. 2013; 16(3):644-57.
- Dal B  MJ, Silva GS, Machado DFGP, Silva RM. Prevalence of depressive symptoms in patients admitted to clinical sector in a general hospital in the South of Santa Catarina. *Rev Bras Clin Med*. 2013; 9(4):264-8.
- Santos MA, Aoki FCOS, Oliveira-Cardoso EA. The significance of death for doctors faced with end-of-life care of patients undergoing bone marrow transplants. *Ci nc Sa de Coletiva*. 2013; 18(9):2625-34.
- Albertoni LI, Santos RD, Cury PM, Pereira PSF, Miyazaki MCOS. [Qualitative analysis of the impact of death on medical students of the S o Jos  de Rio Preto medical school]. *Arq Ci nc Sa de*. 2013; 20(2):49-52.
- Duarte AC, Almeida DV, Popim RC. Death within the medical undergraduate routine: students' views. *Interface (Botucatu)*. 2015; 19(55):1207-19.
- Vianna A, Piccelli H. O estudante, o m dico e o professor de medicina perante a morte e o paciente terminal. *Rev Ass Med Bras*. 1998; 44(1):21-7.
- Massi L, Queiroz SL. Estudos sobre in ciaç o cient fica no Brasil: uma revis o. *Cadernos de Pesquisa*. 2010; 40(139):173-97.
- Massi L, Queiroz SL. Pesquisas sobre In ciaç o Cient fica no Brasil: caracter sticas do seu desenvolvimento nas universidades e contribuiç es para os graduandos. *Revista Brasileira de In ciaç o Cient fica*. 2014; 1(1):38-64.

Concomitant testicular infection by Zika virus and *Schistosoma mansoni* in a Brazilian young boy

LEONARDO SOUZA ALVES^{1*}, CESAR ESTANISLAU², LUCIO BARRETO³, FRANCISCO BATISTA³, NIVALDO TOPPA⁴

¹MD, Urologist. Sociedade Brasileira de Urologia. American Urologic Association. Procriar - Instituto de Urologia e Andrologia, Belo Horizonte, MG, Brazil

²Biologist. Department of Biologic Sciences, Faculdade Newton de Paiva, Belo Horizonte, MG, Brazil

³MD, Faculdade Ciências Médicas de Minas Gerais (FCM-MG), Belo Horizonte, MG, Brazil

⁴Pathologist. Ex-Professor of Pathology, UFMG, Belo Horizonte, MG, Brazil

SUMMARY

The identification of a escrotal mass without pain or report of trauma should be investigated to rule out scrotal cancer. We report the case of a young Brazilian boy who underwent orchiectomy after magnetic resonance imaging (MRI) and duplex scan (DS) indicating a high possibility of cancer. Blood exams ruled out the possibility of cancer. Testicular biopsy was not indicated. After surgery the diagnostic was extensive orchiepididymitis by *Schistosoma*. In endemic areas orchiepididymis by *Schistosoma* should be investigate to avoid unnecessary surgeries. This patient was also infected with Zika virus.

Keywords: Zika virus, *Schistosoma mansoni*, testicle, orchiepididymitis.

Study conducted by Procriar –
Instituto de Urologia e Andrologia,
Belo Horizonte, MG, Brazil

Article received: 10/29//2016

Accepted for publication: 11/20/2016

*Correspondence:

Address: Rua da Bahia, 2.696, sala 1.303
Belo Horizonte, MG – Brazil
Postal code: 30120-016
procriar@gmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.500>

CASE

We report the case of a young Brazilian boy, who was referred with inflammation of the right testicle and epididymis. The patient presented with volumetric expansion but no pain, without any apparent cause. Scrotal trauma or unprotected sexual activity were not reported. The preliminary scans, magnetic resonance imaging (MRI) and duplex scan determinated a possible testicular cancer. Analysis of spermogram showed the presence of immobile and dead sperm. The analysis of sperm culture showed no infection. Laboratory exams included: Alpha-fetoprotein (AFP) blood test, lactate dehydrogenase (LDH) and beta-human chorionic gonadotropin (hCG), all normal. The patient was prescribed the use of antibiotic and anti-inflammatory medication for 10 days, but no reduction in testicular mass size was observed. After talking to the patient about the diagnostic difficulties, we opted for orchiectomy.

Preoperative tests were all normal. The surgery was uneventful, and the patient was discharged on the same day. The examination of the surgical piece demonstrated extensive right testicular and epididymal fibrosis. The microscopic examination of the testis ruled out the possibility of cancer, but confirmed the diagnosis of extensive loss of testicular structure and schistosome egg-induced granulomas (Figure 1). After surgery, the patient's relatives reported that he had had contact with stagnant water

approximately 60 days before the symptoms started. According to the family, the boy was admitted to the hospital with flu-like symptoms, low fever and rashes on chest and lower limbs. At the time of hospitalization, infection with Dengue virus was suspected. Symptomatic treatment was initiated with analgesics. The patient was hospitalized for 48 hours and then discharged. The blood test (RT-PCR) performed at the time of admission confirmed later that the etiology was a Zika virus infection. The patient was discharged with instructions for frequent hydration and no more. After surgery, the patient received oral treatment with oxamniquine to treat infection with *Schistosoma*, being instructed to only have sexual intercourse with the use of condoms for a period of 6 months.

ZIKA VIRUS

Zika virus (ZIKV) is an RNA virus of the Flaviviridae family, related to the Dengue and Yellow fever viruses. It causes Zika fever, a disease with symptoms similar to Dengue fever and Chikungunya, but more lenient (Figure 2).

The virus was first identified in 1947, in Uganda, in a rhesus monkey that was infected with yellow fever virus. The virus was unknown in humans up to that time, and the first report of it infecting humans was in 1954 in Nigeria. The dissemination occurred in countries of Africa and Asia. ZIKV probable transmission route involved the

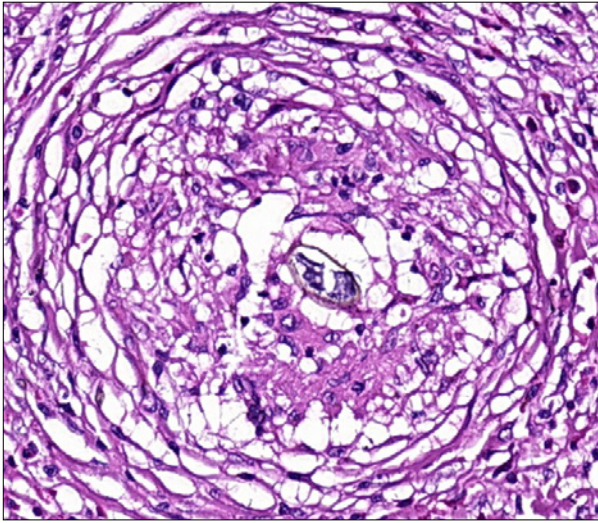


FIGURE 1 Granuloma in fibrosis phase with a viable *S. mansoni* egg in the middle. (Photo by Nivaldo H. Toppa).

2014 FIFA World Cup, also being carried by immigrants from Africa.^{2,3,8,11} Symptoms include: mild fever, pruritus and cutaneous rash, fatigue, myalgia, dehydration, diarrhea, photophobia, dizziness and loss of appetite. These symptoms may remain for 7 to 30 days. Unlike the Dengue virus, the Zika does not usually cause blood dyscrasia.⁵⁻⁸ ZIKV is transmitted through the bite of an infected *Aedes aegypti* mosquito, which is also a vector of Dengue virus and is endemic to the regions affected.^{2-8,19} Transmission through saliva and/or semen is still controversial, although the presence of live ZIKV has been detected in these secretions.⁶⁻⁸ The virus has also been detected in urine. The diagnosis of the virus is usually done clinically. Blood tests are not always available, are costly and take 2 to 7 days to confirm the diagnosis. Enzyme-linked immunosorbent assay (ELISA)-based serological tests can be used for the diagnosis of ZIKV. The test detects the presence of antibodies against ZIKV and, therefore, at the beginning of the symptoms, the test is negative. It should be requested five days after the first signs appear. Real time polymerase chain reaction (RT-PCR) is a method of DNA and RNA amplification that does not use living organisms and can detect ZIKV as symptoms occur.^{6,9-11} ZIKV can be detected in samples of semen or saliva using PCR, but these virus identification kits are not widely available in all countries. The clinical picture triggered by ZIKV resembles a flu-like condition, but chronic complications are more important. Guillain-Barré syndrome (GBS) is a neurological complication that can be fatal, with progressive paralysis of the muscles of the body. In microcephaly, which is brain malformation due to infec-

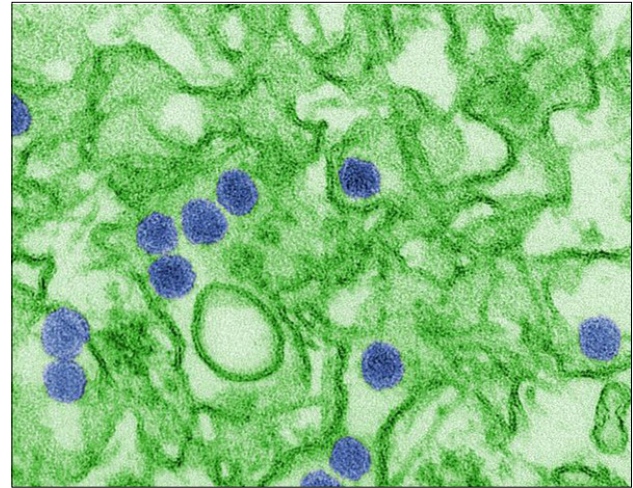


FIGURE 2 Electron micrograph transmission image digitally colored shows Zika virus in blue. (Photo by CDC/Cynthia Goldsmith). 218 x 164 mm (72 x 72 DPI)

tion with the virus, the cephalic perimeter is smaller than usual, leading to permanent neurologic loss. It occurs in fetuses of mothers who were infected with ZIKV.² Treatment is usually supportive and depends on the severity of symptoms. The patient usually remains in the hospital for 24-48 hours, under observation with analgesic and antipyretic drugs only. Despite the production of antibodies against ZIKV and Dengue virus, it is not known whether this is lasting immunity or not.^{9-11,19} In cases like GBS or microcephaly, the patients will need hospitalization and continuous care.

SCHISTOSOMA

Schistosomes are trematode parasites approximately 1 cm (male) to 1.5 cm (female) long. Schistosome infection is frequent in developing countries with low socioeconomic conditions. Schistosomes are found as three different species, and are considered endemic in Central and South America (*S. mansoni*), and in the Middle East and Asia (*S. haematobium* and *S. japonicum*). In the Americas, the disease is known as water belly or snail fever. The parasite is found in *B. glabrata* snails, the intermediate host, in freshwater ecosystems.^{1,13-15,17}

In the reproductive cycle, the parasite infects the snail, where self-reproduction takes place. The eggs are then discarded in standing water. At that point, the parasite is eliminated (cercaria stage) in water, where its definitive host (human) is infected. Once in the human body, *S. mansoni* has tropism for mesenteric plexus, veins in the pelvic region. In these areas, the parasite reproduces once again and the eggs reach the entire body through veins

and lymphatic vessels, especially the liver and the spleen (Figure 3). There are reports of eggs found in the kidneys, bladder, prostate, epididymis and testes, which are usually discovered *post mortem*.¹⁵ The infectious process that follows is due to the intense immune reaction against the eggs of *Schistosoma*. The typical lesion is that of granulomas with spiculated egg in a central position (Figure 1).

The granuloma involves the *Schistosoma* with mast cells, macrophages, multi-nucleated giant cells (Langhans' cells), eosinophils, lymphocytes and fibroblasts. In the process, there is extensive inflammation and fibrosis, egg deposition, and destruction of organ architecture.^{17,18}

DISCUSSION

This is the case of a Brazilian boy, living in an urban area, which starts with a history of testicular increase, with no

apparent cause. The initial clinical report, laboratory tests and imaging methods led to a diagnosis of malignant testicular injury. In cases of testicular lesions with suspicion of testicular cancer, testicular biopsy should not be done, as it can promote the spread of malignant cells and loss of surgical healing potential. In this context, the difficulties related to diagnosis and treatment were properly explained to the patient. After the postoperative diagnosis of schistosomal orchitis, and in the absence of malignant tumor of the testicle, it became clear that the collection of clinical data was incomplete. Contact with still waters and whether it was infested with the intermediate host *S. mansoni* was not investigated. Contact with stagnant water 60 days before the onset of symptoms was later confirmed by the patient. We did not inquire about hospitalization for treatment of ZIKV infection, despite the existence of a positive RT-PCR.

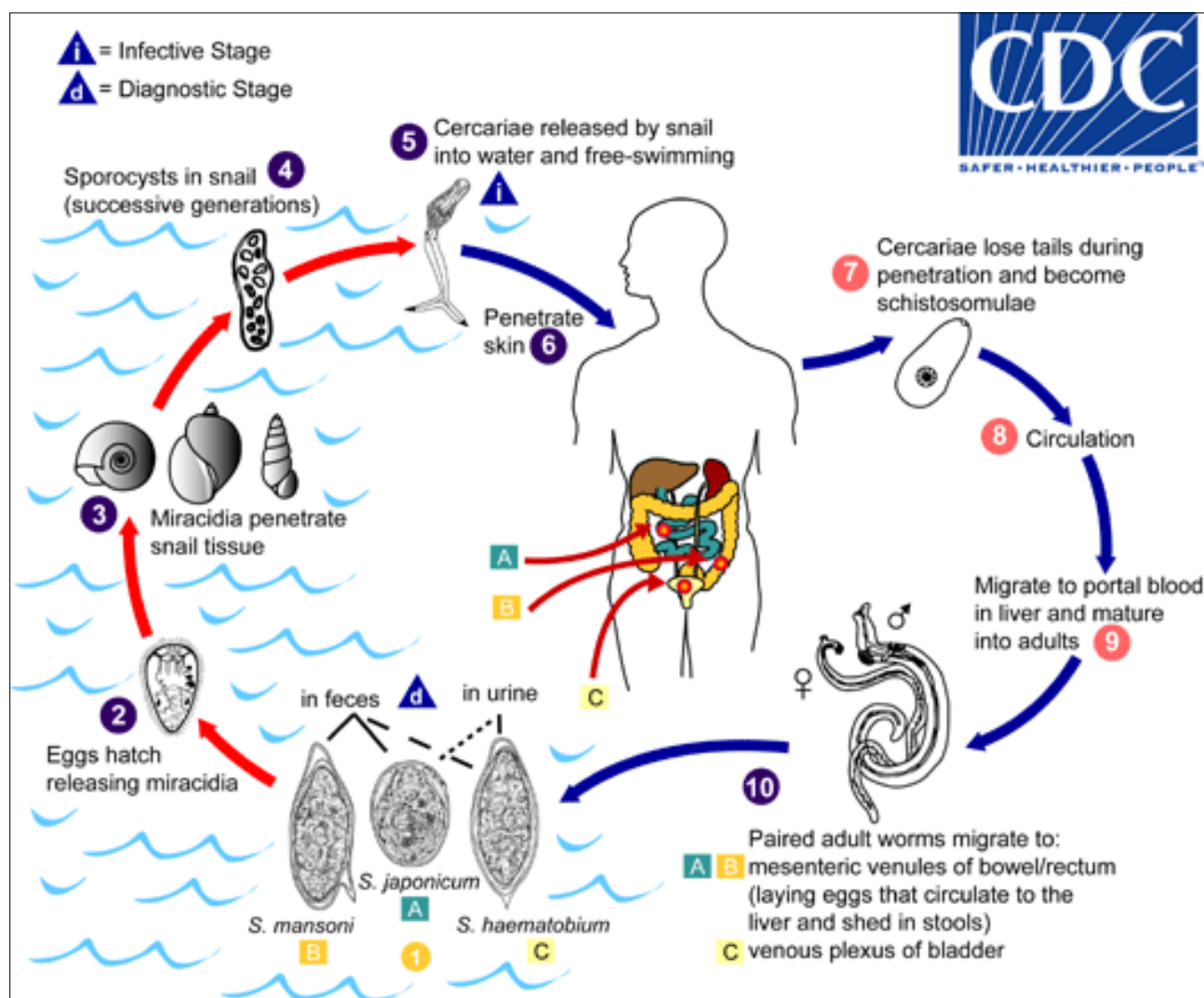


FIGURE 3 Lifecycle of *Schistosoma*. (From <https://www.cdc.gov/parasites/schistosomiasis/biology.html>)

We cannot say if the first infection was that of *Schistosoma* or Zika. However, literature shows that ZIKV can remain viable in the testicle due to the natural barrier that prevents the formation of testicular antibodies for up to 6 months.¹⁴⁻¹⁹ Schistosome can remain alive in a definitive host for up to 20 years.¹⁸ However, with *Schistosoma* infection and the intense inflammation with granuloma formed around the eggs, this protective barrier to ZIKV was lost, which leads us to believe that the virus was “attacked” by the host’s natural defense cells. Unfortunately, we were not able to identify the presence of the virus in the surgical piece due to lack of resources at that time. The literature reports the identification of ZIKV in secretions such as saliva, semen and urine.^{3-5,7,8,10,19} Test kits for these diagnoses are not always available, but lack of identification does not mean necessarily that the microorganism is not present. Examinations can yield false positives due to a window period.^{10-12,19} The patient was told to use condoms for a period of 6 months, in accordance with the guidelines of health agencies such as the CDC, WHO and Anvisa.^{3,6,8,10,11,19}

CONCLUSION

Concurrent infection with the two agents may or may not have been a coincidence. We emphasize that all inhabitants of risky areas, as well as people traveling to these places, can be infected with ZIKV and *Schistosoma*. As the risky areas are endemic for the vectors *Aedes aegypti* (ZIKV) and *Biomphalaria glabrata* (*Schistosoma*), the risk of contracting the two diseases concomitantly is reasonable. The potential complications of two concomitant parasitic infections should determine the efforts to be made by all in order to decrease the prevalence of these diseases. Ultimately, it all comes down to education, basic sanitation and personal hygiene.

RESUMO

Infecção testicular associada com Zika vírus e *Schistosoma mansoni* em jovem brasileiro

A identificação de massa escrotal sem relato de dor ou trauma deve ser investigada a fim de afastar a possibilidade de câncer escrotal. O artigo reporta o caso de um jovem brasileiro que apresentou massa escrotal com essas características. Ressonância nuclear magnética (RNM) e ultrassonografia (US) indicaram grande possibilidade de câncer. Os marcadores tumorais sanguíneos estavam normais, e a biópsia não poderia ser realizada. O resultado anatomopatológico diagnosticou extensa fibrose esquistossomótica, associada a quadro clínico e sorológico

de Zika vírus concomitantemente. Em regiões endêmicas, pacientes com alterações escrotais devem ser pesquisados a fim de evitar cirurgias desnecessárias.

Palavras-chave: vírus Zika, *Schistosoma mansoni*, testículo, orquiepididimitis.

ACKNOWLEDGMENTS

We thank Cynthia Goldsmith, CDC/USA, for the ZIKV microphotography. Also, the US CDC for allowing the use of ZIKV and Schistosome lifecycle figures, and F.G., the patient, who allowed us to write this manuscript.

REFERENCES

- Nussenzweig RS. Parasitic disease as a cause of immunosuppression. *New Engl J Med*. 1982; 306(7):423-4.
- Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barré syndrome—case report, French Polynesia, December 2013. *Euro Surveill*. 2014; 19(9):pii:20720.
- Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis*. 2015; 21(2):359-61.
- Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. *Emerg Infect Dis*. 2015; 21(1):84-6.
- Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol*. 2016; 47(1):6-7.
- Oster AM, Brooks JT, Stryker JE, Kachur RE, Mead P, Pesik NT, et al. Interim guidelines for prevention of sexual transmission of Zika virus - United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2016; 65(5):120-1.
- Musso D, Roche C, Nhan TX, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva. *J Clin Virol*. 2015; 68:53-5.
- Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika virus in semen. *Emerg Infect Dis*. 2016; 22(5):940.
- Hamel R, Dejarnac O, Wichit S, Ekcharyawat P, Neyret A, Luplertlop N, et al. Biology of Zika virus infection in human skin cells. *J Virol*. 2015; 89(17):8880-96.
- Mansuy JM, Dutertre M, Mengelle C, Fourcade C, Marchou B, Delobel P, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? *Lancet Infect Dis*. 2016; 16(4):405.
- Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission—continental United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2016; 65(8):215-6.
- Oster AM, Russell K, Stryker JE, Friedman A, Kachur RE, Petersen EE, et al. Update: Interim guidelines for prevention of sexual transmission of Zika virus—United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2016; 65(12):323-5.
- Katz N, Almeida, K. Esquistossomose, xistosa, barriga d'água. *Ciência Cultura*. 2006; 55(1):38-43.
- De Silva S, Walsh J, Rowan M. Symptomatic *Schistosoma mansoni* infection as an immune restoration phenomenon in a patient receiving antiretroviral therapy. *Clin Infect Dis*. 2006; 42(2):303-4.
- Arban V. Lesions caused by *Schistosoma mansoni* in the genitourinary tract of men. *Am J Clin Pathol*. 1956; 26(9):1010-21.
- Rambau PF, Chandika A, Chalya PL, Jackson K. Scrotal swelling and testicular atrophy due to schistosomiasis in a 9-year-old boy: a case report. *Case Rep Infect Dis*. 2011; 2011:787961.
- Francolugo-Vélez VA, Zarzosa-Alguiar J. Infección del tracto urinario por *Schistosoma haematobium*. Un caso en Cuernavaca, Morelos. México. *Rev Mex Urol*. 2010; 70(3):187-92.
- Iglesias JD. Aspectos médicos das parasitoses humanas. São Paulo: Guanabara Koogan; 1997. p. 186-210.
- Lyle RD, Peterson LR, Jamerson DJ, Powers AM, Honein MA. Zika virus. *N Engl J Med*. 2016; 374(16):1552-63.

Factors associated with burnout syndrome in medical residents of a university hospital

PEDRO ALVES DA CRUZ GOUVEIA^{1*}, MARIA HOSANA CHAVES RIBEIRO NETA¹, CARLOS ALBERTO DE MOURA ASCHOFF², DORIS PIRES GOMES², NADINE ANITA FONSECA DA SILVA², HELTON ALEXSANDRO FIRMINO CAVALCANTI³

¹Internal Medicine Service, Hospital das Clínicas, Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil

²Medicine Course, Health Sciences Center, UFPE, Recife, PE, Brazil

³Psychiatry Division, Universidade de Pernambuco (UPE), Recife, PE, Brazil

SUMMARY

Objective: To determine the prevalence of burnout syndrome among resident physicians of various specialties and to evaluate associated factors.

Method: The Maslach Burnout Inventory questionnaire and a sociodemographic questionnaire were used to evaluate factors associated with the syndrome. Burnout was defined as the association of high emotional exhaustion, depersonalization and low professional achievement. Multivariate analysis was performed after adjustment of the Poisson model with the identification of risk factors and calculation of prevalence ratios (PR). Of the 250 resident physicians registered with Hospital das Clínicas of Pernambuco, 129 participated in the study.

Results: In the three domains that characterize burnout syndrome, we found a low level of professional achievement in 94.6% of resident physicians interviewed, a high level of depersonalization in 31.8%, and 59.7% with a high level of emotional exhaustion. The prevalence of burnout was 27.9%. Having suffered a stressful event in the last six months (PR: 8.10; 95CI 1.2-57.2) and being a student of surgical specialty (PR: 1.99; 95CI 1.2-3.3) were independently associated with burnout.

Conclusion: The prevalence of burnout found in resident physicians is in accordance with previous Brazilian studies. Residents of surgical specialties and those who suffered some stressful event were identified as susceptible in this study. The early identification of risk factors is fundamental for the implementation of preventive measures against burnout syndrome.

Keywords: burnout, medical residency, medical education.

Study performed at Hospital das Clínicas of Universidade Federal de Pernambuco (HC-UFPE), Recife, PE, Brazil

Article received: 10/22/2016

Accepted for publication: 11/20/2016

*Correspondence:

Address: Av. Prof. Moraes Rego, 1.235, Cidade Universitária Recife, PE – Brazil
Postal code: 50670-901
pedroalves@doctor.com

<http://dx.doi.org/10.1590/1806-9282.63.06.504>

INTRODUCTION

The term burnout was coined by psychologist Herbert Freudenberger in 1974 in an article entitled “Staff Burnout,” in which he discusses job dissatisfaction caused by professional stress.¹ Although there is no standard definition for burnout, it is described as a state of physical and mental exhaustion from work when coping methods are insufficient.² Burnout syndrome is defined as a triad composed of three domains: emotional exhaustion, depersonalization and decline in professional achievement.³

Emotional exhaustion reflects the stress dimension of burnout and encompasses feelings of hopelessness, loneliness, depression, anger, impatience, irritability, ten-

sion, decreased empathy, a sense of lack of energy, and worry. Depersonalization is an attempt that a person makes to put distance between themselves and the recipients of the service, actively ignoring the qualities that make them unique individuals, motivating a sense of alienation and indifference towards others. This makes working with other people often unpleasant and unwanted. Low professional achievement or low job satisfaction, in turn, can be described as a feeling that very little has been achieved and what is accomplished is worthless.^{2,4}

The consequences of burnout syndrome on health include: gastrointestinal disorders, prolonged flu symptoms, shortness of breath, hypertension, headache, insomnia,

myalgia, pruritus, allergies, hair loss, sexual dysfunction, demotivation, difficulty concentrating and more.⁵ Also, there is a correlation between burnout and suicidal thinking.⁶ Therefore, this is a public health problem with disastrous consequences that must be prevented in the workplace.

Stressors that are associated with or may increase the possibility of burnout among physicians include: excessive demands that reduce the quality of care, long working hours, numerous work shifts, the need to deal with suffering and death, and more.⁷ In medical training, residency is a critical and very stressful period in which constant overloading and sleep deprivation are observed, as well as possibly fatigue and fear of making mistakes.⁸ It is a favorable period for the development of burnout syndrome, due to its duality of roles (learning and work) and strong pressure derived from preceptors, society and the residents themselves.⁹ Lack of autonomy, competitiveness, new expectations, inadequate support from supervisors and irregular work schedules are other problems of residency that correlate with burnout.¹⁰

The objective of our study was to determine the prevalence of burnout among resident physicians at Hospital das Clínicas – Universidade Federal de Pernambuco (HC-UFPE) and to evaluate its associated factors.

METHOD

This is a cross-sectional descriptive study carried out at the HC-UFPE in October and November 2015. The target population was residents enrolled in the medical residency program that year. Data collection was done through self-administered questionnaires, and confidentiality was maintained. All participants signed a free and informed consent form. There were 250 registered residents, of whom 129 participated in the survey. The total number of residents was not reached due to difficulty in approaching some residents in the following situations: vacation period, external rotation, working hours at the time of questionnaires, non-return of the questionnaires and lack of consent to participate in the survey.

Burnout syndrome was evaluated based on the Maslach Burnout Inventory (MBI), a version adapted to Brazilian Portuguese¹¹ and structured with 22 questions subdivided into the areas of emotional exhaustion, depersonalization and professional achievement. In order to classify the emotional exhaustion domain, we used the following scoring criteria: low (≤ 18 points), moderate (19 to 26 points) and high (≥ 27 points). The classification of the depersonalization domain was done according to the following score: low (≤ 6 points), moderate (seven to 12 points) and high (≥ 13 points). For the professional

achievement domain, the classification was made according to the following criterion: low (≤ 33 points), moderate (34 to 39 points) and high (≥ 40 points). The criterion used in our study to define burnout syndrome was the presence of high values for the emotional exhaustion and depersonalization domains, combined with a low score for professional achievement.^{5,12}

A sociodemographic questionnaire was also used to evaluate factors associated with burnout syndrome. Specialties considered as “surgical clinic” were: general surgery, orthopedics, urology, plastic surgery, surgery of the digestive system, vascular surgery, gynecology and obstetrics, ENT, and ophthalmology. The group named “other clinics” included internal medicine, pediatrics, dermatology, radiology, psychiatry, neurology, infectious diseases, nephrology, cardiology, oncology, endocrinology, rheumatology, gastroenterology, and family and community medicine. The following were considered “stressful events”: personal or family-related health problems, mourning, separation, difficult relationship with boss/colleagues/associates/patients, financial problems, relationship problems with family members. We considered regular physical activity as defined by the World Health Organization: over 150 weekly minutes of moderate activity (brisk walking, dancing, active participation in games and sports with children and walking with pets) or over 75 minutes of intense activity (cycling, aerobic exercises, fast swimming, sports and competitive games).

The data were analyzed using Statistical Package for Social Sciences – SPSS software version 13.0. In order to evaluate the personal and professional profile, habits, level of physical activity and living conditions of the residents participating in the study, percentages were calculated and the frequency distributions of the evaluated factors were constructed. Chi-square test was used to compare proportions.

To evaluate the factors associated (personal and professional profile and daily habits of residents) with burnout syndrome and its subdomains, a contingency table was constructed and the Chi-square test for independence was applied. In cases where the assumptions of the Chi-square test were not confirmed, Fisher’s exact test was applied. All conclusions were taken considering the significance level of 5%. Multivariate analysis for the factors associated with burnout was done by adjusting the Poisson model with robust variance, while factor significance was assessed using Wald statistic. For entry into the model, we considered the variables with $p < 0.2$ in the univariate analysis. To retain the variable in the final model, we calculated the prevalence ratios and considered $p < 0.05$.

The research was performed after analysis and approval by the Ethics Committee of the Health Sciences Center of Universidade Federal de Pernambuco (CEP/CCS/UFPE), in accordance with Resolution No. 466/2012 on “Research involving Human Beings” of the Ministry of Health, Opinion No. 49197615.2.0000.5208.

RESULTS

In relation to the personal profile of the participants, we found that most are in the first or second year of residency (67.4%), aged up to 28 years (52.9%), female (51.9%), not married (66.1%) and do not have children (87.9%). Regarding the professional profile of the residents, we found that most of the students do more shifts to supplement their income (84.5%), work up to an additional 24 hours (76.4%), performed four or more night shifts in the last month (75.6%) and works more than 60 hours per week (56.6%).

About 80% of residents experienced a stressful event in the previous six months, 75% had adequate supervision at the medical residency, and the clinics hospital (HC) was the first place they chose to go (64.3%). Most of the participants do not practice intense physical activity (65.1%) and do drink alcohol (72.7%). As for housing, 50.4% of the residents are from Recife and 72.9% do not live with their parents.

Burnout syndrome was found in 36 of the 129 residents through the MBI questionnaire, resulting in a prevalence of 27.9%. As for the domains of burnout, the majority of the participants presented a high level of emotional exhaustion (59.7%) and a low level of professional effectiveness (94.6%). The level of depersonalization was high in 31.8% of the participants.

Table 1 compares residents who met criteria for burnout and those without the syndrome, illustrating the association with risk factors in the univariate analysis. Area

TABLE 1 Distribution of burnout syndrome according to the personal and professional profile of resident physicians at Hospital das Clínicas of Universidade Federal de Pernambuco.

Factor assessed	Has burnout syndrome		p-value
	Yes	No	
Year of residency			
1 st to 2 nd year	23 (26.4%)	64 (73.6%)	0.59*
3 rd to 5 th year	13 (31.0%)	29 (69.0%)	
Age			
Up to 28 years	20 (31.7%)	43 (68.3%)	0.71*
Older than 28 years	16 (28.6%)	40 (71.4%)	
Sex			
Male	17 (27.4%)	45 (72.6%)	0.90*
Female	19 (28.4%)	48 (71.6%)	
Marital status			
Not married	25 (29.8%)	59 (70.2%)	0.62*
Married	11 (25.6%)	32 (74.4%)	
Has children			
Yes	4 (26.7%)	11 (73.3%)	1.00†
No	31 (28.4%)	78 (71.6%)	
Specialization area			
Surgical medicine	16 (44.4%)	20 (55.6%)	0.01*
Other	20 (21.5%)	73 (78.5%)	
Extra shifts to supplement income			
Yes	31 (28.4%)	78 (71.6%)	0.75*
No	5 (25.0%)	15 (75.0%)	
Weekly hours of work			
Up to 60 hours	12 (21.4%)	44 (78.6%)	0.15*
More than 60 hours	24 (32.9%)	49 (67.1%)	

(Continues)

TABLE 1 (Cont.) Distribution of burnout syndrome according to the personal and professional profile of resident physicians at Hospital das Clínicas of Universidade Federal de Pernambuco.

Factor assessed	Has burnout syndrome		p-value
	Yes	No	
Stressful events in the previous 6 months			
Yes	35 (33.7%)	69 (66.3%)	<0.01*
No	1 (4.0%)	24 (96.0%)	
Adequate supervision during residency			
Yes	24 (25.0%)	72 (75.0%)	0.17*
No	12 (37.5%)	20 (62.5%)	
Regular physical activity			
Yes	9 (20.0%)	36 (80.0%)	0.14*
No	27 (32.1%)	57 (67.9%)	
Use of alcoholic beverages			
Yes	29 (31.2%)	64 (68.8%)	0.21*
No	7 (20.0%)	28 (80.0%)	
Place of origin			
Greater Recife area	21 (32.3%)	44 (67.7%)	0.26*
Other locations	15 (23.4%)	49 (76.6%)	
Lives with			
Parents	14 (40.0%)	21 (60.0%)	0.06*
Other relatives, friends or alone	22 (23.4%)	72 (76.6%)	

* p-value of the Chi-square test for independence; † p-value of Fisher's exact test.

of specialization, stress event in the previous 6 months, supervision of residency, workload, physical activity and living with parents, friends or alone were the variables yielding $p < 0.2$ and thus submitted to multivariate analysis.

Table 2 shows the association between the resident profile and the MBI questionnaire domains. For the emotional exhaustion domain, the variables submitted to multivariate analysis due to $p < 0.2$ were specialization area, having children, performing supplementary shifts to increase income, stress event in the previous six months, supervision at the residency and place of origin. In the depersonalization domain, the variables submitted to multivariate analysis were area of specialization, stress event in the last six months, physical activity and living with parents, friends or alone. For the professional achievement domain, the variables were marital status, having children, stress event in the previous six months and use of alcoholic beverage.

Table 3 shows the final model with the factors that remained independently associated with $p < 0.05$. Burnout was about twice as prevalent in surgical residents (PR: 1.99; 95CI 1.20-3.29), and eight times more frequent in those who experienced stressful event in the previous six months (PR: 8.10; 95CI 1.15-57.16) after control for other covariates. These same factors were independently associated with high emotional exhaustion, while being in a surgical spe-

cialty residency was the only factor that was associated with high depersonalization in the multivariate analysis. No factor was independently associated with low achievement.

DISCUSSION

The prevalence of burnout in medical residency, according to the international literature, ranges from 27 to 75%, depending on the specialty.¹³ Brazilian studies, on the other hand, reveal a prevalence between 20 and 50%, using the same instrument adopted by us in this study: the MBI questionnaire. Half of the residents of internal medicine at a philanthropic hospital in São Paulo met the criteria for burnout in 2012.¹⁴ In a study performed in 2004 at Hospital de Clínicas of Universidade Federal de Uberlândia, the authors found a prevalence of 20.8% of burnout in residents from several specialties,⁹ similar to the figure found in 2009 at Hospital das Clínicas of Universidade Federal de Goiás, which was 18%.⁶ A study with oncology residents only, from several centers in Brazil, identified a high prevalence of burnout (76%). However, using as a criterion the presence of the three dimensions of the syndrome, this value drops to less than 36%.¹⁵ Our study demonstrated a prevalence of 27.9% of burnout syndrome in HC-UFPE residents, which is compatible with the average of other studies conducted in Brazil.

TABLE 2 Distribution of the emotional exhaustion, depersonalization and professional achievement domains, according to the personal and professional profile of resident physicians at Hospital das Clínicas of Universidade Federal de Pernambuco.

Factor assessed	Emotional exhaustion			Depersonalization			Professional achievement		
	Low/ Moderate	High	p-value	Low/ Moderate	High	p-value	Low	Moderate	p-value
Year of residency									
1 st to 2 nd year	33 (37.9%)	54 (62.1%)	0.43*	60 (69.0%)	27 (31.0%)	0.79*	82 (94.3%)	5 (5.7%)	1.00†
3 rd to 5 th year	19 (45.2%)	23 (54.8%)		28 (66.7%)	14 (33.3%)		40 (95.2%)	2 (4.8%)	
Age									
Up to 28 years	23 (36.5%)	40 (63.5%)	0.27*	38 (60.3%)	25 (39.7%)	0.20*	61 (96.8%)	2 (3.2%)	0.25†
Older than 28 years	26 (46.4%)	30 (53.6%)		40 (71.4%)	16 (28.6%)		51 (91.1%)	5 (8.9%)	
Sex									
Male	28 (45.2%)	34 (54.8%)	0.28*	42 (67.7%)	20 (32.3%)	0.91*	57 (91.9%)	5 (8.1%)	0.26†
Female	24 (35.8%)	43 (64.2%)		46 (68.7%)	21 (31.3%)		65 (97.0%)	2 (3.0%)	
Marital status									
Not married	31 (36.9%)	53 (63.1%)	0.43*	55 (65.5%)	29 (34.5%)	0.45*	82 (97.6%)	2 (2.4%)	0.04†
Married	19 (44.2%)	24 (55.8%)		31 (72.1%)	12 (27.9%)		38 (88.4%)	5 (11.6%)	
Has children									
Yes	9 (60.0%)	6 (40.0%)	0.10*	10 (66.7%)	5 (33.3%)	1.00*	12 (80.0%)	3 (20.0%)	0.04†
No	41 (37.6%)	68 (62.4%)		74 (67.9%)	35 (32.1%)		105 (96.3%)	4 (3.7%)	
Specialization area									
Surgical medicine	9 (25.0%)	27 (75.0%)	0.03*	20 (55.6%)	16 (44.4%)	0.06*	34 (94.4%)	2 (5.6%)	1.00†
Other	43 (46.2%)	50 (53.8%)		68 (73.1%)	25 (26.9%)		88 (94.6%)	5 (5.4%)	
Extra shifts to supplement income									
Yes	41 (37.6%)	68 (62.4%)	0.14*	75 (68.8%)	34 (31.2%)	0.74*	103 (94.5%)	6 (5.5%)	1.00†
No	11 (55.0%)	9 (45.0%)		13 (65.0%)	7 (35.0%)		19 (95.0%)	1 (5.0%)	
Weekly hours of work									
Up to 60 hours	25 (44.6%)	31 (55.4%)	0.38*	41 (73.2%)	15 (26.8%)	0.29*	52 (92.9%)	4 (7.1%)	0.47†
More than 60 hours	27 (37.0%)	46 (63.0%)		47 (64.4%)	26 (35.6%)		70 (95.9%)	3 (4.1%)	
Stressful events in the previous 6 months									
Yes	31 (29.8%)	73 (70.2%)	<0.01*	66 (63.5%)	38 (36.5%)	0.02*	100 (96.2%)	4 (3.8%)	0.13†
No	21 (84.0%)	4 (16.0%)		22 (88.0%)	3 (12.0%)		22 (88.0%)	3 (12.0%)	
Adequate supervision during residency									
Yes	43 (44.8%)	53 (55.2%)	0.04*	68 (70.8%)	28 (29.2%)	0.23*	91 (94.8%)	5 (5.2%)	1.00†
No	8 (25.0%)	24 (75.0%)		19 (59.4%)	13 (40.6%)		30 (93.8%)	2 (6.3%)	
Regular physical activity									
Yes	20 (44.4%)	25 (55.6%)	0.48*	35 (77.8%)	10 (22.2%)	0.09*	41 (91.1%)	4 (8.9%)	0.24†
No	32 (38.1%)	52 (61.9%)		53 (63.1%)	31 (36.9%)		81 (96.4%)	3 (3.6%)	
Use of alcoholic beverages									
Yes	35 (37.6%)	58 (62.4%)	0.26*	61 (65.6%)	32 (34.4%)	0.35*	90 (96.8%)	3 (3.2%)	0.09†
No	17 (48.6%)	18 (51.4%)		26 (74.3%)	9 (25.7%)		31 (88.6%)	4 (11.4%)	
Place of origin									
Greater Recife area	21 (32.3%)	44 (67.7%)	0.06*	42 (64.6%)	23 (35.4%)	0.38*	63 (96.9%)	2 (3.1%)	0.27†
Other locations	31 (48.4%)	33 (51.6%)		46 (71.9%)	18 (28.1%)		59 (92.2%)	5 (7.8%)	
Lives with									
Parents	11 (31.4%)	24 (68.6%)	0.21*	20 (57.1%)	15 (42.9%)	0.10*	34 (97.1%)	1 (2.9%)	0.67†
Other relatives, friends or alone	41 (43.6%)	53 (56.4%)		68 (72.3%)	26 (27.7%)		88 (93.6%)	6 (6.4%)	

* p-value of the Chi-square test for independence; † p-value of Fisher's exact test.

TABLE 3 Multivariate analysis of burnout syndrome and associated factors in resident physicians at Hospital das Clínicas of Universidade Federal de Pernambuco.

	Factor assessed	PR	95CI	p-value*
Burnout syndrome	Specialty			
	Surgical medicine	1.99	1.20-3.29	0.008
	Other	1.00	-	-
	Stressful event in the previous 6 months			
	Yes	8.10	1.15-57.16	0.036
No	1.00	-	-	
Emotional exhaustion	Specialty			
	Surgical medicine	1.35	1.04-1.74	0.022
	Other	1.00	-	-
	Stressful event in the previous 6 months			
	Yes	4.32	1.78-10.46	0.001
No	1.00	-	-	
Depersonalization	Specialty			
	Surgical medicine	1.65	1.007-2.71	0.047
	Other	1.00	-	-

PR: prevalence ratio; 95CI: 95% confidence interval; *p-value of the Wald test.

As for Brazilian studies including physicians after completion of residency, the prevalence of burnout is lower. A prevalence of 7.4% was found in 297 intensive care physicians in the city of Salvador.¹⁶ The prevalence was also low (5.1%) among pediatricians and obstetricians/gynecologists of a teaching hospital in Pernambuco.¹² This difference in prevalence can be explained by the characteristics of residents and medical residency. Resident physicians, in addition to experiencing stressing factors that are inherent to the medical profession, are under the pressure of medical residency (training nature and educational structure) and face conflicts that are common to young professionals (seeking independence and autonomy, conflict between work and leisure).⁸ Comparing the level of psychological stress among resident and non-resident physicians of Brazilian university hospitals, greater vulnerability to work stress was demonstrated in residents.¹⁷ In addition, they are less able to cope with stress and feel less confident in accomplishing their tasks.

Regarding the domains of burnout, the high prevalence of low level of professional achievement is worth noting in our work (94.6%). This prevalence was much lower in other studies with physicians living in Brazil, ranging from 17.6 to 33.3%.^{6,9,15} The exception was a study by Fabichak that found 70.8% of the residents with low level of professional achievement.¹⁴ In our study, this can be explained by the period of data collection at the end of a school year, between October and November. Nevertheless, the physical and managerial difficulties experi-

enced in the Unified Health System also contribute to the feeling of low professional achievement. The current study was conducted in a hospital linked to the public health system, whose resident physicians performed a small strike with temporary cessation of care in the period prior to data collection, due to the lack of basic conditions for professional practice. This event may have influenced the low professional achievement observed in our study and reflects the interference of the work environment in the personal satisfaction of the professional. According to Malasch, the lack of professional effectiveness seems to emerge more clearly from the lack of relevant resources, while emotional exhaustion seems to emerge from the presence of work overload.²

In the multivariate analysis, burnout was associated with surgical specialties. Thus, the risk of residents associated with surgical specialties developing burnout was twice as high as the risk of residents of other specialties (p=0.008). Previous studies have found that resident surgeons live under more stress than other medical professionals.^{18,19} A Mexican study found that burnout is more prevalent in residents who work over 80 hours per week, being statistically more frequent in those with surgical specialties.²⁰ Justifications for the association between burnout and surgical specialties were not determined in our study. One possible explanation would be the fact that surgical medicine is an area that demands more workload and has more demanding instructors. The influence of supervisors' behavior on the prevalence of burnout

is known, so that residents who perceive themselves unappreciated by their teams are at greater risk of developing this condition.²¹

Being a resident of surgical areas was also independently associated with greater emotional exhaustion and depersonalization. A study from Uberlândia also showed that residents belonging to surgical areas presented greater depersonalization than those belonging to clinical areas.⁹ Emotional exhaustion was recognized as a problem by surgical residents in South Korea, but directly explored in those programs.¹⁸ This shows that although residents perceive the difficulties, Medical Residency Committees and preceptors do not generally recognize the professionals' susceptibility to burnout.

The other factor associated with burnout in the multivariate analysis was having suffered a stress event in the previous six months. These individuals were eight times more likely to develop burnout compared to those who did not experience a stressful event ($p=0.036$). Stressful events affect the physician in training in a negative way and can cause burnout.²² Stressors inside and outside the scope of medicine are able to deplete the personal resources of residents.¹⁰ In a Canadian study, the main sources of stress were tests and evaluations (38.9%), financial problems (25.5%) and family problems (7.4%).²² We were unable to identify which type of stress event was most common in our sample. Nevertheless, we found that the burnout domain most often implicated was emotional exhaustion.

It is important that residents who are vulnerable to developing burnout syndrome seek psychological counseling. Resident physicians sought the psychological assistance group of the University of São Paulo more in the first year and due to factors related to adaptive crises.²³ Early identification of residents susceptible to burnout would be important in resolving this type of assistance. In addition, Pereira-Lima and Loureiro identified the presence of higher scores for social skills in residents without burnout and mental health problems. Since social skills such as communication, empathy and ability to work as a team can be learned, it is important to develop these skills during medical residency training in order to improve practice.²⁴

CONCLUSION

The prevalence of burnout among resident physicians was 27.9%, consistent with other Brazilian studies. Most residents showed a low level of professional achievement. There was a significant association between burnout syndrome and both the practice of surgical specialties and the occurrence of a stressor event in the previous six months. Characterizing the burnout syndrome in resident physicians

can contribute to the elaboration and consolidation of preventive and therapeutic measures in this population.

RESUMO

Fatores associados à síndrome de *burnout* em médicos residentes de um hospital universitário

Objetivo: Determinar a prevalência da síndrome de *burnout* entre médicos residentes de várias especialidades e avaliar os fatores associados.

Método: Foram aplicados o questionário Maslach Burnout Inventory e um questionário sócio-demográfico para avaliar fatores associados à síndrome. *Burnout* foi definido pela associação de alto desgaste emocional e despersonalização e baixa realização profissional. Análise multivariada foi realizada por meio do ajuste do modelo de Poisson com a identificação dos fatores de risco e calculadas as razões de prevalência (RP). Dos 250 médicos residentes cadastrados no Hospital das Clínicas de Pernambuco, 129 participaram do estudo.

Resultados: Nos três domínios que caracterizam a síndrome de *burnout*, encontramos um baixo nível de realização profissional em 94,6% dos médicos residentes entrevistados, alto nível de despersonalização em 31,8% e 59,7% com alto nível de desgaste emocional. A prevalência de *burnout* encontrada foi de 27,9%. Ter sofrido evento estressante nos seis meses anteriores (RP: 8,10; IC 95% 1,2-57,2) e cursar especialidade cirúrgica (RP: 1,99; IC 95% 1,2-3,3) estiveram associados de forma independente ao *burnout*.

Conclusão: A prevalência de *burnout* encontrada em médicos residentes está de acordo com estudos brasileiros prévios. Residentes de especialidades cirúrgicas e aqueles que sofreram evento estressor foram identificados como susceptíveis neste estudo. A identificação precoce dos fatores de risco é fundamental para a implementação de medidas preventivas para o não desenvolvimento da síndrome.

Palavras-chave: *burnout*, residência médica, educação médica.

REFERENCES

1. Freudenberger HJ. Staff burnout. *J Soc Issues.* 1974; 30(1):159-65.
2. Maslach C, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol.* 2001; 52:397-422.
3. Prins JT, Gazendam-Donofrio SM, Tubben BJ, van der Heijden FM, van de Wiel HB, Hoekstra-Weebers JE. Burnout in medical residents: a review. *Med Educ.* 2007; 41(8):788-800.
4. Trigo TR, Teng CT, Hallak JEC. Síndrome de burnout ou estafa profissional e os transtornos psiquiátricos. *Rev Psiquiatr Clín.* 2007; 34(5):223-33.

5. Ruiz CO, Rios FL. El burnout o síndrome de estar quemado en los profesionales sanitarios: revisión y perspectivas. *Int J Clin Health Psychol*. 2004; 4(1):137-60.
6. Soares LR, Lopes TMO, Silva MAO, Ribeiro MVA, Almeida Júnior MP, Silva RA, et al. Burnout e pensamentos suicidas em médicos residentes de hospital universitário. *Rev Bras Educ Med*. 2012; 36(1):77-82.
7. Thomas NK. Resident burnout. *JAMA*. 2004; 292(23):2880-9.
8. Martins LAN. Natureza e magnitude do estresse na residência médica. *Rev Assoc Med Bras*. 1998; 44(1):28-34.
9. Lima FD, Buunk AP, Araújo MBJ, Chaves JGM, Muniz DLO, Queiroz LB. Síndrome de burnout em residentes da Universidade Federal de Uberlândia. *Rev Bras Educ Med*. 2007; 31(2):137-46.
10. Dyrbye L, Shanafelt T. A narrative review on burnout experienced by medical students and residents. *Med Educ*. 2016; 50(1):132-49.
11. Lautert L. O desgaste profissional do enfermeiro [tese]. Salamanca: Facultad de Psicología, Universidade Pontificia de Salamanca; 1995.
12. Lima RAS, de Souza AI, Galindo RH, Feliciano KVO. Vulnerabilidade ao burnout entre médicos de hospital público do Recife. *Ciênc Saúde Coletiva*. 2013; 18(4):1051-8.
13. Ishak WW, Lederer S, Mandili C, Nikravesh R, Seligman L, Vasa M, et al. Burnout during residency training: a literature review. *J Grad Med Educ*. 2009; 1(2):236-42.
14. Fabichak C, Junior JSS, Morrone LC. Síndrome de burnout em médicos residentes e preditores organizacionais do trabalho. *Rev Bras Med Trab*. 2014; 12(2):79-84.
15. Cubero DI, Fumis RR, de Sá TH, Dettino A, Costa FO, Van Eyl BM, et al. Burnout in medical oncology fellows: a prospective multicenter cohort study in Brazilian institutions. *J Cancer Educ*. 2016; 31(3):582-7.
16. Tironi MOS, Sobrinho CLN, Barros DS, Reis EJ, Filho EDM, Almeida A, et al. Professional burnout syndrome among intensive care physicians in Salvador, Brazil. *Rev Assoc Med Bras*. 2009; 55(6):656-62.
17. Katsurayama M, Gomes NM, Becker MAD, Santos MC, Makimoto FH, Santana LLO, et al. Avaliação dos níveis de estresse psicológico em médicos residentes e não residentes de hospitais universitários. *Psicol Hosp (São Paulo)*. 2011; 9(1):75-96.
18. Kang S, Jo HS, Boo YJ, Lee JS, Kim CS. Occupational stress and related factors among surgical residents in Korea. *Ann Surg Treat Res*. 2015; 89(5):268-74.
19. Maher Z, Milner R, Cripe J, Gaughan J, Fish J, Goldberg AJ. Stress training for the surgical resident. *Am J Surg*. 2013; 205(2):169-74.
20. López-Morales A, González-Velázquez F, Morales-Guzmán MI, Espinoza-Martínez CE. Síndrome de burnout en residentes con jornadas laborales prolongadas. *Rev Med Inst Mex Seguro Soc*. 2007; 45(3):233-42.
21. Prins JT1, Gazendam-Donofrio SM, Dillingh GS, van de Wiel HB, van der Heijden FM, Hoekstra-Weebers JE. The relationship between reciprocity and burnout in Dutch medical residents. *Med Educ*. 2008; 42(7):721-8.
22. Matheson KM, Barrett T, Landine J, McLuckie A, Soh NL, Walter G. Experiences of psychological distress and sources of stress and support during medical training: a survey of medical students. *Acad Psychiatry*. 2016; 40(1):63-8.
23. Souza EN, Gianini RJ, Azevedo Neto RS, Eluf-Neto J. Perfil do médico residente atendido no Grupo de Assistência Psicológica ao Aluno (GRAPAL) da Faculdade de Medicina da Universidade de São Paulo. *Rev Assoc Med Bras*. 2009; 55(6):684-91.
24. Pereira-Lima K, Loureiro SR. Burnout, anxiety, depression, and social skills in medical residents. *Psychol Health Med*. 2015; 20(3):353-62.

Geographical distribution of medical graduates from a public university

OSCARINA DA SILVA EZEQUIEL^{1*}, GIANCARLO LUCCHETTI¹, ALESSANDRA LAMAS GRANERO LUCCHETTI¹, MARIA HELENA SENGER², LUCAS BRAGA³, RAFAEL LACERDA³, MARLON FILIPPO³, FERNANDO COLUGNATI⁴, DANETTE MCKINLEY⁵, ELIANA AMARAL⁶

¹MD, PhD, Faculdade de Medicina da Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, MG, Brazil

²MD, PhD, Faculdade de Ciências Médicas e da Saúde, Pontifícia Universidade Católica de São Paulo (PUC-SP), São Paulo, SP, Brazil

³Medical Student, Faculdade de Medicina da UFJF, Juiz de Fora, MG, Brazil

⁴PhD, Faculdade de Medicina da UFJF, Juiz de Fora, MG, Brazil

⁵PhD, Foundation for Advancement of International Medical Education and Research (FAIMER)

⁶MD, PhD, Faculdade de Ciências Médicas da Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

SUMMARY

Objective: To evaluate the geographic distribution and career trajectory of medical graduates and the factors associated with their choice of practice location.

Method: A cross-sectional study involving graduates from December 2001 to December 2010 was conducted. A self-administered questionnaire collected demographics and geographic information (place of birth, place of residence at the time of medical school admission, place of residency training and practice location), and reason for choosing the current location. Statistical analyses assessed trends in geographic distribution of graduates, and identified factors associated with location choice (through the population density of the location chosen for professional practice).

Results: A total of 563 graduates completed the questionnaire. Of those, 4.3% (n=24) reported family medicine as their medical specialty, 19.9% (n=112) reported other primary care specialties (internal medicine, pediatrics, surgery and obstetrics-gynecology) and the others chose subspecialties. Larger cities were more likely to be chosen for practice, particularly for newly-graduated doctors. Job invitations received during medical residency training increased the likelihood of choosing high-populated cities. In contrast, job invitations received during medical school increased the likelihood of choosing cities less populated. Amongst those in cities with lower population density, proximity to family members was an additional influencing factor; those who chose more densely populated cities did so because of better infrastructure and recreational options.

Conclusion: Most of the physicians included in this study pursue subspecialties training and were practicing medicine in large cities. Knowing the multiple factors that influenced the choice of practice location can assist in planning future strategies to reduce physician workforce misdistribution.

Keywords: physicians distribution, primary health care, professional practice location.

Study conducted at Faculdade de Medicina da Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil

Article received: 10/26/2016

Accepted for publication: 12/19/2016

*Correspondence:

Address: Av. Eugênio do Nascimento, s/n
Juiz de Fora, MG – Brazil
Postal code: 36038-330
oscarinauffj@gmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.512>

INTRODUCTION

One of the challenges of providing health care for all is distributing the physician workforce to meet the health needs of the population, including those in remote areas and living under adverse socioeconomic and geographic

conditions.^{1,2} Besides meeting the needs of the population, there is also the goal of strengthening primary health care (PHC), since general practitioners act as gatekeepers in relation to other levels of care.³ Studies investigating the distribution of medical workforce, the allocation of re-

sources and initiatives for locating doctors in certain areas, as well as exploring the reasons for choosing primary care, are important to identify new strategies to address these challenges.^{3,4}

The problem of an uneven distribution of doctors is universal. Despite a gradual increase in the number of doctors in rural areas in the United States, there is still a shortage of general practitioners and specialists.⁵ Similarly, in Greece, a striking predominance of physicians in urban regions was also reported.⁶ Although there are many reasons for misdistribution, preference for specialties to the detriment of general practitioners is considered a determinant factor of this shortage in countries such as the United States, Australia, Canada and France.^{7,8} In fact, the number of physicians in the secondary and tertiary healthcare levels are greater than those in primary care in Spain and Brazil.⁹⁻¹¹

In Brazil, although the health system is decentralized, physicians are primarily located in urban locations, with a high concentration in large cities.¹² Since almost one quarter of Brazil's inhabitants live in rural areas in the North and Northeastern states of the country,¹³ recruiting physicians to practice in remote areas in Brazil is urgent in order to achieve the goals of the proposed health system.^{11,12,14} According to a representative survey, there were 399,692 practicing physicians in 2015 in Brazil, resulting in an approximate rate of 1.95 workers per 1,000 inhabitants. However, significant differences in the distribution of these professionals among the different regions of Brazil were observed, resulting in lower rates in the North (1.09 per 1,000 inhabitants) and Northeast (1.3 per 1,000 inhabitants) compared to the national rate, with a predominance of doctors practicing in larger cities.¹²

Earlier research showed that more than two-thirds of the Brazilian physicians practice in a city other than the one where they graduated and a third of them return to their hometowns.¹⁵ Attraction to larger cities was a determining factor for location choice, despite whether the physicians earned their degree at that same location or not.¹⁵ While the location of postgraduate training (i.e. medical residency) was found to affect the country's aggregate supply of physicians, medical school location did not have the same impact.¹⁶

There are complex interactions between factors contributing to geographic misdistribution and the specialty choice of health professionals. Research has shown that reasons include regional, sociocultural and economic factors, as well as personal reasons related to quality of life, individual characteristics or conditions of professional practice, such as the number of hospital beds and access to other professionals.^{1,17,18} Some authors classify

factors affecting choice of practice location into individual (age, gender, marital status, background), organizational (job, resources, team, financial incentives) and environmental (regulation, culture, security) factors.^{1,19-23} The ability to provide quality services, less social isolation, professional and financial incentives are associated with the choice to practice in rural locations.¹⁹

Although there have been studies documenting the misdistribution of physicians based on practice location and specialty choice, there is little research examining the career trajectory of medical doctors and seeking to understand the determining factors for misdistribution of the workforce.^{1,2,12,21} Knowing the factors associated with physician career choices can help create recruitment strategies intended to promote a more equitable distribution.

Therefore, our study aimed to describe the practice locations and specialty choices of graduates from a Brazilian public medical school, and to identify associated factors.

METHOD

We conducted a cross-sectional study with graduates from a public medical school at the Federal University of Juiz de Fora (UFJF), Brazil. UFJF is located in the state of Minas Gerais, Southeast Brazil, which is an economically developed area in Brazil.¹³ All graduates from December 2001 to December 2010 were invited to participate. Those who dropped out of medical school or who were not practicing medicine were excluded (Figure 1).

The database provided by the university administration included information on 1,642 graduates. To establish initial contact, from October to December 2014, e-mails were sent to all eligible graduates inviting them to participate in the study. In order to increase the response rate, the study was promoted through social media (Facebook) and additional contacts were obtained by phone. Graduates were excluded if they could not be contacted by e-mail, phone or Facebook (Figure 1). Those who provided incomplete responses and those who did not respond after four contact attempts were excluded.

Initial contact was made between December 2014 and March 2015. The invitation contained an explanation of the research objectives and a request to send the link to an electronic questionnaire, via REDCap® (Research Electronic Data Capture). The invitation was sent through e-mail or Facebook, and contained an embedded consent form. Participation was based on electronic consent.

The self-administered questionnaire contained 55 questions, taking around 20 minutes to complete. A pilot testing with faculty members helped to improve the questionnaire and test electronic submission.

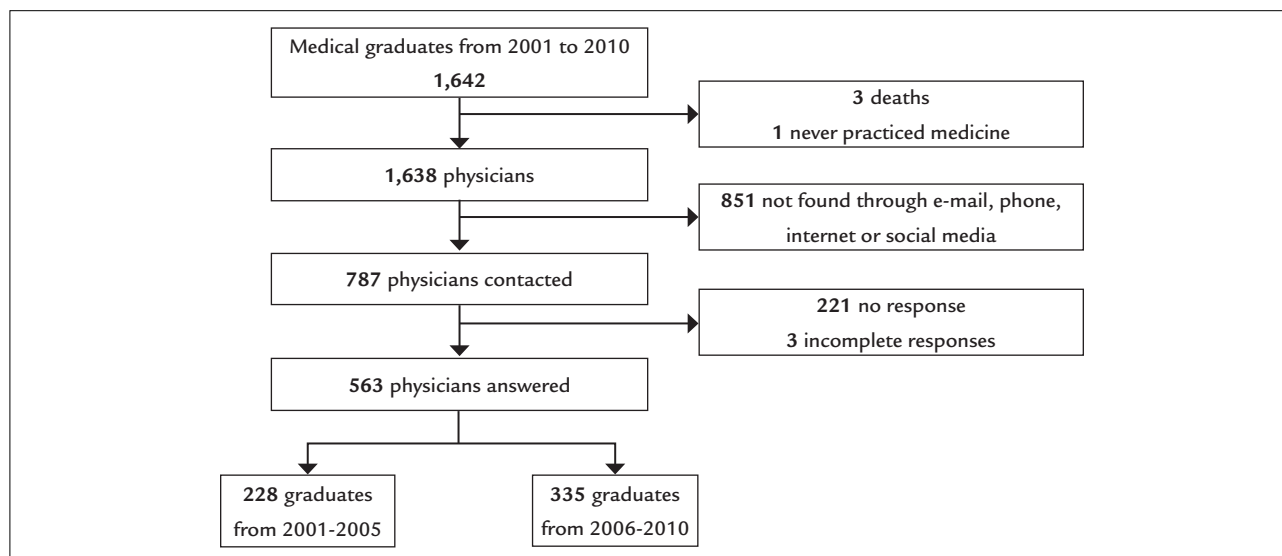


FIGURE 1 Composition of the sample of graduates from 2001 to 2010.

Data included sociodemographic characteristics (i.e., gender, age, income) and geographic location, such as place of birth, place of residence at the time of medical school admission, place of residency training and practice location; as well as reason for choosing current location. To study factors associated with choice of practice location, participants were asked to select one or more of the following reasons, checking all that applied: no reason; invitation received during medical school training; invitation received during residency training; invitation received from a family member; labor market favorable to specialty; family members lived in the city (including spouse); friends lived in the city; town with favorable educational, recreational and entertainment conditions for children and family. Participants were asked whether they completed medical residency, and if they had, they were asked which specialty they chose. The selections included family medicine, general internal medicine, general pediatrics, obstetrics-gynecology, general surgery or other specialties (i.e., cardiology, vascular surgery, and ophthalmology) and whether they worked as a faculty members.

Data were exported from REDCap to Excel for Windows and statistical analysis was performed using SPSS software version 21.0 (SPSS Inc.). Descriptive statistics (frequency, means and standard deviations) for gender, residency completion, specialty, medical teaching and income, and for variables related to place of birth, place of residence when entering medical school, medical residency location and practice location were calculated.

As it was possible that more recent graduates had not yet completed their specialty (or subspecialty) training, we divided the sample into two distinct groups based on year of graduation:

- Group 1: Those who graduated between 2001 and 2005, more likely to have completed residency and to have selected a practice location; and
- Group 2: Those who graduated between 2006 and 2010, who may still be in residency training.

Comparisons between the groups were made based on sex, residency completion, practice specialty, faculty appointment, income, and the size of the practice location using Chi-square statistics. Group comparisons based on age, density and population of the practice location used t-tests. We selected population density (people per sq. km) as our dependent variable, a proxy of development, including workforce, infrastructure and service availability. To evaluate geographic distribution of graduates, we considered the population density of place of birth, place of residence at the time of medical school admission, place of residency training and place of practice location.¹³

We used repeated measures analysis of variance (ANOVA) with location characteristics as the dependent variable and time (birth, medical school, residency, practice) as the independent variables. Post hoc analyses using the Bonferroni test were conducted for statistically significant ANOVA findings. Finally, we used multiple linear regression models (stepwise method) to establish the factors associated with choice of cities for

housing in relation to population density of cities chosen for professional practice for each group.

In order to assess which factors were associated with the choice of practice location for all graduates and group 1, we used a multiple linear regression analysis. Group 2 was not included in a separate regression analysis because these physicians may not have completed their specialty training and, therefore, their current practice location may reflect their location of training, not the choice for practice. The dependent variable was population density of the location chosen for professional practice and the independent variables were sex, age, average monthly income, residency completion, year of graduation, working in the PHC unit, and reason for choosing practice location (no reason; invitation received during medical school training; invitation received during residency training; invitation received from a family member; labor market favorable to specialty; family members lived in the city including spouse; friends lived in the city; town with favorable educational, recreational and entertainment conditions for children and family).

R² was used to assess the adequacy of the model. We used $p < 0.05$ for all analyses and the 95% confidence interval was calculated for a regression coefficient.

The Research Ethics Committee at the University Hospital/UFJF approved the project (no. 790823). An electronic consent form was signed before answering the electronic questionnaire.

RESULTS

There were 1,642 medical graduates identified between 2001 and 2010. We excluded three individuals who died after graduating, as well as one graduate who never practiced medicine. We obtained e-mail addresses from 787 (48.05%) professionals, and 566 responded to the questionnaire, finding three questionnaires incomplete. The final sample consisted of 563 respondents (34.4% of 1,638 graduates; 71.5% of 787 graduates with contact information). Of the

787 graduates with contact information, 450 (79.9%) accessed the questionnaire through a Facebook link and 113 (20.1%) through an e-mail link. The number of respondents by year of program completion ranged from 39 (completion in 2003) to 73 (completion in 2007 or 2010).

Most graduates (86.5%) resided in the state of Minas Gerais (state of medical school) at the time they began undergraduate medical training. Graduates were practicing in 23 of the 26 states of Brazil, with the highest concentration in the states of Minas Gerais (58.1%), São Paulo (17.4%) and Rio de Janeiro (11.7%). They undertook residency training in Minas Gerais (46%), São Paulo (20.4%) and Rio de Janeiro (16.3%).

Twenty-four physicians (24/4.3%) practiced family medicine, 112 (19.9%) practiced other primary care specialties including pediatrics, obstetrics-gynecology, internal medicine and surgery, and 427 (75.8%) chose other specialties or subspecialties.

An analysis of all graduates showed that reasons for choosing practice location in smaller cities included family members living there ($p \leq 0.001$), the perception that the location had favorable educational opportunities ($p = 0.013$), working in PHC Unit ($p = 0.019$), and receiving an invitation during medical school training ($p = 0.003$). For those choosing larger cities, the reasons were that the location had favorable recreational and entertainment conditions ($p < 0.001$), having received an invitation during residency training ($p = 0.007$) and in the final year of medical training ($p < 0.001$) (Table 1).

Since those who graduated more recently were likely to be in their location of residency training, we divided respondents based on graduation year (Table 2). Group 1 was comprised of the 228 respondents who graduated between 2001 and 2005 (40.5%); and group 2 was composed of the 335 respondents who graduated between 2006 and 2010 (59.5%). Those graduating earlier had higher incomes ($p < 0.001$), were older ($p < 0.001$), more

TABLE 1 Factors associated with choosing a practice location according to population density: All respondents.

	B (SE)	Beta	t	p
City density				
Constant	336516.4 (82789.9)		-4.065	<0.001
Family members lived in the city	-1742.2 (241.4)	-0.286	-7.216	<0.001
Town with favorable recreational and entertainment conditions	1015.3 (264.7)	0.172	3.836	<0.001
Town with favorable educational conditions	-676.9 (270.2)	-0.114	-2.505	0.013
Work in Primary Health Care Unit	-905.9 (386.5)	-0.098	-2.344	0.019
Invitation received during residency training	677.6 (251.4)	-0.110	2.696	0.007
Invitation received during medical school	-1032.8 (340.8)	-0.119	-3.031	0.003
Year of medical school program completion	169.2 (41.2)	0.168	4.107	<0.001

TABLE 2 Socioeconomic characteristics, professional profile and size of city of residence for medical school graduates.

Characteristics	Group 1 (n=228)	Group 2 (n=335)	p ¹
	N (%)	N (%)	
Sex (%)			0.001
Male	131 (57.7%)	147 (43.9%)	
Female	96 (42.3%)	188 (56.1%)	
Completed residency			0.206
Yes	206 (91.2%)	296 (88.6%)	
No	20 (8.8%)	38 (11.4%)	
Medical specialty			0.137
Primary care ²	60 (26.5%)	74 (22.2%)	
Other	166 (73.5%)	260 (77.8%)	
Faculty appointment			<0.001
Yes	52 (23.1%)	29 (8.8%)	
No	173 (76.9%)	300 (91.2%)	
Income			<0.001
Less than R\$10,000.00	31 (14.0%)	119 (36.2%)	
R\$10,000 – 20,000.00	113 (51.1%)	146 (44.4%)	
More than R\$20,000.00	77 (34.8%)	64 (19.5%)	
City size – practice location			0.045
Large	143 (63.6%)	243 (73.2%)	
Medium	47 (20.9%)	47 (14.2%)	
Small	35 (15.6%)	42 (12.7%)	
	Mean (SD)	Mean (SD%)	p³
Age	36.4 (1.9)	31.6 (2.5)	<0.001
Practice location population density	1622.7 (2407.0)	2879.0 (3144.3)	<0.001
Practice location population	1,501,744.99 (2,498,877.54)	3,012,194.04 (3,952,865.48)	<0.001

¹Chi-square test.²Primary care specialties include family medicine, general pediatrics, general internal medicine, general surgery and obstetrics-gynecology.³t-test.

likely to be male ($p=0.001$), reported working as faculty members more often ($p<0.001$) and lived in cities with lower population density ($p<0.001$) (Table 2).

Figure 2 shows that graduates migrated from less populated cities to more populated cities during the course of their training and initial career, compared with birthplace and location of medical school. The mean population density of the birthplaces was 909.2 people per sq. km for group 1 and 927.4 for group 2. In contrast, their residence at the start of medical school had lower mean population density, 466.3 people per sq. km for group 1 and 662.6 for group 2. Location of residency training occurred in higher density cities (mean population density: 3,093.7 people per sq. km of land area for group 1 and 4,074.0 for group 2).

Practice location mean population densities were lower: 1,764.3 people per sq. km of land area for group 1 and 3,080.7 for group 2. Physicians who had been practicing

longer tended to return to cities with lower density, while those who had completed their training more recently tended to report living in larger cities. There was a significant difference between the population density of cities over the course of their careers for groups 1 and 2 (within group, $p<0.001$), as well as between groups ($p<0.05$), except for those whose birth location was a densely populated city.

The significant predictors for those graduating between 2001 and 2005 who chose smaller cities as practice locations included having family members there ($p<0.001$) and receiving an invitation during medical school training ($p=0.027$). For those who chose larger cities, the factors identified were that the location offered better recreational activities and entertainment ($p=0.003$), they tended to be female ($p=0.012$) and had received an invitation during residency training ($p=0.009$) (Table 3).

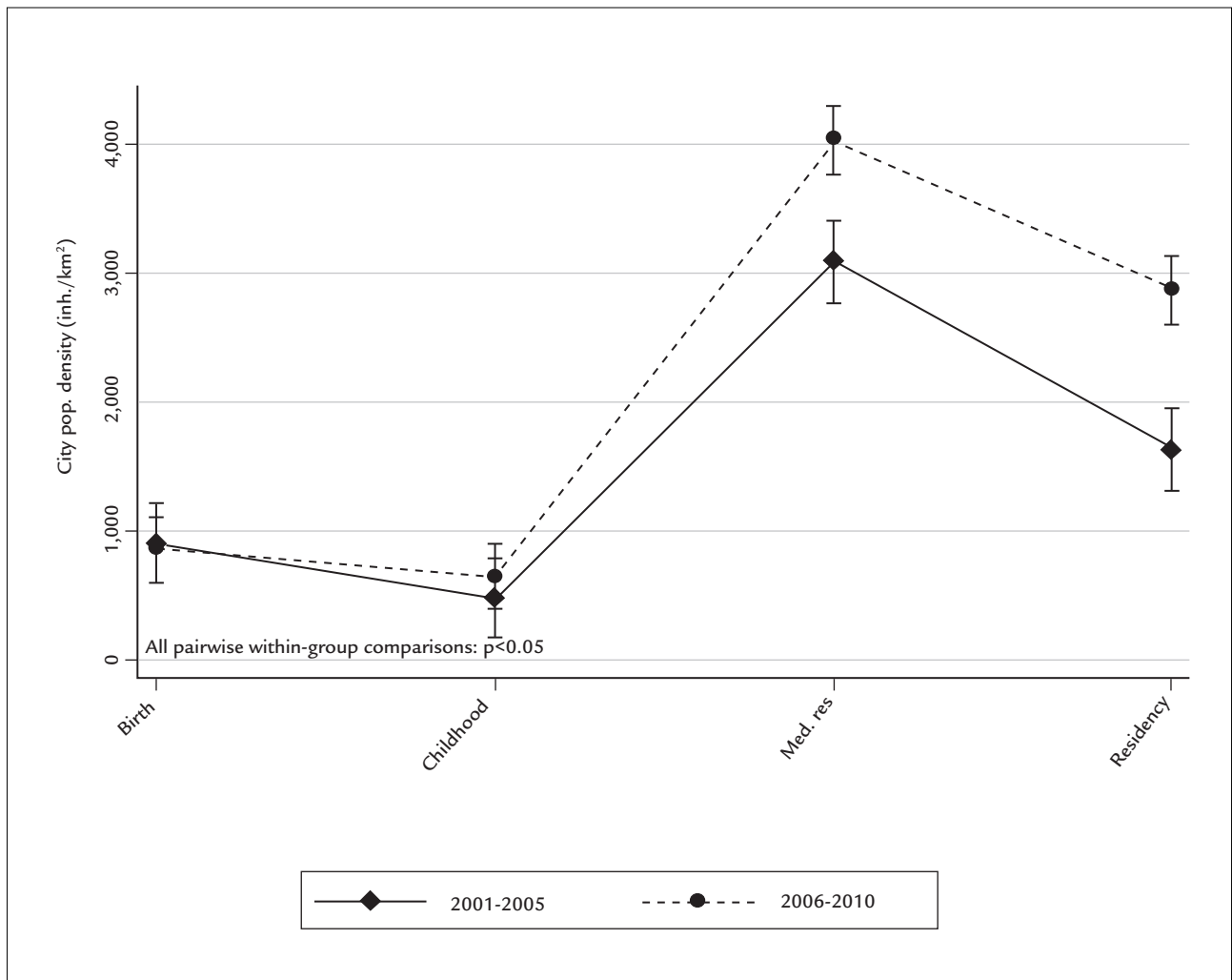


FIGURE 2 Population density of the cities chosen by graduates for living from birth to residency: (Birth) Place of birth, (Childhood) Place of residence when entering medical school, (Med. res) Place of residency training, (Residency) Place of practice location.

TABLE 3 Factors associated with choosing a practice location according to population density: Physicians that graduated between 2001 and 2005.

	B (SE)	Beta	t	p
City density				
Graduates 2001-2005^a				
Constant	370.7 (533.2)		0.695	0.488
Family members lived in the city	-1228.8 (322.6)	0.247	-3.809	<0.001
Town with favorable recreational and entertainment conditions Female	934.9 (309.4)	-0.193	3.021	0.003
Female	798.7 (314.1)	0.165	2.543	0.012
Invitation received during residency training	845.9 (321.5)	0.170	2.631	0.009
Invitation received during medical school	-1047.1 (469.9)	-0.142	-2.228	0.027

^aR=0.399; R-square=0.159.

^bR=0.403; R-square=0.163.

This model includes sex, age, average monthly income, residency completion, graduates working in PHC Unit and reasons for choosing practice location (no reason; invitation received during medical school training; invitation received during residency training; invitation received from a family member; labor market favorable to specialty; family members lived in the city including spouse; friends lived in the city; town with favorable educational, recreational and entertainment conditions for children and family).

DISCUSSION

Previous publications have shown an unequal distribution of the medical workforce and sought to understand the reasons for misdistribution. In 1963, there was a substantially greater number of doctors *per capita* in areas of greater economic income in US urban areas.²⁴ More recent research showed that the situation persists.²⁵ Also, in Canada, there were many specialists and fewer general practitioners and family physicians practicing in areas of higher socioeconomic level.²⁶ These results corroborate the findings of our study; larger cities were those more likely to be chosen as practice location, particularly for more recent graduates.

Factors leading to the choice of larger cities included residency training, similar to other studies in Brazil²⁷ and the US.¹⁶ Some authors found the choice for professional practice related to the location of medical schools.^{9,28} In contrast, for other authors, location of medical school was not related to choice of practice location.¹⁶ Although 86.5% of the respondents were born in the state where the school was located, only 58.1% remained there after graduation, practicing mainly where they completed residency training.

Doctors with less training time tended to live in cities with greater population densities. This is probably because these professionals are still considering opportunities for employment. Perhaps, with time, this group will show the same pattern as those who graduated earlier, migrating to cities with lower population density in search of better quality of life and greater proximity to their original households.^{22,27} Invitation to practice in a specific location was also an important determinant of choice. When the invitation came during residency training, there was an increased likelihood for choosing larger cities, as residency programs are mostly available in these locations. In contrast, respondents invited during medical school training chose less populated cities.

As in other studies, family issues determined where to settle down,^{29,30} including motivation to return to less densely populated cities.^{31,32} On the one hand, family location attracted physicians to smaller cities; on the other hand, more entertainment opportunities influenced the choice for more densely populated cities, with better infrastructure and recreational options.

In the present study, we noticed two distinct profiles in accordance with the time of graduation. First, there was a lower percentage of male doctors in the cohort graduating after 2005, corroborating with worldwide trends on feminization of the medical profession.^{2,12} Also, higher income was observed for the cohort of earlier graduates, probably due to the time spent in the profession.

Furthermore, the majority of physicians chose to specialize to the detriment of a primary health practice. Only a quarter of graduates opted for family medicine, general pediatrics, obstetrics-gynecology, general internal medicine and general surgery, and 90% had residency training. There was no difference between groups 1 and 2. In Britain, there is a trend toward more equitable distribution, perhaps driven by the character of the local health system, while this was not observed in Japan.³³ Choosing specialties other than primary care is not surprising, since those professionals tend to have higher wages and greater increase in income over the years.³⁴

In order to develop incentives to improve physician distribution in Brazil and increase access to PHC, many government policies have been implemented. These include more vacancies for training in medicine and residency programs, spread out at various Brazilian regions, as well as guidelines on curricular changes directing training toward PHC.^{35,36} However, results from the literature on the impact of these policies to attract and retain doctors remains controversial, with multiple confounding factors such as the size of the city where medical schools are located.¹ The same discussion is observed in relation to different educational interventions when examined as a factor in physician workforce retention predictor in rural or underserved areas.^{17,19}

Understanding the complex relationship between the factors that motivate doctors in their choice of workplace can help to define strategies to enhance provision of services in remote and rural areas. Studies show that the simple increase in physician supply did not reduce the distribution disparities. Thus, proposals for a better distribution of health professionals should rely on knowledge of the determining factors for choosing the place for their professional practice, which includes family composition and socioeconomic and cultural issues at the organizational level, as well as other factors related to the environment and their own training. A broad view of the multidimensional nature of choice of specialty and practice location, along with the creation of attractive conditions in remote areas, small towns and rural areas seems to be indispensable for a real change. This is an intersectorial challenge to be faced, associated with the regional development as a whole.

Our study has some limitations. We were successful in obtaining 34.4% of respondents among all graduates in the study period, 71.5% of those who could be located. It is worth noting that this fact was possible because, in addition to the more conventional method of collecting this information such as e-mail and telephone, we used

social networking for both the request and distribution of the questionnaire. In the current investigation, 79.9% of the respondents answered the questionnaire by clicking on a Facebook link. Nevertheless, this may represent sampling bias, since participants are likely to be those with greater electronic access (e-mail and social networks). Usually, response rates based on mailed questionnaires studies reach an average of 20 to 30%.^{9,28} It is likely that younger respondents in locations with better infrastructure were more likely to respond to the survey.

Despite that, our study adds to existing literature as it highlights the importance of using different media to survey and contact graduates. In addition, we examined the influence of different factors other than those commonly reported in the literature such as the invitation to work in a location at the time of medical school completion, location of residency training, and impact of the size difference between the cities of origin, medical school and residency on the distribution of physicians in Brazil.

One of the difficulties encountered in studies involving the population of graduates is access to the target population. In Brazil, it is not routine to follow them throughout their careers. Another potential limitation is that the migration of those who graduated more recently (2006 through 2010) may not yet be complete. It will be necessary to see whether this group shows similar patterns to those who have been in the workforce for a longer period of time.

CONCLUSION

In conclusion, our study showed that most physicians still select large cities as practice location and pursue specialist training rather than PHC. While residency and more recreational opportunities are the attractions in major urban centers, family issues and invitations at the time of medical school completion favor the choice of settling in smaller cities. These findings may help in the planning of future strategies to reduce misdistribution of the medical workforce.

RESUMO

Distribuição geográfica e trajetória dos médicos egressos de instituição pública

Objetivo: Avaliar a distribuição geográfica e a trajetória dos médicos e fatores associados à escolha para o local da prática médica.

Método: Estudo transversal envolvendo graduados entre 2001 a 2010, utilizando-se questionário autoaplicado com

dados sociodemográficos, informações de localização geográfica (local de nascimento, local onde residia quando entrou na faculdade de medicina, local onde realizou a residência médica e local de prática profissional), e as razões para escolha do local de sua fixação. Análises estatísticas avaliaram as tendências da distribuição dos egressos e os fatores associados com a escolha do local para a prática médica.

Resultados: 563 egressos completaram o questionário. Destes, 4,3% (n=24) eram médicos de família, 19,9% (n=112) tinham especialidades em grandes áreas (medicina interna, pediatria, cirurgia e ginecologia-obstetrícia), enquanto os outros escolheram subespecialidades. Houve predomínio da escolha de cidades de grande porte para a prática profissional. Convites para trabalhar recebidos durante a residência médica aumentaram a escolha de cidades de maior densidade populacional. Por outro lado, os convites recebidos durante a graduação influenciaram a escolha de cidades de mais baixa densidade populacional. Para estes últimos, a presença da família no local foi fator de influência, enquanto, para os que escolheram cidades de maior densidade populacional, os fatores de influência foram melhor infraestrutura e mais opções de diversão.

Conclusão: A maioria dos médicos deste estudo fixou-se em grandes cidades e escolheu subespecialidades. Conhecer os múltiplos fatores que influenciaram a escolha do local para prática profissional pode auxiliar no planejamento de estratégias para reduzir a má distribuição do trabalho médico.

Palavras-chave: distribuição de médicos, atenção primária à saúde, área de atuação profissional.

REFERENCES

1. Lehmann U, Dieleman M, Martineau T. Staffing remote rural areas in middle- and low-income countries: a literature review of attraction and retention. *BMC Health Serv Res.* 2008; 8:19.
2. Scollan-Koliopoulos M. OECD. Health at a Glance 2011: OECD Indicators. Paris: OECD Publishing; 2011.
3. Awosogba T, Betancourt JR, Conyers FG, Estapé ES, Francois F, Gard SJ, et al. Prioritizing health disparities in medical education to improve care. *Ann N Y Acad Sci.* 2013; 1287:17-30.
4. Mason J. Review of Australian government health workforce programs. 2013.
5. Ricketts TC. Workforce issues in rural areas: a focus on policy equity. *Am J Public Health.* 2005; 95(1):42-8.
6. Huber M, Stanciole A, Wahlbeck K, Tamsna N, Torres F, Jelfs E, et al. Quality in and equality of access to healthcare services. Brussels, European Commission, DG Employment, Social Affairs & Equal Opportunities. 2008:196-201.
7. Rosenblatt RA, Hart LG. Physicians and rural America. *West J Med.* 2000; 173(5):348.
8. Jeffe DB, Whelan AJ, Andriole DA. Primary care specialty choices of United States medical graduates, 1997-2006. *Acad Med* 2010; 85(6):947-58.
9. Castellanos MEP, Silveira AdFMH, Martins LC, Nascimento VBd, Silva CSd, Bortollotte FHB, et al. Perfil dos egressos da Faculdade de Medicina do ABC: o que eles pensam sobre atenção primária em saúde? *Arq bras ciênc saúde.* 2009; 34(2):71-9.

10. Machado MH. Os médicos no Brasil: um retrato da realidade. Rio de Janeiro: SciELO-Editora FIOCRUZ; 1997.
11. Sakai MH, Cordoni Junior L. Os egressos da medicina da Universidade Estadual de Londrina: sua formação e prática médica. Espaço para Saúde. 2004; 6(1):34-47.
12. Scheffer M. Demografia médica no Brasil: cenários e indicadores de distribuição: relatório de pesquisa–fevereiro de 2015. São Paulo: Conselho Regional de Medicina do Estado de São Paulo; 2015.
13. IBGE. Instituto de Geografia e Estatística 2015 [cited 2015 Jul. 20]. Available from: <http://www.ibge.gov.br/home/estatistica/economia/comercioeservico/pas/analisespas99.shtm#>.
14. Póvoa L, Andrade MV. Distribuição geográfica dos médicos no Brasil: uma análise a partir de um modelo de escolha locacional. Cad Saúde Pública. 2006; 22(8):1555-64.
15. Scheffer M. Demografia médica no Brasil (Vol. 2). São Paulo: Conselho Federal de Medicina e Conselho Regional de Medicina do Estado de São Paulo. 2013.
16. Whitcomb ME. New medical schools in the United States. N Eng J Med. 2010; 362(14):1255-8.
17. Rabinowitz HK, Diamond JJ, Veloski JJ, Gayle JA. The impact of multiple predictors on generalist physicians' care of underserved populations. Am J Public Health. 2000; 90(8):1225-8.
18. Wibulpolprasert S. Inequitable distribution of doctors: can it be solved? Human Resources for Health Development Journal. 1999; 3(1):2-22.
19. Dieleman M, Kane S, Zwanikken P, Gerretsen B. Realist review and synthesis of retention studies for health workers in rural and remote areas. WHO. 2011.
20. Dussault G, Franceschini MC. Not enough there, too many here: understanding geographical imbalances in the distribution of the health workforce. Hum Resour Health. 2006; 4:12.
21. Meliala A, Hott K, Trisnantoro L. Addressing the unequal geographic distribution of specialist doctors in Indonesia: the role of the private sector and effectiveness of current regulations. Soc Sci Med. 2013; 82:30-4.
22. Wibulpolprasert S, Pengpaibon P. Integrated strategies to tackle the inequitable distribution of doctors in Thailand: four decades of experience. Hum Resour Health. 2003; 1(1):12.
23. Wilson N, Couper I, De Vries E, Reid S, Fish T, Marais BJ. A critical review of interventions to redress the inequitable distribution of healthcare professionals to rural and remote areas. Rural Remote Health. 2009; 9(2):1060.
24. Rimlinger GV, Steele HB. An economic interpretation of the spatial distribution of physicians in the US. Southern Economic Journal. 1963; 30(1):1-12.
25. Salsberg E, Grover A. Physician workforce shortages: implications and issues for academic health centers and policymakers. Acad Med. 2006; 81(9):782-7.
26. Krishnan V. A macro model of change in specialty and spatial distribution of physicians in Canada, 1971-1981. Socioecon Plann Sci. 1992; 26(2):111-27.
27. Albuquerque CPd. Inequality in the distribution of rheumatologists in Brazil: correlation with local of medical residency, Gross Domestic Product and Human Development Index. Rev Bras Reumatol. 2014; 54(3):166-71.
28. Caovilla F, Leitzke L, Menezes HS, Martinez PF. Perfil do médico egresso do Curso de Medicina da Universidade Luterana do Brasil (Ulbra). Rev AMRIGS. 2008; 52(2):103-9.
29. Brooks RG, Walsh M, Mardon RE, Lewis M, Clawson A. The roles of nature and nurture in the recruitment and retention of primary care physicians in rural areas: a review of the literature. Acad Med. 2002; 77(8):790-8.
30. Hancock C, Steinbach A, Nesbitt TS, Adler SR, Auerswald CL. Why doctors choose small towns: a developmental model of rural physician recruitment and retention. Soc Sci Med. 2009; 69(9):1368-76.
31. Kristiansen IS, Førde OH. Medical specialists' choice of location: the role of geographical attachment in Norway. Soc Sci Med. 1992; 34(1):57-62.
32. Lin G, Rosenthal TC, Horwitz M. Physician location survey: self-reported and census-defined rural/urban locations. Soc Sci Med. 1997; 44(11):1761-6.
33. Matsumoto M, Inoue K, Farmer J, Inada H, Kajii E. Geographic distribution of primary care physicians in Japan and Britain. Health Place. 2010; 16(1):164-6.
34. Bodenheimer T. Primary care—will it survive? N Eng J Med. 2006; 355(9):861-4.
35. Brasil. Lei N° 12.871, de 22 de outubro de 2013. Programa Mais Médicos 2013 [cited 2016 Jul. 20]. Available from: http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2013/Lei/L12871.htm.
36. Brasil. Resolução n° 3, de 20 de junho de 2014. Diretrizes Curriculares Nacionais do Curso de Graduação em Medicina. Ministério da Educação. 2014.

Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: A parallel, case-control study comprising adults and elderly

BEHROOZ SHOKOUHI¹, KAVEH REZAEI BOOKANI², HOSSEIN GHASEMI³, MAHMOUD KHALOUEI⁴, NAGHMEH JAVANSHIR REZAEI⁵,

SIMIN MIRAKHOR SAMANI^{6*}

¹Department of Pathology, Tabriz University of Medical Sciences, Tabriz, Iran

²Internal Medicine Department, Medstar Harbor Hospital, Baltimore, Maryland, USA

³Department of Internal Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁴Department of Emergency Medicine, Bam University of Medical Sciences, Bam, Iran

⁵Department of Microbiology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

⁶Department of Pathology, Qazvin University of Medical Sciences, Qazvin, Iran

SUMMARY

Objective: To examine the diagnostic and prognostic performances of serum procalcitonin (PCT) in adult and elderly patients with bloodstream infections (BSIs).
Method: A total of 176 patients with culture-proven BSIs and 200 healthy counterparts were studied prospectively. Participants were studied in two adult (age ≤ 65 years, n=92) and elderly (age > 65 years, n=84) groups. Admission serum PCT level was measured using a standard enzyme-linked immunosorbent assay (ELISA) technique.

Results: The mean serum PCT level (in ng/mL) was significantly higher in cases than in controls (0.18 vs. 0.07, p=0.01 in adults; 0.20 vs. 0.07, p=0.002 in elderly). At cut-off values of 0.09 ng/mL in adults and 0.08 ng/mL in the elderly, the corresponding sensitivity and specificity were 82.6 and 82.0% in adults, and 69.1 and 70.0% in elderly, respectively. At a cut-off value of 0.2 ng/mL, the sensitivity and specificity of serum PCT in predicting 28-day mortality were 81 and 81.7% in adults, and 75 and 80.4% in elderly, respectively.

Conclusion: Although admission serum PCT is a sensitive and specific biomarker for the diagnosis of BSIs in patients younger than 65 years old, its short-term prognostic value is comparable between adults and the elderly.

Keywords: procalcitonin, bloodstream infections, age.

Study conducted at the Department of Pathology, Qazvin University of Medical Sciences, Qazvin, Iran

Article received: 11/26/2016
 Accepted for publication: 12/4/2016

*Correspondence:
 Department of Pathology, Qazvin University of Medical Sciences
 Qazvin – Iran
 Postal code: 212234
 samanilab@yahoo.com

<http://dx.doi.org/10.1590/1806-9282.63.06.521>

INTRODUCTION

Bloodstream infections (BSIs) are very common and potentially lethal, particularly in the elderly and among immunocompromised patients.¹ Early diagnosis and implementation of an appropriately therapy, however, could reduce the morbidity and mortality associated with BSIs.²

Blood culture is generally considered the method of choice for the diagnosis of sepsis, but it is time-consuming, i.e., results are typically available only after 12-48 hours. In addition, skin contamination may mislead physicians in some cases.^{3,4} As a result, since uncertain exclusion of sepsis from a differential diagnosis list in acute stages is risky, the administration of empiric antibiotics is usually inevitable and has untoward consequences.⁵

To preclude this shortcoming, researchers have tried to find an accurate test for the diagnosis of BSI at early stages. In 1993, Assicot et al.⁶ found that serum procalcitonin (PCT) levels rise when sepsis or other significant bacterial infections occur. Soon later, several studies suggested that serum PCT could be used as a sensitive biomarker to detect or rule out BSIs in patients with suspected bacterial infections and systemic inflammatory response syndrome (SIRS).^{7,8} Despite many studies and even some meta-analyses, the topic is still a matter of heated debate due to inconsistent findings.⁹⁻¹⁴ Such heterogeneity might arise from using different subgroups of patients,⁹ inconsistency in defining bacteremia and septicemia¹⁰⁻¹² and severe methodological flaws (such as using a small sample size and problematic grouping).¹³

A factor that has been neglected in previous studies is the patients' age.¹² This may also affect the prognostic value of PCT in patients with BSIs.¹⁵ As to address this limitation, we have performed this study to examine diagnostic and prognostic values of serum PCT in the management of adult and elderly patients with BSIs, separately.

METHOD

From April 2013 through June 2016, a total of 206 adult hospitalized patients with culture-proven BSIs and 200 healthy random volunteers from patients' families were prospectively enrolled into this case-control study. Patients with renal disease/malignancy (n=14), immune problems (n=6), recent trauma/surgery (n=6) and a history of recent antibiotic therapy for more than 48 hours (n=4) were excluded, yielding 176 patients in the case group for final analysis (Figure 1). The ethics committee of our university approved our study and informed written consents were obtained from all of the participants.

Participants were divided into groups based on age, namely adults (up to 65 years) and elderly (65 plus years), with both case and control sets as follows: 92 cases vs. 100 controls and 84 cases vs. 100 controls, respectively.

A case with BSI (bacteremia or sepsis) was reported when any pathogenic bacterial species excluding coagulase-

-negative staphylococci, aerobic and anaerobic diphtheroids, *Micrococcus* species, and *Bacillus* species¹⁶ was recovered in 1 or 2 sets of aerobic and anaerobic blood cultures.

Bacteremia was defined as the presence of viable bacteria in the blood; and sepsis was defined when the bacteremia was accompanied by the systemic inflammatory response syndrome (SIRS) as recognized by the presence of at least two of the following: (i) body temperature > 38°C or < 36°C, (ii) heart rate > 90 beats/min, (iii) respiratory rate > 20 breaths/min or PaCO₂ < 32 mmHg, and (iv) white blood cell count > 12,000 cells/mm³, < 4,000 cells/mm³, or > 10% band.¹⁷ Most probable sources of BSIs and the types of isolated microorganisms were also reported.

The admission serum PCT level was measured in ng/mL with enzyme-linked immunosorbent assay (ELISA) using a standard autoanalyzer (Elecsys 2010, Roche, Switzerland) according to the manufacturer's guideline.

All patients were followed up for 28 days and the prognostic ability of PCT for predicting 28-day mortality was also examined.

Statistical analysis

The statistical analyses were performed using the SPSS software version 22.0 (IBM Inc., USA). A normal distribution of quantitative data was assured using the Kol-

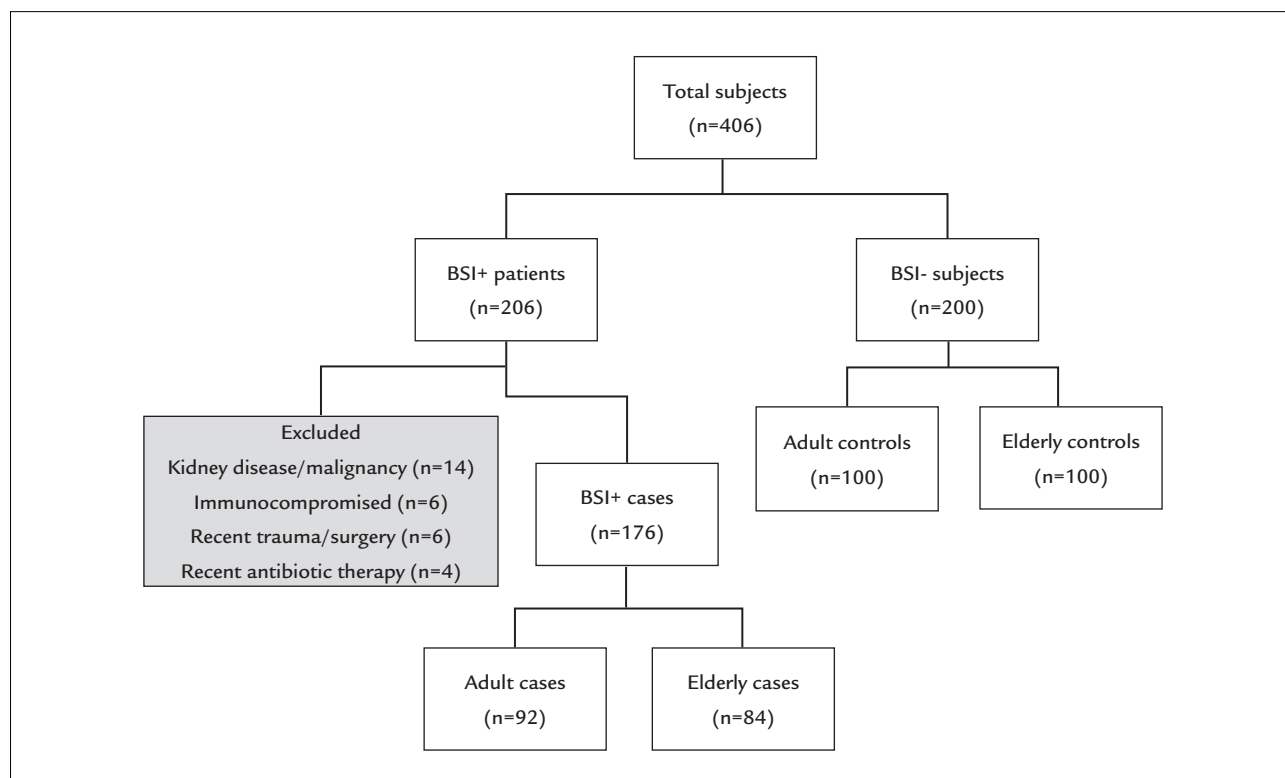


FIGURE 1 Flowchart of case and control study groups.

mogorov-Smirnov test. The quantitative data were presented as mean±standard deviation or mean (standard error of the mean). Independent samples t-test and the Chi-square test were used for comparisons. The Pearson coefficient (r) was employed to assess correlations. Receiver operator characteristic (ROC) curves were plotted to detect area under the curve (AUC) and optimal cut-off levels. A p-value of less than 0.05 (two-tailed) was considered statistically significant.

RESULTS

Demographics of the study population in two adult and elderly groups are summarized and compared between cases and controls in Table 1. Accordingly, the groups were comparable in terms of sex and age of participants.

Sepsis was diagnosed in 42 patients (45.7%) in the adult group and in 44 patients (52.4%) in the elderly group. Within a 28-day follow-up time, 21 patients (22.8%) died in the adult group and 28 patients (33.3%) died in the elderly group.

Most probable sources and microbial etiologies of BSI in the case groups are shown in Table 2. Accordingly, both in the adult and elderly groups, urinary tract and respiratory infections were the most frequent possible

sources of BSIs and *Staphylococcus aureus* and *E. coli* were the most commonly isolated bacteria, respectively.

There was no significant difference between males and females for the mean serum PCT level (0.13 [0.02] ng/mL vs. 0.18 [0.03] ng/mL, respectively; p=0.18). Patients' age and serum PCT level did not correlate significantly in the case groups (r=0.5, p=0.60). No significant correlation was found between serum procalcitonin level and age in adult (r=0.2, p=0.19) or elderly (r=0.02, p=0.91) groups.

In both the adult and elderly groups, mean serum PCT levels were significantly higher in cases than in controls (p=0.01 and 0.002, respectively). Between patients in adult and elderly groups, however, no significant difference was found for the mean serum procalcitonin level (p=0.54).

The AUC of serum PCT level for predicting BSI was 0.81 (95% confidence interval [95CI] 0.71-0.91; p<0.001) in the adult group and 0.73 (95CI 0.63-0.84; p<0.001) in the elderly group. Accordingly, the optimal cut-off level of serum PCT was 0.09 ng/mL (sensitivity, 82.6%; specificity, 82.0%) in the adult group and 0.08 ng/mL (sensitivity, 69.1%; specificity, 70.0%) in the elderly group.

In both the adult and elderly groups, mean serum PCT levels were significantly higher in dead versus surviving patients after 28 days (p<0.001 for both).

TABLE 1 Demographic data of the study population.

Variable	Adults		p-value	Elderly		p-value	
	Cases (n=92)	Controls (n=100)		Cases (n=84)	Controls (n=100)		
Sex	Male	54 (58.7)	56 (56)	0.79	50 (59.5)	56 (56)	0.73
	Female	38 (41.3)	44 (44)		34 (40.5)	44 (44)	
Age (y)		42.96±11.16 (19-63)	44.74±12.63 (23-65)	0.47	74.14±7.11 (66-90)	72.18±5.86 (66-91)	0.15

Data are presented as frequency (%) or mean±standard deviation (minimum-maximum).

TABLE 2 Probable sources and etiologies of bloodstream infection in adult and elderly patients.

Variable	Groups		
	Adults (n=92)	Elderly (n=84)	
Source of infection	Urinary tract	38 (41.3)	32 (38.1)
	Respiratory system	22 (23.9)	24 (28.6)
	Abdomen	14 (15.2)	11 (13.1)
	Neuromeningeal	3 (3.3)	4 (4.8)
	Multiple	15 (16.3)	13 (15.5)
Bacteria	<i>Staphylococcus aureus</i>	44 (47.8)	41 (48.8)
	<i>E. coli</i>	40 (43.5)	37 (44)
	<i>Klebsiella</i>	3 (3.3)	0 (0)
	<i>Enterobacter</i>	2 (2.2)	2 (2.4)
	<i>Pseudomonas</i>	1 (1.1)	0 (0)
	Miscellaneous	2 (1.1)	4 (4.8)

Data are presented as frequency (%).

The AUC of serum PCT level for predicting 28-day mortality was 0.82 (95% confidence interval [95CI] 0.70-0.94; $p < 0.001$) in adults and 0.83 (95CI 0.73-0.92; $p < 0.001$) in the elderly. Accordingly, the optimal cut-off level of serum PCT was 0.2 ng/mL in both the adult and elderly groups, with a sensitivity of 81 and 75% and specificity of 81.7 and 80.4%, respectively.

DISCUSSION

Conventional strategies such as using clinical symptoms and biological markers of inflammation, e.g. leukocytes and C-reactive protein, have had poor diagnostic value to detect or rule out bacteremia and sepsis in previous reports, with an estimated false-negative rate of 15-50%.^{1,18}

In normal conditions, serum PCT is produced by the C-cells in the thyroid gland and all is cleaved to calcitonin, calcitonin-related protein and an N-terminal residue. During clinically significant infections such as bacteremia and sepsis, however, the serum level of PCT rises dramatically. Although the exact source of this acute-phase reactant protein is not known, it is thought to be related to extra-thyroid tissues, because patients with previous total thyroidectomy still exhibit high levels of procalcitonin in their serum during infection.¹⁹

Some investigators have suggested serum PCT as an appropriate tool to differentiate bacterial infections from SIRS caused by viruses or noninfectious conditions such as trauma, burns and organ malfunction.²⁰ Even though, for the purpose of BSI management, PCT has been found superior to conventional diagnostic methods in terms of test speed and accuracy in several studies, there is still no general consensus in this regard or in suggesting a widely accepted cut-off value despite the availability of several case-control studies and large meta-analyses.⁹⁻¹⁴ For example, in a study by Liaudat et al.²¹ that included 50 hospitalized bacteremic patients and 150 controls, at cut-off values of 0.5 and 0.2 ng/mL the sensitivity and specificity of PCT to detect BSIs were 56-92% and 83-43%, respectively. Sudhir et al.¹ included 100 patients with sepsis in their study and reported a high sensitivity value (94%) for serum PCT to detect BSIs. In a recent study, Wang et al.²² used serum PCT for the diagnosis of BSIs in a retrospective design. The best cut-off value was reported at 0.80 ng/mL, with a sensitivity and specificity of 83 and 65%, respectively. They suggested serum PCT as a reliable marker to exclude bacteremia in patients with suspected BSIs. In another series by Riedel et al.²³ comprising 295 patients with symptoms suggestive of systemic infection and 16 patients with definite diagnosis of BSIs, the sensitivity and specificity of PCT assay with a calcu-

lated threshold of 0.1475 ng/mL to detect BSIs were 75 and 79%, respectively. Accordingly, they suggested PCT as a useful marker to rule out sepsis and systemic inflammation in emergency departments. In other studies,^{24,25} the suggested optimal cut-off points for serum PCT varied between 0.1 to 2.0 ng/mL, with sensitivity and specificity values ranging from 35 to 97% and 78 to 99%, respectively. In a recent meta-analysis by Hoeboer et al.,¹⁴ the diagnostic accuracy of serum procalcitonin for bacteremia was examined. In all, 58 studies including 3,420 patients with bacteremia were reviewed. At a cut-off value of 0.5 ng/mL, the overall sensitivity and specificity of this biomarker were 76 and 69%, respectively. The authors, however, concluded that due to the heterogeneity of available studies, further research is needed in this regard.

According to a report, age and past medical history are two important parameters that might contribute to such heterogeneity.²⁶ For instance, it has been shown that false-positive results of PCT testing are frequent among patients with renal problems.²³

To exclude these potential confounding factors, we only included patients with intact renal function and normal immune system. In addition, the diagnostic performance of serum PCT was examined separately in adults (18-65 years) and the elderly (over 65 years) in our study. Based on our findings, at optimal cut-off values of 0.09 ng/mL for adults and 0.08 ng/mL for the elderly, serum PCT was accompanied with a better diagnostic performance in the former (sensitivity and specificity of 82.6 and 82% in adults versus 69.1 and 70% in the elderly, respectively).

The usefulness of serum PCT to manage patients with suspected BSIs has rarely been examined in the elderly.²⁷ It is still not clear how the age of patients may affect serum levels of PCT during BSIs. In a recent study by Stucker et al.,²⁸ and, in accordance with our findings, the authors concluded that serum PCT should not be considered a reliable indicator of BSIs among the elderly.

Whenever sepsis occurs, the innate immune response is activated by releasing various cytokines such as interleukins 1, 6 and 8, tumor necrosis factor- α , and interferon- γ from the endothelial and epithelial cells and macrophages.²⁹ When this reaction is extensive and diffused, endothelial cell damage may ensue, which in turn may cause hemodynamic changes and organ failure.²⁷ Among the elderly and immunocompromised patients, however, the classic signs of sepsis may be missing because of decreased inflammatory responses in such patients.³⁰ In addition, it has been shown that serum PCT levels correlate positively with the severity of inflammatory responses to infections.³¹ This can explain why serum procalcitonin is a more reli-

able indicator of BSIs under 65 years of age. To the best of the authors' knowledge, ours is the first study in the literature that assesses the diagnostic performance of serum PCT among adults and the elderly in parallel.

It should be kept in mind that BSIs are more common among the elderly. Besides a high prevalence, comorbid chronic diseases that usually develop with advanced age, a compromised immune system, inability to communicate adequately with the physician, and nonspecific signs and symptoms of infection further deteriorate the prognosis of BSIs in the elderly.⁸ So, as a second goal, we examined the prognostic utility of serum PCT in predicting 28-day mortality among adult and elderly patients. In conformity with some recent studies,^{15,32-34} we showed that, at a cut-off value of 0.2 ng/mL in both groups, this biomarker is a good indicator of short-term mortality (sensitivity and specificity of around 80%). Again, our study is the first in the medical literature to report an almost equal performance of serum PCT to predict mortality in both adult and the elderly patients with BSIs.

In addition to its high accuracy to detect BSIs, serum PCT has been suggested as an inexpensive biomarker that is not affected by viral infections or inflammatory reactions of non-infectious origin. It is capable to detect bacteremia rapidly (< 1 hour) and has an established prognostic significance as well as longer half-life in the systemic circulation (25-30 h) compared to other conventionally used cytokines. In addition, analyzing the serum level of this biomarker requires only a small amount of blood sample.^{23,35,36}

Despite significant advantages of our study, such as using matching groups of patients and controls as to age, past medical history and ethnicity,¹ a state-of-the-art, up-to-date technology to determine serum PCT levels, culture-proven final diagnosis in all participants, and the study on a rather large number of patients, it may be found limited in terms of not incorporating the severity of BSIs in the final conclusion.

Finally, since in the elderly the studied variable is prognostic rather than diagnostic, it is likely that the rise of procalcitonin is time-dependent in this age group. So, further longitudinal studies should be considered in the future.

CONCLUSION

We showed that serum PCT can be used more reliably in adults than in the elderly with suspected BSIs. The short-term prognostic value of this biomarker, however, does not differ considerably between old and younger patients.

REFERENCES

1. Sudhir U, Venkatachalaiah RK, Kumar TA, Rao MY, Kempegowda P. Significance of serum procalcitonin in sepsis. *Indian J Crit Care Med.* 2011; 15(1):1-5.
2. Jaimes F, Arango C, Ruiz G, Cuervo J, Botero J, Velez G, et al. Predicting bacteremia at the bedside. *Clin Infect Dis.* 2004; 38(3):357-62.
3. Vorwerk C, Loryman B, Coats TJ, Stephenson JA, Gray LD, Reddy G, et al. Prediction of mortality in adult emergency department patients with sepsis. *Emerg Med J.* 2009; 26(4):254-8.
4. Kassis C, Rangaraj G, Jiang Y, Hachem RY, Raad I. Differentiating culture samples representing coagulase-negative staphylococcal bacteremia from those representing contamination by use of time-to-positivity and quantitative blood culture methods. *J Clin Microbiol.* 2009; 47(10):3255-60.
5. Riedel S, Bourbeau P, Swartz B, Brecher S, Carroll KC, Stamper PD, et al. Timing of specimen collection for blood cultures from febrile patients with bacteremia. *J Clin Microbiol.* 2008; 46(4):1381-5.
6. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993; 341(8844):515-8.
7. Shen CJ, Wu MS, Lin KH, Lin WL, Chen HC, Wu JY, et al. The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. *Eur J Clin Microbiol Infect Dis.* 2013; 32(6):807-14.
8. Yilmaz H, Duran L, Yanik K, Altuntaş M, Sünbül M. Differences in the effectiveness of serum biomarkers for the diagnosis of bacterial infections in adult and elderly patients admitted to the emergency department. *Turk J Med Sci.* 2015; 45(3):553-7.
9. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis.* 2007; 7(3):210-7.
10. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013; 13(5):426-35.
11. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis.* 2004; 39(2):206-17.
12. Lee SH, Chan RC, Wu JY, Chen HW, Chang SS, Lee CC. Diagnostic value of procalcitonin for bacterial infection in elderly patients - a systemic review and meta-analysis. *Int J Clin Pract.* 2013; 67(12):1350-7.
13. Jones AE, Fiechtel JF, Brown MD, Ballew JJ, Kline JA. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med.* 2007; 50(1):34-41.
14. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2015; 21(5):474-81.
15. Liu D, Su L, Han G, Yan P, Xie L. Prognostic value of procalcitonin in adult patients with sepsis: a systematic review and meta-analysis. *PLoS One.* 2015; 10(6):e0129450.
16. Richter SS, Beekmann SE, Croco JL, Diekema DJ, Koontz FP, Pfaller MA, et al. Minimizing the workup of blood culture contaminants: implementation and evaluation of a laboratory-based algorithm. *J Clin Microbiol.* 2002; 40(7):2437-44.
17. Chanmugam AS, Rothman R, Desai SV, Putman SB. *Infectious disease emergencies.* Oxford; New York: Oxford University Press; 2016.
18. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, Mudde AH, Dofferhoff TS, Richter C, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore).* 2007; 86(1):26-38.
19. Uusitalo-Seppälä R, Koskinen P, Leino A, Peuravuori H, Vahlberg T, Rintala EM. Early detection of severe sepsis in the emergency room: diagnostic value of plasma C-reactive protein, procalcitonin, and interleukin-6. *Scand J Infect Dis.* 2011; 43(11-12):883-90.
20. Fraunberger P, Wang Y, Holler E, Parhofer KG, Nagel D, Walli AK, et al. Prognostic value of interleukin 6, procalcitonin, and C-reactive protein levels in intensive care unit patients during first increase of fever. *Shock.* 2006; 26(1):10-2.
21. Liaudat S, Dayer E, Praz G, Bille J, Troillet N. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. *Eur J Clin Microbiol Infect Dis.* 2001; 20(8):524-7.
22. Wang H, Yin F, Shen DX, Zhang YJ, Luo YP, Liu CJ, et al. Predictive value of procalcitonin for excluding bloodstream infection: results of a retrospective study and utility of a rapid, quantitative test for procalcitonin. *J Int Med Res.* 2013; 41(5):1671-81.

23. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol.* 2011; 135(2):182-9.
24. Cornelissen CG, Frechen DA, Schreiner K, Marx N, Krüger S. Inflammatory parameters and prediction of prognosis in infective endocarditis. *BMC Infect Dis.* 2013; 13:272.
25. Mencacci A, Leli C, Cardaccia A, Meucci M, Moretti A, D'Alò F, et al. Procalcitonin predicts real-time PCR results in blood samples from patients with suspected sepsis. *PLoS One.* 2012; 7(12):e53279.
26. Caterino JM, Scheatzle MD, Forbes ML, D'Antonio JA. Bacteremic elder emergency department patients: procalcitonin and white count. *Acad Emerg Med.* 2004; 11(4):393-6.
27. Lai CC, Chen SY, Wang CY, Wang JY, Su CP, Liao CH, et al. Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. *J Am Geriatr Soc.* 2010; 58(3):518-22.
28. Stucker F, Herrmann F, Graf JD, Michel JP, Krause KH, Gavazzi G. Procalcitonin and infection in elderly patients. *J Am Geriatr Soc.* 2005; 53(8):1392-5.
29. Russell JA. Management of sepsis. *N Engl J Med.* 2006; 355(16):1699-713.
30. Steichen O, Bouvard E, Grateau G, Bailleul S, Capeau J, Lefèvre G. Diagnostic value of procalcitonin in acutely hospitalized elderly patients. *Eur J Clin Microbiol Infect Dis.* 2009; 28(12):1471-6.
31. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med.* 2000; 26(Suppl 2):S148-52.
32. Azevedo JR, Torres OJ, Czecko NG, Tuon FF, Nassif PA, Souza GD. Procalcitonin as a prognostic biomarker of severe sepsis and septic shock. *Rev Col Bras Cir.* 2012; 39(6):456-61.
33. Kibe S, Adams K, Barlow G. Diagnostic and prognostic biomarkers of sepsis in critical care. *J Antimicrob Chemother.* 2011; 66 Suppl 2:ii33-40.
34. Rajkumari N, Mathur P, Sharma S, Gupta B, Bhoi S, Misra MC. Procalcitonin as a predictor of sepsis and outcome in severe trauma patients: a prospective study. *J Lab Physicians.* 2013; 5(2):100-8.
35. Heper Y, Akalin EH, Mistik R, Akgöz S, Töre O, Göral G, et al. Evaluation of serum C-reactive protein, procalcitonin, tumor necrosis factor alpha, and interleukin-10 levels as diagnostic and prognostic parameters in patients with community-acquired sepsis, severe sepsis, and septic shock. *Eur J Clin Microbiol Infect Dis.* 2006; 25(8):481-91.
36. Viallon A, Guyomarc'h S, Marjolle O, Berger C, Carricajo A, Robert F, et al. Can emergency physicians identify a high mortality subgroup of patients with sepsis: role of procalcitonin. *Eur J Emerg Med.* 2008; 15(1):26-33.

Mueller-Hillis maneuver and angle of progression: Are they correlated?

SOFIA MENDES^{1*}, RITA SILVA¹, INÊS MARTINS¹, SUSANA SANTO¹, NUNO CLODE¹

¹MD, Department of Obstetrics, Gynecology and Reproductive Medicine, Hospital de Santa Maria, Lisboa, Portugal

SUMMARY

Objective: Mueller-Hillis maneuver (MHM) and angle of progression (AOP) measured by transperineal ultrasound have been used to assess fetal head descent during the second stage of labor. We aimed to assess whether AOP correlates with MHM in the second stage of labor.

Method: A prospective observational study including women with singleton pregnancy in the second stage of labor was performed. The AOP was measured immediately after the Mueller-Hillis maneuver. A receiver-operating characteristics (ROC) curve analysis was performed to determine the best discriminatory AOP cut-off for the identification of a positive MHM. A p-value less than 0.05 was considered statistically significant.

Results: One hundred and sixty-six (166) women were enrolled in the study and 81.3% (n=135) had a positive MHM. The median AOP was 143° (106° to 210°). The area under the curve for the prediction of a positive maneuver was 0.619 (p=0.040). Derived from the ROC curve, an AOP of 138.5° had the best diagnostic performance for the identification of a positive MHM (specificity of 65% and a sensitivity of 67%).

Conclusion: An AOP of 138° seems to be associated with a positive MHM in the second stage of labor.

Keywords: second stage of labor, angle of progression, Mueller-Hillis maneuver, intrapartum, ultrasonography.

Study conducted at the Departamento de Obstetrícia, Ginecologia e Medicina da Reprodução, Hospital de Santa Maria, Lisboa, Portugal

Article received: 11/24/2016

Accepted for publication: 12/4/2016

*Correspondence:

Departamento de Obstetrícia,
Ginecologia e Medicina da Reprodução,
Hospital de Santa Maria
Address: Av. Prof. Egas Moniz
Lisboa – Portugal
Postal code: 1649-035
sofiamentes01@gmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.527>

INTRODUCTION

Spontaneous vaginal delivery is the desirable mode of delivery for most pregnancies. However, some women fail to progress into second stage of labor and require obstetric intervention. Progression of labor is traditionally assessed by digital examination. In 1885, Mueller¹ described a maneuver in which an assistant applies fundal pressure and a second examiner determines descent of the fetal presenting part. The technique was modified by Hillis² in 1930 to allow its execution by a single person, and later became known as Mueller-Hillis maneuver (MHM). According to March et al., a positive Mueller-Hillis maneuver should reassure the clinician of an exceptional likelihood of achieving a vaginal delivery.³ Thorp et al.,⁴ however, failed to prove its utility to predict dystocia. Moreover, for the determination of fetal head station, several other studies showed that digital vaginal examination⁵⁻⁷ is subjective with high inter-observer variability. Intrapartum transperineal ultrasonography (ITU) has been suggested as a much more reliable method for assessing fetal head descent, as it provides

objective and reproducible results.⁸ It is neither time-consuming nor causes discomfort of the patient.⁹ However, it may not be available everywhere. The angle of progression measured by transperineal ultrasound in the second stage of labor has been shown to be useful in predicting spontaneous vaginal delivery.^{10,11}

The aim of our study was to assess whether the angle of progression correlates with the Mueller-Hillis maneuver in the second stage of labor.

METHOD

From November 2014 to September 2015, we conducted a prospective observational study at our unit. Pregnant women with a single fetus in cephalic presentation in the early second stage of labor were included.

The examination was performed using the modified Mueller-Hillis maneuver. With the patient in lithotomy position, the examining fingers were inserted into the vagina and the ischial spines and fetal head were identified. Pressure was then applied transabdominally with the op-

posite hand on the uterine fundus. The descent of the head with reference to the interspinous line was evaluated. The examination was performed between contractions. A positive Mueller-Hillis maneuver was defined as descent of the fetal head of at least one centimeter. Any lesser degree of descent was defined as a negative result. After clinical evaluation, transperineal ultrasound was performed. The ultrasound transducer was placed on the perineum in a mid-sagittal position between the labia, below the pubic symphysis. A sagittal view with clear visualization of the pubic symphysis and of the fetal skull was obtained. Two lines were drawn: a line parallel to the long axis of the symphysis and a line tangential to the fetal head. The so-called angle of progression between the constructed lines was then measured directly on the screen and registered on each patient file.¹⁰ The measurement was performed between contractions.

Both examinations were performed by eight different clinicians with at least two years of experience. All of them received training on how to do transperineal ultrasound. MHM and AOP were measured by two different clinicians that were blinded to the findings of each other in order to avoid bias.

For ultrasound evaluation, we used a portable machine (ALOKA® IP-1233).

Baseline sociodemographic and clinical characteristics were summarized using descriptive statistics. The primary endpoint was to assess the correlation between AOP and a positive Mueller-Hillis maneuver, which was evaluated using a receiver-operating characteristic (ROC) curve. Additionally, an analysis to assess if AOP or MHM influenced the type of delivery (normal vs. instrumental) was performed.

Chi-square test was used to evaluate nominal variables and ANOVA, t-test and Kruskal-Wallis were used for quantitative variables. Results were considered statistically significant when p-value was < 0.05. The statistical analysis was performed using SPSS software version 20.0.

RESULTS

One hundred and sixty-six (166) women were enrolled during the study. The mean maternal age was 30.1 (± 5.3) years. The mean gestational age was 39.1 (± 1.4) weeks. One hundred and one (101/60.8%) women were nuliparous and 65 (39.2%) were multiparous. Oxytocin was administered to 161 (97%) women and regional anesthesia was given to 164 (98.7%) women. Seventy-five (75) women had normal vaginal delivery, while 91 had instrumental vaginal delivery and, of these, two had a failed trial of instrumental delivery and one had cesarean section. The mean birth weight of newborns was 3,305 (± 392) grams. The patient characteristics are shown in Table 1.

TABLE 1 Description of study population – patient characteristics.

	N (%) or median (range)
Age (years)	31 (15-43)
Race	
Caucasian	141 (84.9)
African	22 (13.3)
Other	3 (1.8)
Parity	
Nuliparous	101 (60.8)
Multiparous	65 (39.2)
Gestational age (weeks)	39 (32-41)
< 37	7 (4.2)
≥ 37	159 (95.8)
Body mass index	
< 30	133 (80.1)
≥ 30	33 (19.9)
Labor induction	
Yes	53 (31.9)
No	110 (66.3)
Labor augmentation with oxytocin	
Yes	16 (9.7)
No	5 (3)
Regional anesthesia	164 (98.7)
Delivery	
Mode of delivery	
Normal	75 (45.2)
Instrumental vaginal delivery	89 (53.6)
Prolonged 2 nd stage of labor	70 (78.6)
Fetal distress	15 (16.8)
Shorten the 2 nd stage of labor	
Cesarean section	4 (4.5)
Failure to progress in 2 nd stage of labor	2 (1.2)
Fetal birth weight (g)	3,282 (2,100-4,410)
Apgar score < 7 at the 5 th minute	0

The median AOP was 143° (106° to 210°). One hundred and thirty-five (135/80.8%) women had a positive MHM. A ROC curve was plotted, evaluating the sensibility and specificity of each measured AOP for predicting a positive/negative MHM. The area under the ROC curve was 0.619 (95CI 0.493-0.745), suggesting a poor performance of AOP for the prediction of the maneuver (Figure 1). Considering the whole range of measured AOP, an angle of 138.5° was associated to the maximum Youden index and therefore to the best performance (66.7% sensibility and 64.5% specificity) on MHM prediction.

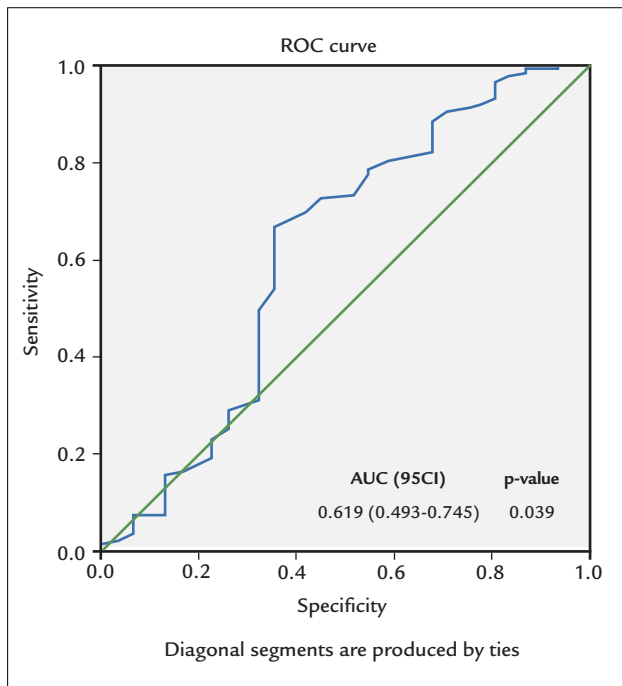


FIGURE 1 ROC curve to determine the best discriminatory AOP cut-off for the identification of a positive MHM.

No differences were found in AOP considering fetal position, but the proportion of positive/negative MHM was significantly different between anterior and transverse positions. Regarding the AOP or MHM and fetal head stations no significant differences were noted (Table 2). Moreover, no differences between the type of delivery and AOP or MHM were found. However, when instrumental vaginal delivery for fetal distress or shortening of the 2nd stage were excluded, the difference became statistically significant for both methods (Table 3).

DISCUSSION

The main objective of the obstetrician is to promote the safe birth of a healthy baby. Most births occur vaginally and spontaneously; however, there are situations in which this is not possible. The success of an instrumental vaginal delivery depends on a proper obstetric assessment prior to the procedure. Patients who are inappropriately qualified for vaginal instrumental delivery (too high position of fetal head) are at an increased risk of complications after multiple vacuum traction or failed forceps procedure. The Mueller-Hillis maneuver constitutes one of the first attempts to predict dystocia. Thorp et al.⁴ performed MHM on 106 pregnant women after active labor was diagnosed. The authors couldn't find any differences in the rate of abdominal delivery or operative

vaginal delivery whether the maneuver was positive or negative. On the other hand, March et al.³ concluded that a positive maneuver in the second stage of labor is strongly associated with a vaginal delivery and that a negative one associates significantly with prolonged second stage, and higher cesarean section rate. Despite these conflicting results and lack of other studies, the Mueller-Hillis maneuver is still being used.

Intrapartum ultrasound has been suggested to overcome the subjectivity of clinical assessment. Various ultrasound measurements have been proposed. The angle of progression was describe by Barbera et al.¹⁰ who showed that an angle of at least 120° was always associated with subsequent spontaneous vaginal delivery with a good intra- and inter-observer variability. Torkildsen et al.¹¹ and Eggbo et al.¹² reported that for primiparous women with prolonged first stage of labor, the AOP could predict the probability of a vaginal delivery being the optimal cut-off 110°. Kalache et al.¹³ reported that for pregnant women in a prolonged second stage of labor, there is a 90% chance of vaginal delivery with an AOP of 120°. However, the value of AOP associated with spontaneous delivery is not consensual, since studies pointed out higher values for AOP.^{14,15}

Globally, in our study, AOP showed a poor correlation with MHM, indicated by a low AUC. Nevertheless, we have found that AOP over 138.5° had the best diagnostic performance for the identification of positive MHM in the early second stage of labor but with a low sensibility and specificity that preclude its use for clinical practice.

We included women with indication to expedite delivery not only due to dystocia but also to fetal distress. None of the methods are expected to be used to predict situations that require prompt obstetric interventions. In fact, when excluding cases of fetal distress/shortened second stage of labor, both AOP and MHM seemed to be associated with type of delivery. The main purpose of our study, however, was to find a relation between the maneuver and AOP and not between both methods and the type of delivery. Nevertheless, a subanalysis was made excluding cases of fetal distress, and the results were similar (data not shown).

To our knowledge, ours is the first study to correlate MHM with AOP; however, there are important limitations. We made a single measurement of the AOP after MHM but, since labor is a dynamic process, repeating measurements of both angle and MHM every 30 minutes might be helpful. In fact, Ghi et al.¹⁴ reported that, in the first 40 minutes of the second stage of labor, AOP was useful for predicting mode of delivery but afterwards the difference lost its statistical difference. Moreover, as previ-

TABLE 2 Position and head station – only assessed by clinical examination.

	N (%)	Median AOP (range)	p-value	MHM		p-value
				Positive	Negative	
Position						
Anterior	105 (63.3)	143 (108-210)	0.288	90	14	0.020
Posterior	47 (28.3)	142 (106-179)		37	11	
Transverse	14 (8.4)	141 (123-165)		8	6	
Head Station						
≤ 0	22 (13.2)	135 (123-163)	0.406	17	4	0.310
1	73 (43.7)	144 (106-210)		56	17	
2	62 (37.1)	142 (113-179)		52	10	
3	10 (6.0)	141.5 (129-170)		10	0	

TABLE 3 Type of delivery and MHM and AOP*.

Type of delivery (N=147)	Mean AOP (SD)	p-value	MHM		p-value
			Positive	Negative	
Normal	145.33 (±13.7)	0.034**	67	8	0.005**
Instrumental vaginal delivery	140.52 (±14.7)		67	22	
Cesarean section	129.5 (±12.0)		1	1	

*Excluding instrumental vaginal deliveries indications: "fetal distress" and "shorten the 2nd stage of labor".

** t-student, comparing normal vs. operative delivery (instrumental plus cesarean).

** Chi-square test, considering normal vs. operative delivery (instrumental plus cesarean).

ously recorded,¹⁶ uterine contractions and active maternal pushing seem to affect AOP in the second stage of labor. We made a single measurement of the AOP after the MHM and not during the maneuver and therefore we do not know if this could change the results.

In our study, both examinations were performed immediately after full cervical dilation was determined, i.e., in the early second stage of labor. Consistent timing for the examination enables a more accurate correlation of both methods but it is difficult to exactly assess the moment of full cervical dilation. Moreover, other variables might have affected the maneuver's outcome, such as maternal habitus, position of the head, flexion/extension of the head, force applied or resistance of the maternal abdomen. Fetuses presenting as occiput posterior position are thought to follow different paths of descent¹⁶ and, since we did not evaluate separately this subset of fetuses, which might have been a limitation of our study. Lastly, because ultrasound measurements and clinical assessments were performed by residents with different levels of experience, and this variable may influence the clinical evaluation,¹⁷ the inverse correlation between lower head station and higher AOP was not seen in our population.

If one method can predict spontaneous delivery with a high likelihood, it may prevent unnecessary obstetric

interventions. The ideal method for obstetric assessment is one that is available worldwide, easy to perform and reproducible. Regardless of the individual value of the MHM and AOP as previously reported to predict the type of delivery (which is debatable in both methods), our data failed to find a strong correlation between these methods.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Manobra de Mueller-Hillis e ângulo de progressão: eles estão correlacionados?

Objetivo: A manobra de Mueller-Hillis (MHM) e o ângulo de progressão da apresentação (AOP) medido através de ecografia transperineal têm sido utilizados para avaliar a descida do polo cefálico durante o segundo estágio do trabalho de parto. O objetivo do nosso trabalho foi avaliar se o AOP se correlaciona com a MHM no segundo estágio do trabalho de parto.

Método: Conduzimos um estudo observacional e prospectivo. Incluímos mulheres com gravidez unifetal com feto em apresentação cefálica, no segundo estágio do

trabalho de parto. O AOP foi medido imediatamente após a manobra de Mueller-Hillis. Foi construída uma curva ROC (*receiver-operating characteristics*) para determinar o melhor AOP para a identificação de uma manobra positiva. Um valor *p* inferior a 0,05 foi considerado estatisticamente significativo.

Resultados: Cento e sessenta e seis mulheres (166) foram incluídas no estudo, e em 81,3% (n=135) a MHM foi positiva. A mediana do AOP foi de 143° (106° a 210°). A área abaixo da curva para a previsão de uma manobra positiva foi 0,619 (*p*=0,040). Derivado da curva ROC, um AOP de 138,5° teve o melhor desempenho diagnóstico para a identificação de uma MHM positiva (especificidade de 65% e sensibilidade de 67%).

Conclusão: Um AOP de 138° parece estar associado com uma MHM positiva no segundo estágio de trabalho de parto.

Palavras-chave: segundo estágio do trabalho de parto, ângulo de progressão, manobra de Mueller-Hillis, intraparto, ecografia.

REFERENCES

- Mueller P. About the prognosis for delivery with a narrow pelvis. *Arch Gynaekol.* 1885; 27:311-2.
- Hillis DS. Diagnosis of contracted pelvis by impression method. *Surg Gynecol Obstet.* 1930; 51:852-4.
- March MR, Adair CD, Veille JC, Burrus DR. The modified Mueller-Hillis maneuver in predicting abnormalities in second stage labor. *Int Journal of Gynecology and Obstetrics.* 1996; 55(2):105-9.
- Thorp JM, Pahel-Short L, Bowes WA Jr. The Mueller-Hillis maneuver: can it be used to predict dystocia? *Obstet Gynecol.* 1993; 82(4 Pt 1):519-22.
- Dupuis O, Silveira R, Zentner A, Dittmar A, Gaucherand P, Cucherat M, et al. Birth simulator: reliability of transvaginal assessment of fetal head station as defined by the American College of Obstetricians and Gynecologists classification. *Am J Obstet Gynecol.* 2005; 192(3):868-74.
- Buchmann E, Libhaber E. Interobserver agreement in intrapartum estimation of fetal head station. *Int J Gynecol Obstet.* 2008; 101(3):285-9.
- Tutschek B, Torkildsen EA, Eggebo TM. Comparison between ultrasound parameters and clinical examination to assess fetal head station in labor. *Ultrasound Obstet Gynecol.* 2013; 41(4):425-9.
- Chou MR, Kreiser D, Taslimi MM, Druzin ML, El-Sayed YY. Vaginal versus ultrasound examination of fetal occiput position during the second stage of labor. *Am J Obstet Gynecol.* 2004; 191(2):521-4.
- Rozenberg P, Porcher R, Salomon LJ, Boitrot F, Morin C, Ville Y. Comparison of the learning curves of digital examination and transabdominal sonography for the determination of fetal head position during labor. *Ultrasound Obstet Gynecol.* 2008; 31(3):332-7.
- Barbera AF, Pombar X, Perugini G, Lezotte DC, Hobbins JC. A new method to assess fetal head descent in labor with transperineal ultrasound. *Ultrasound Obstet Gynecol.* 2009; 33(3):313-9.
- Torkildsen EA, Salvesen KÅ, Eggebo TM. Prediction of delivery mode with transperineal ultrasound in women with prolonged first stage of labor. *Ultrasound Obstet Gynecol.* 2011; 37(6):702-8.
- Eggebo TM, Hassan WA, Salvesen KÅ, Lindtjorn E, Lees CC. Sonographic prediction of vaginal delivery in prolonged labor: a two-center study. *Ultrasound Obstet Gynecol.* 2014; 43(2):195-201.
- Kalache KD, Dückelmann AM, Michaelis SA, Lange J, Cichon G, Dudenhausen JW. Transperineal ultrasound imaging in prolonged second stage of labor with occipitoanterior presenting fetuses: how well does the "angle of progression" predict the mode of delivery? *Ultrasound Obstet Gynecol.* 2009; 33(3):326-30.
- Ghi T, Youssef A, Maroni E, Arcangeli T, De Musso F, Bellussi F, et al. Intrapartum transperineal ultrasound assessment of fetal head progression in active second stage of labor and mode of delivery. *Ultrasound Obstet Gynecol.* 2013; 41(4):430-5.
- Kameyama S, Sato A, Miura H, Kumagai J, Sato N, Shimizu D, et al. Prediction of spontaneous vaginal delivery by transperineal ultrasound performed just after full cervical dilation is determined. *J Med Ultrasonics.* 2016; 43(2):243-8.
- Tutschek B, Braun T, Chantraine F, Henrich W. A study of progress of labour using intrapartum translabial ultrasound, assessing head station, direction, and angle of descent. *BJOG.* 2011; 118(1):62-9.
- da Costa AG, Barros JG, Clode N, da Graça LM. Levels of agreement between clinical examination and transabdominal ultrasound evaluation of fetal head position in the second stage of labor. *J Matern Fetal Neonatal Med.* 2016; 29(3):473-6.

Thrombocytopenia as a marker of liver steatosis in a low-endemic area for schistosomiasis mansoni

ALBA OTONI¹, CARLOS MAURICIO DE FIGUEIREDO ANTUNES², FERNANDA FERREIRA TAVARES³, DÉBORA HELOÍSA QUADROS ARAÚJO⁴,

THIAGO DE ALMEIDA PEREIRA¹, LEONARDO CAMPOS DE QUEIROZ⁵, FREDERICO FIGUEIREDO AMÂNCIO⁶, JOSÉ ROBERTO LAMBERTUCCI^{7*}

¹PhD in Health Sciences, Department of Infectology and Tropical Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

²PhD in Epidemiology, Department of Epidemiology, Instituto de Ensino e Pesquisa da Santa Casa de Belo Horizonte, Belo Horizonte, MG, Brazil

³MSc in Health Sciences, Department of Infectology and Tropical Medicine, UFMG, Belo Horizonte, MG, Brazil

⁴Nursing Student, Undergraduate Program, Universidade Federal de São João del-Rei, São João del-Rei, MG, Brazil

⁵MD, Radiologist. PhD in Health Sciences, Department of Infectology and Tropical Medicine, UFMG, Belo Horizonte, MG, Brazil

⁶PhD in Infectious Diseases and Tropical Medicine; MD, Infectious Disease Physician, Belo Horizonte, MG, Brazil

⁷PhD in Infectious Diseases and Tropical Medicine; MD, Professor at UFMG, Belo Horizonte, MG, Brazil

SUMMARY

Introduction: Thrombocytopenia is commonly found in patients living in highly endemic areas for *Schistosoma mansoni*. Recently, different degrees of liver steatosis have also been associated with low platelet counts worldwide. We investigated the association of platelet counts with hepatosplenic schistosomiasis and with liver steatosis in an area of low prevalence of schistosomiasis in Brazil.

Method: Pains, a city in the state of Minas Gerais, Brazil, had a population of 8,307 inhabitants and a schistosomiasis prevalence of 8%. Four micro-areas comprising 1,045 inhabitants were selected for this study. Blood sample was collected and a complete blood count (CBC) was performed. Eighty-seven (87) patients had low platelet counts (group 1 – 8.3%) and 94 volunteers presenting normal CBC were randomized (group 2 – 8.9%). They underwent clinical and ultrasound examinations. Liver steatosis was determined as either present or absent using abdominal ultrasound. A spleen > 12 cm in length, measured by ultrasound (US), was considered to be increased. Data collected were analyzed using SPSS software version 19.0.

Results: Twenty-two patients (22/25.3%) in group 1 had liver steatosis compared with 11 volunteers (11.7%) in group 2 (p=0.02). Hepatosplenic schistosomiasis was diagnosed in two patients (p>0.05).

Conclusion: Thrombocytopenia was not a good marker of hepatosplenic schistosomiasis mansoni in a low prevalence area in Brazil. Liver steatosis was associated with thrombocytopenia in our study.

Keywords: fatty liver, *Schistosoma mansoni*, thrombocytopenia.

Study conducted at the Department of Infectology and Tropical Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

Article received: 12/1/2016

Accepted for publication: 12/19/2016

*Correspondence:

Departamento de Infectologia e Medicina Tropical – UFMG
Address: Av. Alfredo Balena, 190
Belo Horizonte, MG – Brazil
Postal code: 30130-100
lamber@uai.com.br

<http://dx.doi.org/10.1590/1806-9282.63.06.532>

INTRODUCTION

It has been estimated that 230 million people worldwide are infected with *Schistosoma* spp., with an additional 779 million at risk of infection. Currently, 2 to 6 million individuals are considered infected in Brazil.¹

Most of the infected individuals are asymptomatic, but 5 to 10% develop periportal liver fibrosis with portal hypertension and splenomegaly. Pathologically dense bands of fibrosis around the portal tract are typical of *Schistosoma mansoni*.²

Schistosomal periportal fibrosis is usually assessed using imaging methods, and abdominal ultrasonography (US) has become the imaging technique of choice.³ However, the identification of other non-invasive, inexpensive, and simple routine laboratory tests for use as surrogate markers is of interest.⁴⁻⁶

Recently, thrombocytopenia has been shown to identify hepatosplenomegaly in *Schistosoma*-endemic areas and is a promising marker of hepatosplenic schistosomiasis mansoni. Drummond et al., working in an area of moder-

ate to high endemicity, showed that thrombocytopenia (platelets $< 143,000/\text{mm}^3$) separated individuals with and without hepatosplenic schistosomiasis.⁶

Liver steatosis (also called fatty liver) refers to the abnormal retention of lipids within a cell. Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease worldwide with prevalence estimates ranging from 25 to 45% in most studies.^{7,8} It covers a wide spectrum of hepatic disorders including plain steatosis and steatohepatitis (steatosis with inflammation) that can progress to liver fibrosis and cirrhosis.^{9,10}

In the present study, we investigated the association of thrombocytopenia with hepatosplenic schistosomiasis and liver steatosis in an area of low prevalence of schistosomiasis in the Southeast of Brazil.

METHOD

This is a cross-sectional study carried out from July to November 2014, including residents of a lowly endemic area for *Schistosoma mansoni*.

Study location

Pains is a city with 8,307 inhabitants, distant 217 km from Belo Horizonte, capital of the state of Minas Gerais, Brazil. It has a total area of 418 km², with a population density of 19 people/km² and human development index (HDI) of 0.783.¹¹

During the period of data collection, prevalence of schistosomiasis in this area was at 8% based on two quantitative stool examinations. All inhabitants from four micro-regions, namely Alvorada, Vila Crispin, Matinha and Posto Agropecuário, totaling 1,637 individuals aged 9-92 years, were invited to participate in our study.

Study population

After signing an informed consent, a complete blood count (CBC) of 1,045 participants were performed. Eighty-seven (87) patients had low platelet counts (group 1 – 8.3%) and 94 randomly chosen volunteers had normal CBC (group 2 – 8.9%). Information on demographics, clinical examination and the results of the Kato-Katz stool examination technique¹² were stored in a data bank for data analysis using SPSS 19.0 software.

Clinical examination

The 181 participants underwent anamnesis and physical examination carried out by one of the authors (JRL). Particular attention was given to the abdominal examination, specifically the right hepatic lobe, which was examined

along the anterior axillary line, and the left hepatic lobe, examined along a line passing through the xiphoid process. The spleen was palpated and measured under the left costal margin with the patient in the dorsal decubitus position during deep inspiration.

Diagnosis of hepatosplenic schistosomiasis

The diagnosis was based on the following criteria: clinical evidence (hepatomegaly and splenomegaly) and ultrasound showing characteristic periportal fibrosis of the liver.

Ultrasound

All participants underwent abdominal US examination using a portable Medison Sonoace 1500 system with a 3.5-MHz probe (Samsung, Korea), being examined according to the protocol proposed by the World Health Organization (WHO) for US assessment of *Schistosoma*-related morbidity.¹³ In our study, we used a spleen size cut-off point of > 12 cm (longitudinal diameter).

Liver steatosis

US evaluation of fatty liver typically consists of a qualitative visual assessment of hepatic echogenicity, measurements of the difference between the liver and kidney in echo amplitude, evaluation of echo penetration into the deep portion of the liver, and determination of the clarity of blood vessel structures in the liver (Figure 1A). Steatosis was characterized as present or absent.^{14,15}

Ethical considerations

This study was approved by the Human Research Ethical Board of the Federal University of São João del-Rei and of the Faculty of Medicine of the Federal University of Minas Gerais (number 856.022).

Statistical analysis

Questionnaire data and results of physical exams and US were transferred into an EpiData database, software version 3.1 (EpiData Association, Odense, Denmark), and analyzed using the Statistical Package for Social Sciences (SPSS) 19.0 (SPSS, IBM Company, Chicago, IL). Categorical variables were compared using χ^2 Pearson test. Whenever variables in the univariate analysis presented $p < 0.20$ they were included in the multivariate logistic regression analysis to evaluate the association with thrombocytopenia $< 143,000/\text{mm}^3$. Multivariate logistic regression was also performed to identify the independent association of significant variables with the presence of liver steatosis.

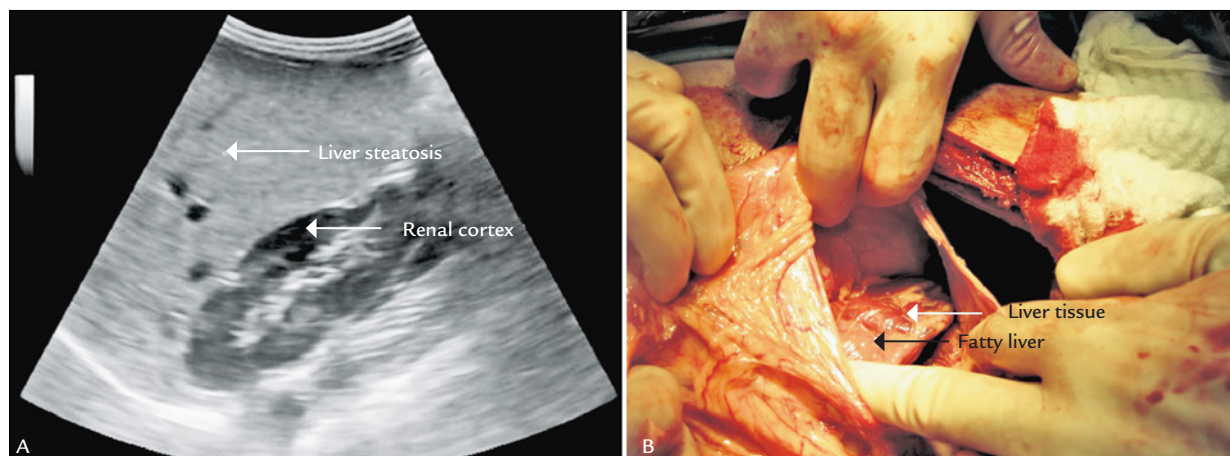


FIGURE 1 A. Ultrasonography of liver steatosis. B. Hepatosplenic schistosomiasis and liver steatosis.

RESULTS

The demographic and clinical data of the participants are summarized in Table 1. All variables in the univariate analysis with $p < 0.20$ were included in the model and age, gender, skin color, body mass index (BMI), general health status and liver steatosis were selected for further analysis. In the multivariate analysis, except for age, no significant correlation was detected, but a high frequency of liver steatosis called attention and we decided to investigate the association with other variables.

The association of liver steatosis with thrombocytopenia and BMI was found significant in the multivariate logistic regression (Table 2).

DISCUSSION

Our study revealed a significant association of liver steatosis with body mass index (BMI) ($p < 0.01$) and thrombocytopenia ($p < 0.02$). Unexpectedly, no correlation was found between thrombocytopenia and hepatosplenic schistosomiasis in this lowly endemic area for *Schistosoma*. In previous studies, thrombocytopenia was a good marker of schistosomiasis in highly endemic areas.^{5,7} This opens new ways of approaching the subject. NAFLD was associated with thrombocytopenia presently and has been described previously.^{16,17} Additionally, the association of steatosis with schistosomiasis may aggravate liver disease, increasing the frequency of fibrosis, portal hypertension and liver cirrhosis.

In areas of high standard of living, the relation between thrombocytopenia and liver steatosis is a possible explanation for the finding of low platelet counts in the blood. In a lowly endemic area for schistosomiasis, as in the present study, only 2 out of 181 (1.1%) individuals had typical periportal fibrosis caused by schistosomiasis and portal hypertension.

With the rising prevalence of obesity and metabolic disorders, liver steatosis has become a leading cause of chronic liver disease in Western countries. For example, steatosis is described in 46% of heavy drinkers, 40-69% of patients with diabetes and in 50-80% of the obese population.^{18,19} In Brazil, obesity is also a serious public health problem. However, social classes are not homogeneously distributed in the country: there is an increasing group of high and middle class people in the southeast, and smaller areas of low income people in the northeast of Brazil.²⁰

Pains is a city located in a high- and middle-income area and most people were well nourished (35.9% of the population was overweight or obese) by the time of our study, while in the northeast of Minas Gerais the prevalence of overweight is low. The medical, educational and social assistance was superior in Pains than those offered in other poorer areas. Moreover, the Brazilian Program for Schistosomiasis Control has been active in the last 10 years in this city.

A number of studies demonstrated an association between platelet counts and the severity of liver injury.²¹⁻²⁵ Yoneda et al. and Ruiz-Arguelles et al. concluded that NAFLD should be considered as a cause of thrombocytopenia.^{16,17}

Normally, the spleen stores one-third of the platelets that are produced in the body, maintaining a balance with the circulating platelets. Patients with cirrhosis, schistosomiasis, portal hypertension or splenomegaly may have significant degrees of "apparent" thrombocytopenia (with or without leukopenia and anemia), but they rarely have clinical bleeding, since their total platelet mass is usually normal.

Whether the presence of schistosomal periportal fibrosis is associated with NAFLD would be an interesting topic for further study. In our hospital, one patient underwent surgical intervention for treatment of portal

TABLE 1 Demographic and clinical variables of groups 1 (with thrombocytopenia) and 2 (without thrombocytopenia) in Brazil from July to November 2014.

Demographic variables	Thrombocytopenia		p-value*
	No (n=94) Group 2	Yes (n=87) Group 1	
Genre			
Male	64 (68.1%)	48 (55.2%)	0.074
Age			
Median	22.0	53.0	<0.001
Color			
White	34 (36.2%)	46 (52.9%)	
Black	27 (28.7%)	11 (12.6%)	0.078
Dark-skinned	33 (34%)	25 (28.7%)	
Use of alcohol			
Yes	26 (27.7%)	23 (26.4%)	0.823
No	65 (69.1%)	62 (71.3%)	
Clinical variables	Thrombocytopenia		p-value*
	No (n=94) Group 2	Yes (n=87) Group 1	
General state			
Good	92 (97.9%)	76 (87.4%)	0.019
Regular	1 (1.1%)	10 (11.5%)	
Body mass index (BMI)			
Median	22.1	24.8	<0.001
Hepatosplenic schistosomiasis			
Yes	1 (1.0%)	1 (1.1%)	
No	93 (98.9%)	86 (98.8%)	0.954
Liver steatosis			
Yes	11 (11.7%)	22 (25.3%)	
No	83 (88.3%)	65 (74.7%)	0.021
Gastrointestinal bleeding			
Yes	6 (6.4%)	7 (8.0%)	0.679
No	86 (91.5%)	79 (90.8%)	
Platelets			
Median	218,000	123,000	0.958

Logistic regression χ^2 Pearson test.**TABLE 2** Association between the independent variables body mass index (BMI) and thrombocytopenia and the presence of liver steatosis. Pains, state of Minas Gerais/Brazil from July to November 2014.

Independent variables	Odds ratio (95CI)	p-value*
BMI	1.21 (1.2-1.8)	<0.001
Thrombocytopenia < 143,000/mm ³	16.66 (1.4-93.2)	0.024

*Multivariate logistic regression.

hypertension, and a photograph documented the association during the surgical procedure (Figure 1B).

The association of thrombocytopenia with hepatosplenic schistosomiasis motivated our study. Our intention was to investigate the soundness of using thrombocytopenia as a marker of hepatosplenic schistosomiasis. In the end, thrombocytopenia was, in fact, associated with NAFLD. A possible explanation for disagreement is that the association of thrombocytopenia with hepatosplenic schistosomiasis previously occurred in highly endemic areas,⁶ while, presently, our investigation was performed in an area of low prevalence (8%) and low morbidity (two patients with hepatosplenic schistosomiasis). We conclude that thrombocytopenia is a good marker of liver steatosis in this lowly endemic area for schistosomiasis. The association of schistosomiasis with thrombocytopenia was not confirmed in the present study.

ACKNOWLEDGMENTS

We thank Mrs. Virgina Vilela Rabelo, Municipal Secretary of Pains and Miss Sandra Costa Drummond (Secretary of Minas Gerais State) for their help during the development of all stages of this study. We also acknowledge Mr. Francisco for his technical assistance. We thanks the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (Fapemig, Brazil) and Conselho Nacional de Desenvolvimento Científico e Tecnológico of the Ministry of Science, Technology and Innovation of Brazil (CNPq) for funding this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Trombocitopenia como marcador de esteatose hepática em áreas de baixa endemicidade de esquistossomose mansoni

Introdução: Trombocitopenia é um achado comum em pacientes que residem em áreas com alta endemicidade de esquistossomose mansônica. Recentemente, diferentes graus de esteatose hepática também têm sido associados a níveis baixos de plaquetas em todo o mundo. Investigamos a associação de níveis séricos de plaquetas com a forma grave da esquistossomose e com esteatose hepática em área de baixa prevalência de esquistossomose no Brasil.

Método: Pains, cidade localizada no estado de Minas Gerais/Brasil, tem população de 8.307 habitantes e prevalência de esquistossomose de 8%. Em quatro microáreas dessa região, 1.045 habitantes foram avaliados para o estudo. Amostra de sangue foi coletada para realização do

hemograma. Oitenta e sete (87) pessoas com níveis baixos de plaquetas formaram o grupo 1 (8,3%), e 94 voluntários com hemograma normal foram randomizados para compor o grupo 2 (8,9%). Todos os participantes dos grupos 1 e 2 foram submetidos a exame clínico e ultrassonografia (US) abdominal. Esteatose hepática foi caracterizada como presente ou ausente pela ultrassonografia (US) abdominal. Baços com mais de 12 cm de comprimento à US foram considerados aumentados. Os dados coletados foram analisados pelo programa de estatística SPSS 19.0.

Resultados: Vinte e dois (22) indivíduos do grupo 1 (25,3%) e 11 do grupo 2 apresentaram esteatose hepática (11,7%) ($p=0,02$). Esquistossomose hepatoesplênica foi diagnosticada em dois pacientes ($p>0,05$).

Conclusão: Trombocitopenia não foi um bom marcador de esquistossomose mansônica hepatoesplênica em área de baixa prevalência da esquistossomose no Brasil. Esteatose hepática foi associada com trombocitopenia no presente estudo.

Palavras-chave: esteatose hepática, *Schistosoma mansoni*, trombocitopenia.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Vigilância da Esquistossomose Mansoni: diretrizes técnicas / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. 4. ed. Brasília: Ministério da Saúde; 2014. 146 p.
2. Lambertucci JR. Revisiting the concept of hepatosplenic schistosomiasis and its challenges using traditional and new tool. Rev Soc Bras Med. 2014; 47(2):120-36.
3. Voieta I, Queiroz LC, Andrade LM, Silva LC, Fontes VF, Barbosa Jr A, et al. Imaging techniques and histology in the evaluation of liver fibrosis in hepatosplenic schistosomiasis mansoni in Brazil: a comparative study. Mem Inst Oswaldo Cruz. 2010; 105(4):414-21.
4. Lambertucci JR, Silva Santos LC, Antunes CM. Aspartate aminotransferase to platelet ratio index blood platelet count are good markers for fibrosis evaluation in schistosomiasis mansoni. Rev Inst Med Trop. 2007; 40(5):599.
5. Lambertucci JR, dos Santos Silva LC, Andrade LM, de Queiroz LC, Carvalho VT, Voieta I, et al. Imaging techniques in the evaluation of morbidity in schistosomiasis mansoni. Acta Trop. 2008; 108(2-3):209-17.
6. Drummond SC, Pereira PN, Otoni A, Chaves BA, Antunes CM, Lambertucci JR. Thrombocytopenia as a surrogate marker of hepatosplenic schistosomiasis in endemic areas for Schistosomiasis mansoni. Rev Soc Bras Med Trop. 2014; 47(2):218-22.
7. Willians CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and a liver biopsy: a prospective study. Gastroenterology. 2011; 140(1):124-31.
8. Lee SS, Park SH. Radiologic evaluation of nonalcoholic fatty liver disease. World J Gastroenterol. 2014; 20(23):7392-402.
9. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol. 2015; 13(4):643-54.
10. Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al.; LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol. 2013; 59(3):550-6.

11. Pains [cited 2015 Oct. 11]. Available from: <http://www.pains.mg.gov.br/>.
12. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. *Rev Inst Med Trop.* 1972; 14(6):397-400.
13. World Health Organization. Ultrasound in schistosomiasis. A practical guide to the standardized use of ultrasonography for the assessment of schistosomiasis-related morbidity. UNDP/World Bank/WHO/Special Programme for Research & Training in Tropical Diseases (TDR). World Health Organization / TDR / STR / SCH document. Geneva, Switzerland, 2000 [cited 2015 Oct. 11]. Available from: <http://www.who.int/tdr/publications/documents/ultrasound-schistosomiasis.pdf>.
14. Seong HP, Seung SL. Radiologic evaluation of nonalcoholic fatty liver disease. *Worl J Gastroenterol.* 2014; 20(23):7392-402.
15. Papagianni M, Sofogianni A, Tziomalos K. Non-invasive methods for diagnosis of nonalcoholic fatty liver disease. *World J Hepatol.* 2015; 7(4):638-48.
16. Ruiz-Argüelles GJ, Velazquez-Sanchez-De-Cima S, Zamora-Ortiz G, Hernandez-Reyes J, Ruiz-Delgado GJ. Nonalcoholic fatty liver disease may cause thrombocytopenia. *Acta Haematol.* 2014; 132(2):159-62.
17. Yoneda M, Fujii M, Sumida Y, Hyogo H, Itoh Y, Ono M, et al.; Japan Study Group of Nonalcoholic Fatty Liver Disease. Platelet count for predicting fibrosis in nonalcoholic fatty liver disease. *J Gastroenterol.* 2011; 46(11):1300-6.
18. Lazo M, Clark J. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Semin Liver Dis.* 2008; 28(4):339-50.
19. Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med.* 2000; 132(2):112-7.
20. Brasil, Ministério da Saúde. VIGITEL, BRASIL. Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. 2014 [cited 2015 Oct. 11]. Available from: <http://apsredes.org/site2013/vocesaudavel/files/2015/05/PPT-Vigitel-2014-.pdf>.
21. Kajihara M, Okazaki Y, Kato S, Ishii H, Kawakami Y, Ikeda Y, et al. Evaluation of platelet kinetics in patients with liver cirrhosis: similarity to idiopathic thrombocytopenic purpura. *J Gastroenterol Hepatol.* 2007; 22(1):112-8.
22. Park KS, Lee YS, Park HW, Seo SH, Jang BG, Hwang JY, et al. Factors associated or related to with pathological severity of nonalcoholic fatty liver disease. *Korean J Intern Med.* 2004; 19(1):19-26.
23. Kaneda H, Hashimoto E, Yatsuji S, Tokushige K, Shiratori K. Hyaluronic acid levels can predict severe fibrosis and platelet counts can predict cirrhosis in patients with nonalcoholic fatty liver disease. *J Gastroenterol Hepatol.* 2009; 21(9):1459-65.
24. Aster RH. Pooling of platelets in the splenic. *J Clin Invest* 1996; 45(5):645-57.
25. Schmidt KG, Rasmussen JW, Bekker C, Madsen PE. Kinetics and in vivo distribution of 111-In-labelled autologous platelets in chronic hepatic disease: mechanisms of thrombocytopenia. *Scand J Haematol.* 1985; 34(1):39-46.

Analysis of the availability of the resources necessary for urgent and emergency healthcare in São Paulo between 2009-2013

SILVANA HEBE COIMBRA^{1*}, ELIETE DOMINGUEZ LOPEZ CAMANHO², LINDOLFO CARLOS HERINGER¹, RICARDO VIEIRA BOTELHO¹,
CIDIA VASCONCELLOS¹

¹Graduate Program, Instituto de Assistência Médica ao Servidor Público Estadual, São Paulo, SP Brazil

²Fundação para o Desenvolvimento Científico e Tecnológico da Odontologia, São Paulo, SP Brazil

SUMMARY

Introduction: The Regulatory Complex is the structure that operationalizes actions for making resources available to meet the needs of urgent and emergency care in the municipality of São Paulo. In the case of urgent care, needs are immediate and associated with high morbidity and mortality.

Objective: To identify the most frequently requested resources, the resolution capacity and the mortality rate associated with the unavailability of a certain resource.

Method: Our study was based on data from medical bulletins issued by the Urgent and Emergency Regulation Center (CRUE) in the city of São Paulo from 2009 to 2013.

Results: 91,823 requests were made over the five years of the study (2009 to 2013). Neurosurgery requests were the most frequent in all years (4,828, 5,159, 4,251, 5,008 and 4,394, respectively), followed by computed tomography (CT) scans, adult intensive care unit (ICU) beds, cardiac catheterization, and pediatric ICU beds. On average, requests for neurosurgery, adult ICU, pediatric ICU, CT scans, catheterization and vascular surgery were answered in 70%, 27%, 39%, 97%, 87% and 77% of cases. The total number of deaths relating to requests for neurosurgery, CT scans, adult ICU, pediatric ICU, catheterization and vascular surgeon assessment were 182, 9, 1,536, 1,536, 135, 49 and 24 cases, respectively.

Conclusion: There is a lack of resources to meet urgent and emergency needs in the city of São Paulo.

Keywords: health systems, health care coordination and monitoring, emergency medical services, health care (public health), unified health system, neurosurgery.

Study conducted by the Health Sciences Graduate Program at Instituto de Assistência Médica ao Servidor Público Estadual, São Paulo, SP Brazil

Article received: 10/11/2016
Accepted for publication: 11/20/2016

*Correspondence:

Address: Av. Ibirapuera, 981,
Cedep, 2º andar
São Paulo, SP – Brazil
Postal code: 04029-000
silvanasalomao@uol.com.br

<http://dx.doi.org/10.1590/1806-9282.63.06.538>

INTRODUCTION

The metropolitan areas of large urban centers require a large amount of resources for the treatment of the population's health.¹ In urgent and emergency cases, these needs are immediate due a high morbidity and mortality.²⁻⁴

The Regulatory Complex is the structure that operationalizes actions for making resources available to a particular population, providing them according to pre-established criteria and protocols to be followed. It was created to ensure access to the resources by the many existing demands.⁵

In this sense, "regulation" means the intermediation of actions to improve access in a planned manner, in order to reduce shortfalls in the pursuit of efficiency, quality and effectiveness.⁶

The Municipal Regulatory Complex of São Paulo is administrated by the Municipal Health Department (SMS)

and regulates the population's access to health resources in the city of São Paulo.⁷

OBJECTIVE

To identify the need for the most frequently requested resources, the resolution capacity and mortality rate associated with the unavailability of the resource and trends throughout the years of our study.

METHOD

Our study was based on data from medical bulletins issued by the Urgent and Emergency Regulation Center (CRUE) in the city of São Paulo from 2009 to 2013.

The survey was conducted with consent of the SMS of São Paulo and approval by the Research Ethics Committee (No. 519,944, February 2014). There are no conflicts of interest among any of the authors in relation to this manuscript that need to be declared.

Variables included

The need for urgent and emergency resources

The six most frequently requested resources for emergency care in the city of São Paulo (absolute figures) in the five years of the study were tabulated. Absolute figures and proportions for the other requested resources were described, as well as the trends per year.

Resolution of requests

Resolution capacity was defined by the number of cases resolved and their percentage in relation to the number of requests. These were described per year of the study.

Deaths per type of request

The number of deaths related to certain request and the percentage in relation to the number of requests and their trends per year were described. Deaths were noted as one of the types of outcomes (resolution) of the request.

Use of the Zero Vacancy ("Vaga Zero") tool

A separate analysis of the Zero Vacancy tool used for care requiring neurosurgical evaluation. The Zero Vacancy tool is based on the Federal Board of Medicine (CFM) no. 1671/03, published in the Federal Official Gazette in July 2003, in accordance with MS (Ministry of Health) Ordinance no. 2048/2002. It states that, even in situations where there are no vacant beds for patient hospitalization, the hospital unit must still guarantee care. From the point of view of urgent and emergency care, there is a tool for access of patients at imminent death risk in the case of inexistent local resources or the refusal of the evaluation from the referential service. Therefore, the amount of care provided with the Zero Vacancy tool was recorded as an increasing percentage over the years of study.

Trends were evaluated between the years of the study in the resource requests, resolution of resources and fatality trends (deaths).

Statistical analysis

EPI INFO 6.0 software and Excel spreadsheets were used.

Data treatment and analysis was performed descriptively, with numbers and percentages.

RESULTS

Need for resources

Largest resource requests

A total of 91,258 requests were made over the five years of the study (2009 to 2013).

The six largest requests were described per year of the study (Figure 1).

Neurosurgery requests were the most frequent in all years. Between 2009 and 2013, 4,828, 5,159, 4,251, 5,008 and 4,394 requests were made, respectively.

CT scan requests were the second most frequent. The type of CT scan most frequently requested was skull. The number of requests per year was 2,946, 2,612, 2,287, 1,641 and 3,106, respectively.

Adult intensive care unit (ICU) beds were the third most frequent request, totaling 2,809, 3,164, 1,869, 1,691 and 1,496, respectively, over the years studied.

The request for cardiac catheterization appeared in the year 2010 for the first time on record, as the fourth most frequent request. Between 2009 and 2013, 811, 1,041, 1,803 and 1,146 examinations were requested, respectively.

Pediatric ICU admission was the fifth cause of requests. These occurred at a frequency of 897, 1,002, 822, 818 and 686, respectively. Other less frequent requests were described in Figure 1.

Resolutions of requests

The resolution of the requested resources were described in absolute figures and as a proportion of the resolutions in relation to the requested resource, over the five years of the study (Figure 1).

Requests for neurosurgery, adult ICU, pediatric ICU, CT scans, catheterization and vascular surgery were answered (resolved) in 70%, 27%, 39%, 97%, 87% and 77% of cases, respectively.

Deaths by type of unanswered request (Table 1)

Over the five years of the study, the total number of deaths relating to requests for neurosurgery, CT scans, adult ICU, pediatric ICU, catheterization and vascular surgeon assessment were 182, 9, 1,536, 135, 49 and 24 cases, respectively.

Use of the Zero Vacancy tool

The Zero Vacancy tool was used 298, 535, 512, 690 and 814 times in the years 2009 to 2013, respectively (Figure 2).

TABLE 1 Number of deaths/year (per type of request).

Request	Number of deaths					Total
	2009	2010	2011	2012	2013	
Neurosurgery	25	27	28	58	44	182
Tomography	1	3	1	3	1	9
Adult ICU	301	472	303	243	217	1,536
Pediatric ICU	15	28	30	40	22	135
Catheterization	-	5	17	15	12	49
Vascular surgery	-	3	4	7	10	24

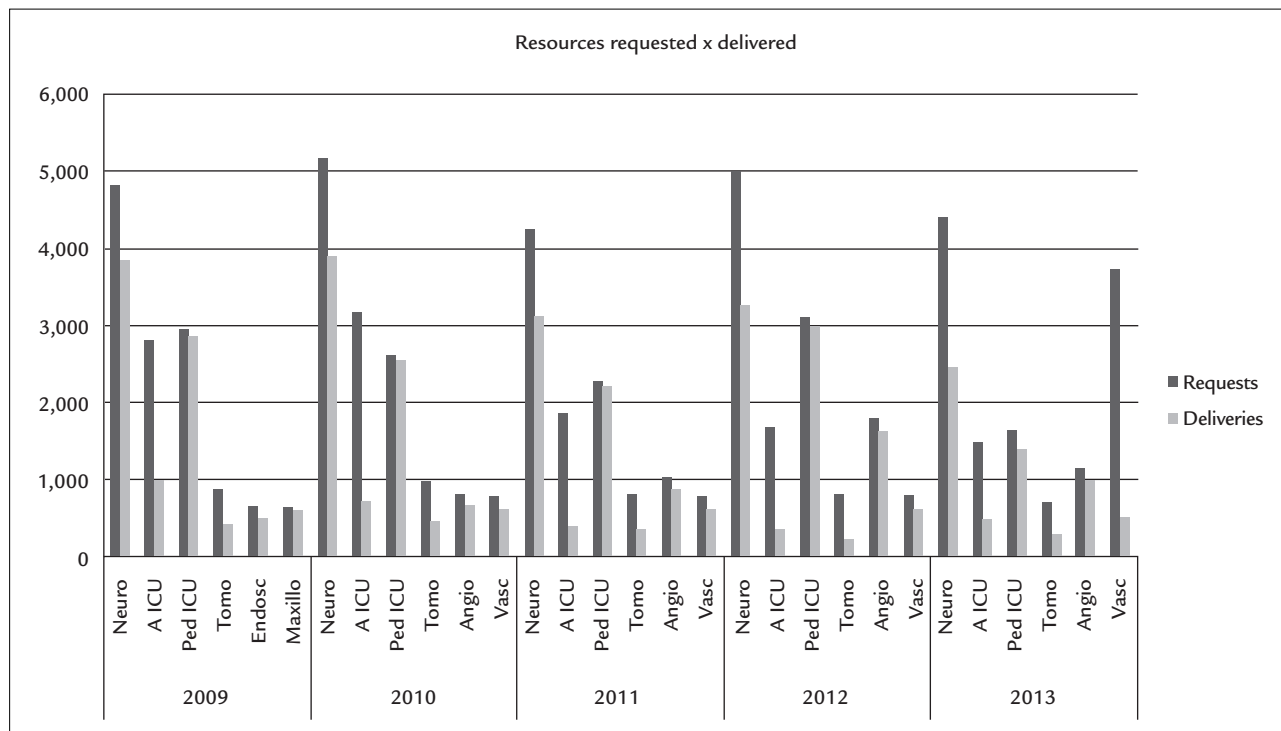


FIGURE 1 Trends in resources requested and delivered from 2009 to 2013.

Neuro: neurosurgery; A ICU: adult ICU; Tomo: CT scan; Ped ICU: pediatric ICU; Endosc: endoscopy; Angio: angiography; Vasc: vascular surgery; Maxillo: oral and maxillofacial surgery.

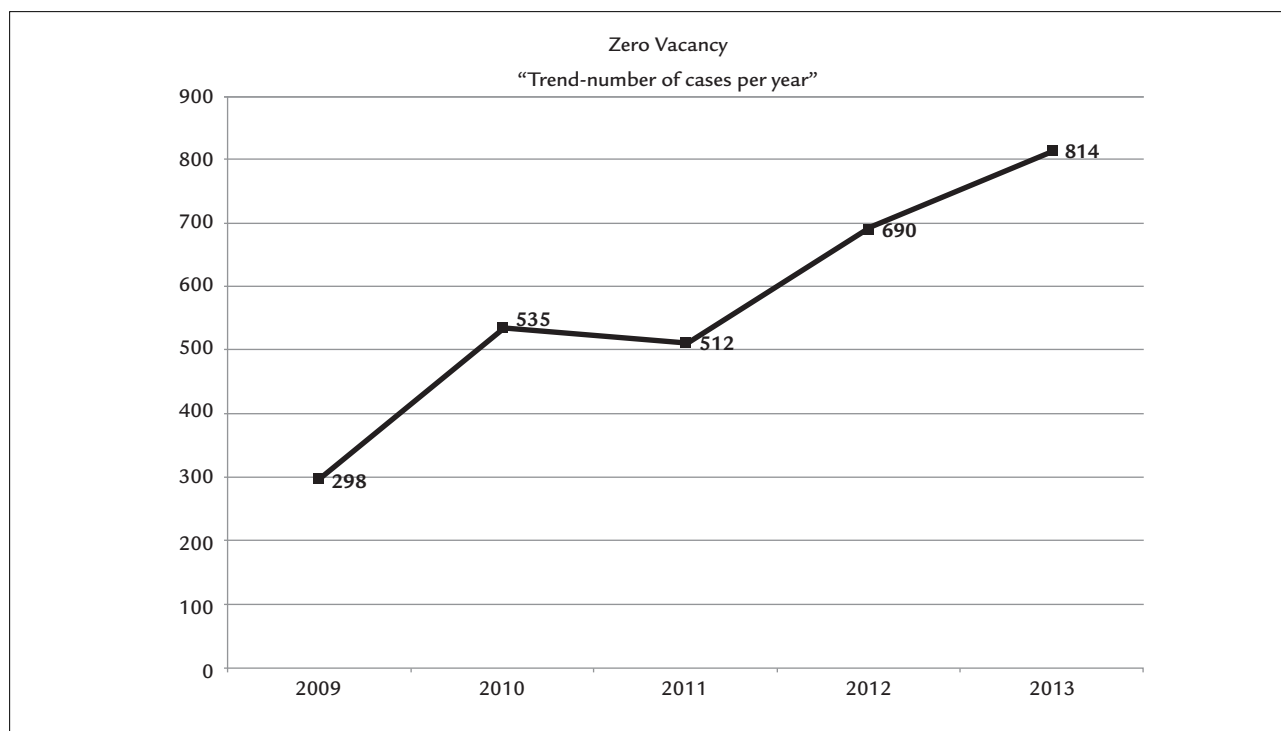


FIGURE 2 Trends in neurosurgery request resolution, such as Zero Vacancy, per year.

Trends

Trends in resource requests

The requests for neurosurgery remained high throughout the period but stable, with no upward or downward trends. Catheterization requests also remained stable (Figure 1).

Tomography and adult ICU beds had a decrease in requests. In 2009, 2,946 tomography scans were requested, and 1,641 in the year 2013. In 2009, 2,809 beds were requested at the adult ICU, while in 2013 this number was 1,496. Vascular surgery had an increase of 4.7 times in the number of requests over the five years studied (Figure 1).

Trends in resource resolutions

There was a trend towards a decrease in resolutions for neurosurgery. The percentage of resolutions in the other requests was stable. The resolution percentage related to the need for pediatric and adult ICU resources was very low, at 39 and 27%, respectively.

Trends in mortality (Table 1)

The average mortality rate associated with the need for adult ICU is 8.4 times that of neurosurgery. The trend of fatality rates in the adult ICU, although high, decreased between 2010 to 2013, falling from 472 deaths to 217. The mortality of neurosurgery and vascular surgery shows an upward trend over the period.

Trends in the use of the Zero Vacancy tool

The Zero Vacancy tool was used more times in 2013 than in 2009, thus showing an upward trend of use (Figure 2). This trend increased inversely with the availability of the “neurosurgery” resource at the CRUE of São Paulo.

DISCUSSION

In Brazil, the annual investment in the health area is 4.1% of the gross domestic product (GDP), which is considered insufficient in providing care and access for all.¹

At the time of the study, the city of São Paulo, Brazil’s most populous city, had a population of 10,886,518 inhabitants, and was 9th in total area.²

The implementation of the Regulatory Complex was undertaken to prioritize the flow of care and reconcile the needs with the capacity of each health unit.⁶ The CRUE-SP regulates the inter-hospital flow of emergency care in the city of São Paulo for diagnosis, clinical evaluation, surgical or ICU needs linked to the public health-care system (SUS). It is estimated that the absence of the CRUE’s intervention in the regulation would lead to greater mortality among patients.

In order to evaluate the capacity to meet the needs of urgencies and emergencies in the years 2009 to 2013, we investigated the most frequent requests. Neurosurgery evaluation (NCR), vascular surgery evaluation, CT scans, adult ICU, catheterization and pediatric ICU were the greatest care needs.

Tomography requests were met in 98 to 99% of cases. The lack of local imaging resources implies the need for referral to the Regulation Center in order to remedy these local shortcomings, as recommended by the Organization for Economic Cooperation and Development (OECD).⁸

Catheterization requests were incorporated into the CRUE-SP in 2010 and met in 80 to 88% of cases.

Adult ICU requests were only met in 20.8 to 36% of requests, due to lack of resources.

For the pediatric ICU, there was an average request resolution of 40% of requests.

The resource most often requested among all was the neurosurgical service. There is a lack of neurosurgical care in the network.⁹ Head trauma and stroke are a frequent cause of demand for imaging examinations for diagnosis, intensive care, neurosurgical evaluation and treatment. These are serious conditions, with a high potential for morbidity and mortality.¹⁰

A discussion on the trends in the provision of resources and their consequences is required. The mortality of the most requested resource, that is, neurosurgery, increased in 2012 and 2013. Resolution of the neurosurgery resource has been gradually decreasing and the use of the Zero Vacancy tool has been increasing, probably to resolve the demand for the latter. We do not have information on the prognosis of patients cared for under the Zero Vacancy tool.

Mortality related to lack of cardiac catheterization has decreased, probably due to greater supply of the resource through centers that carry out the procedure contracted by the SMS.

Mortality due to lack of vascular surgery continued increasing in the years investigated.

Less frequent needs such as oral and maxillofacial surgery, endoscopy etc., which only appeared among the most frequent requests in the first year, also deserve the attention of specific studies.

The data shows the lack of resources to meet urgent and emergency needs in the city of São Paulo. The trends showed no improvement in the number of resource requests in the years studied. There is high mortality associated with the request for adult and pediatric ICU beds.

There was an increased use of the Zero Vacancy resource in the demand for neurosurgery, as opposed to a progressive decrease in the resolution of neurosurgery services.

Knowledge of the real needs of the population has not been established since SMS Ordinance 245/2007.¹¹ The study and mapping of these needs has the potential to reveal the lack of resources and the risks to the population, in order to guide the allocation of the necessary resources.

CONCLUSION

The most requested resource was neurosurgery, followed by CT scans, adult ICU beds, cardiac catheterization and pediatric ICU beds. There was a downward trend in neurosurgery resolutions associated with increased use of the Zero Vacancy resource. Resolution of pediatric and adult ICU needs was low. There was significant mortality associated with the lack of resources.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

RESUMO

Análise da disponibilidade de recursos necessários para o atendimento de urgência e emergência em saúde no município de São Paulo entre 2009-2013

Introdução: O Complexo Regulador é a estrutura que operacionaliza as ações de acesso aos recursos para atendimento de urgência e emergência médicas no município de São Paulo. Nas urgências, as necessidades são imediatas e associadas a elevada morbidade e mortalidade.

Objetivo: Identificar os recursos mais frequentemente solicitados, a capacidade de resolução e o índice de mortalidade associado à falta do recurso.

Método: Este trabalho foi baseado nos dados dos boletins médicos da Central de Regulação de Urgência e Emergência (CRUE) do Município de São Paulo, nos anos de 2009 a 2013.

Resultados: Foram feitas 91.823 solicitações nos cinco anos do estudo (2009 a 2013). As solicitações de neurocirurgia foram as mais frequentes em todos os anos (4.828, 5.159, 4.251, 5.008 e 4.394, respectivamente), seguidas pela tomografia, vaga de UTI adulto, cateterismo cardíaco e UTI

pediátrica. Em média, os pedidos de neurocirurgia, UTI adulto, UTI infantil, tomografia, cateterismo e cirurgia vascular foram atendidos em 70%, 27%, 39%, 97%, 87% e 77% dos casos. O número total de óbitos associados à falta de recurso para neurocirurgia, tomografia, UTI adulto, UTI infantil, cateterismo e avaliação de cirurgião vascular foram de 182, 9, 1.536, 135, 49 e 24 casos, respectivamente.

Conclusão: Há elevada falta de recursos para suprimimento das necessidades de urgência e emergência no município de São Paulo.

Palavras-chave: sistemas de saúde, regulação e fiscalização em saúde, serviços médicos de emergência, serviços de saúde, sistema único de saúde, neurocirurgia.

REFERENCES

1. Paulus Júnior A, Cordoní Júnior L. Políticas públicas de saúde no Brasil. Espaço Saúde. 2006; 8(1):13-9.
2. Barbosa DV. Regulação médica do fluxo das urgências: análise do complexo regulador de Goiânia [dissertation]. Anápolis (GO): UNIEVANGÉLICA – Centro Universitário de Anápolis; 2012.
3. Dallari SG, Pittelli SM, Pirotta WR, Oliveira ML. Atendimento médico e urgência na grande São Paulo. Saúde Soc. 2001; 10(2):75-99.
4. Martins EFF. Avaliar o cumprimento do protocolo nacional de traumatismo crânio-encefálico no serviço de urgência do hospital de Santo Antônio [dissertation]. Porto (Portugal): Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto; 2011. Available from: <https://repositorio-aberto.up.pt/bitstream/10216/52783/2/Tese%20Mestrado%2020Eduarda%20Martins%20texto%20corrido.pdf>.
5. Brasil. Ministério da Saúde. Portaria n° 373, de 27 de fevereiro de 2002. Available from: http://bvsmms.saude.gov.br/bvs/sadelegis/gm/2002/prt0373_27_02_2002.html
6. Paim J, Travassos C, Almeida C, Bahia L, Macinko J. The Brazilian health system: history, advances, and challenges. Lancet. 2011; 377(9779):1778-97.
7. Brasil. Ministério da Saúde. Portaria n° 1.559, de 1 de agosto de 2008. Available from: http://bvsmms.saude.gov.br/bvs/saudelegis/gm/2008/prt1559_01_08_2008.html
8. Santos DL, Leite HJ, Rasella D, Silva SA. Capacidade de produção e grau de utilização de tomógrafo computadorizado no Sistema Único de Saúde. Cad Saúde Pública. 2014; 30(6):1293-304.
9. Brasil. Ministério da Saúde. Secretaria de Vigilância à Saúde. Instituto Brasileiro de Geografia e Estatística – IBGE. Sistema de informações de mortalidade 2013. Available from: <http://ces.ibge.gov.br/base-de-dados/metadados/ministerio-da-saude/sistema-de-informacoes-de-mortalidade-sim>.
10. Martins SCO, Seewald RA, Brondani R, Alves CV. Doença cerebrovascular. In: Chaves MF, Finkelsztejn A, Stefani MA, editors. Rotinas em neurologia e neurocirurgia. Porto Alegre: Artmed; 2008. p. 93-6.
11. São Paulo. Secretaria Municipal de Saúde de São Paulo. Portaria n° 245/2007 – CIRS/SMS.G. Normatiza o fluxo de atenção às urgências e emergências no âmbito do Município de São Paulo. Diário Oficial do Município de 31 de mar de 2007, folha 24.

Hospitalization due to exacerbation of COPD: “Real-life” outcomes

LILIA AZZI COLLET DA ROCHA CAMARGO^{1*}, MARIA VERA OLIVEIRA CASTELLANO², FÁBIO CHECCHIA FERREIRA³, FLÁVIO VIEIRA DE FARIA³, NELSON CARVAS JR.⁴

¹MD, MSc in Health Sciences from Instituto de Assistência Médica ao Servidor Público Estadual (Iamspe). Assistant Physician of the Pulmonology Service, Hospital do Servidor Público Estadual (HSPE), São Paulo, SP, Brazil

²MD, Director of the Pulmonology Service, HSPE, São Paulo, SP, Brazil

³MD, Specialist in Pulmonology, Pulmonology Service, HSPE, São Paulo, SP, Brazil

⁴Specialist in Statistics and Graduate Program Student at Iamspe, São Paulo, SP, Brazil

SUMMARY

Introduction: Hospitalization due to chronic obstructive pulmonary disease exacerbation (eCOPD) may indicate worse prognosis. It is important to know the profile of hospitalized patients and their outcome of hospitalization to customize and optimize treatment.

Method: Evaluation of patients hospitalized for eCOPD, with ≥ 10 pack/years and ≥ 1 previous spirometry with airway obstruction over the course of one year at the pulmonology service of a general hospital, applying: COPD assessment test (CAT); mMRC and Visual Analogue Scale (VAS) for dyspnea; hospitalized anxiety and depression questionnaire (HAD); Divo's comorbidities and Cote index; spirometry; and laboratory tests including number of eosinophils, C-reactive protein (CRP), brain natriuretic protein (BNP). Patient progression, number of days of hospitalization and hospitalization outcomes were observed.

Results: There were 75 (12%) hospitalizations for eCOPD, with 27 readmissions, nine of which during a period ≤ 30 days after hospital discharge. The main outcomes were: number of days of hospitalization (17 ± 16.5 [2-75]); hospital discharge (30 [62.5%] patients); discharge/rehospitalization (18 [37.5%] patients), eight of them more than once; death (7 [14.5%] patients), five during rehospitalization. We analyzed 48 patients in their first hospitalization. The sample comprised a heterogeneous group separated in three clusters according to age, FEV₁, body mass index (BMI) and CAT. The clusters did not correlate with the main outcomes.

Conclusion: Hospitalization for eCOPD is frequent. The number of readmissions was high and associated with death as an outcome. Patients hospitalized for eCOPD were a heterogeneous group separated in three clusters with different degrees of disease severity and no correlation with hospitalization outcomes.

Keywords: hospitalization for exacerbation of COPD, COPD exacerbation, COPD assessment test, Visual Analogue Scale, COPD death.

Study conducted at the Serviço de Pneumologia do Hospital do Servidor Público Estadual (HSPE), São Paulo, SP, Brazil

Article received: 10/30/2016

Accepted for publication: 11/20/2016

*Correspondence:

Address: Rua Pedro de Toledo, 1.800, 10º andar, ala central São Paulo, SP – Brazil
Postal code: 04029-000
liliaacolcam@gmail.com

<http://dx.doi.org/10.1590/1806-9282.63.06.543>

INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) in São Paulo in men and women is 14 and 18%, respectively. Its diagnosis is made by spirometry and COPD is known to be an under- or overdiagnosed disease for a number of reasons.^{1,2} Episodes of more severe respiratory symptoms requiring change in routine medication used by patients with COPD are considered exacerbations of the disease (eCOPD). Hospital treatment may be necessary due to significant clinical repercussions, insufficient resources at home, failure of outpatient treatment, diagnostic uncertainty, significant comorbidities, and advanced age.³

Cases of eCOPD accounted for 5.8% of all respiratory hospitalizations from 1995 to 2000 in Brazil, and 12% of the patients admitted for eCOPD died.⁴ Between 2000 and 2010, eCOPD was the fifth largest cause of hospitalization through the Brazilian Unified Health System of patients over 40 years of age, with approximately 200,000 admissions and annual expenditure of approximately 72 million reais.⁵

Comorbidities in patients with COPD are important in relation to the outcomes of COPD exacerbations.⁶ Aging is characterized by a mild chronic inflammatory status responsible for the development of comorbidities.

More than half of patients over 65 years old have more than three comorbidities, and one-fifth have more than five.⁷ There is also the development of mood disorders such as anxiety and depression. Both increase physical disability, morbidity and consumption of medical resources,⁸ and can be easily assessed using the Hospital Anxiety and Depression (HAD) Scale validated in Brazil.⁹

Patients with COPD must be evaluated with objective and validated instruments, such as the mMRC scale and the Visual Analogue Scale (VAS) for breathlessness.¹⁰ The COPD Assessment Test (CAT) is multidimensional; it includes items such as respiratory symptoms, dyspnea, daily life activity, sleep and general condition, measuring the impact of the disease on the patient's life both in periods of stability and exacerbation.¹¹⁻¹³

The objective of our study was to evaluate hospitalizations for eCOPD, the profile of patients hospitalized for this condition (demographics, CAT, mMRC, VAS, HAD), duration of hospitalization, and outcomes of the hospitalizations in the pulmonology ward of a general hospital.

METHOD

We included consecutive patients hospitalized in the pulmonology ward of Hospital do Servidor Público Estadual de São Paulo (HSPE) between May/2013 and May/2014, referred from the Emergency Room, the pulmonology outpatient clinic or transferred from another service, with a diagnosis of eCOPD and at least one spirometry result prior to hospitalization showing airflow obstruction characterized by forced expiratory volume in one second over forced vital capacity (FEV₁/FVC) ratio lower than the lowest limit of normality, smoking load ≥ 10 years/pack and capable to respond to mMRC, VAS, CAT e HAD.

The data used in the analysis of the patients were only related to the first hospitalization for eCOPD in the study period. Data from readmission due to eCOPD of patients already included in the study were not considered for analysis except in cases of death.

Assessment at admission to our ward consisted of standardized anamnesis, revision of medical records, application of the mMRC, VAS, CAT and HAD scales, laboratory tests (leukometry and differential leukogram, C-reactive protein [CRP] and brain natriuretic peptide [BNP]), and radiological examinations. Clinical analyses of leukometry and differential leukogram were performed using an Advia 2120i Siemens device, whose results are reviewed within preestablished cut-off parameters: there is revision in the case of leukocytes above 13,000 and eosinophilia above 15%. Plasma CRP is measured using immunoturbidimetric assay (Beckman Coulter AU 680 and/or 5,800 analyzers)

with cut-off point at 0.5 mg/dL. BNP is measured using a chemiluminescence method on a Siemens Centaur device with a cut-off point of 100 picograms (pg)/mL.

Patients received standard treatment for COPD exacerbation.^{14,15} Antibiotics were prescribed after evaluation of symptoms, leukometry, CRP, and radiological and tomographic findings.

Comorbidities

After listing the comorbidities, we separated the relevant ones according to the study by Divo et al.,⁶ in which 12 comorbidities showed independent risk of death:

- Oncological: Lung, pancreatic and esophageal cancer and, for women, breast cancer.
- Pulmonary fibrosis.
- Cardiac: Atrial fibrillation/flutter, congestive heart failure, coronary artery disease.
- Gastrointestinal: Duodenal/gastric ulcer, hepatic cirrhosis.
- Endocrine: Diabetic neuropathy.
- Psychiatric: Anxiety.

Then, we graded the comorbidities according to the Cote index (value ≥ 4 indicates a high probability of death):

- Breast (female), pancreatic, esophageal or lung cancer: 6 points.
- Anxiety among women: 6 points.
- Other cancers, hepatic cirrhosis, atrial fibrillation/flutter, diabetes with neuropathy, and pulmonary fibrosis: 2 points.
- Congestive heart failure, gastric/duodenal ulcer, coronary artery disease: 1 point.

The study protocol was approved by the HSPE Research Ethics Committee under No. 608,487. All participating patients read and signed the informed consent form.

Statistical analysis

Descriptive analysis of the data on hospitalization frequency, anthropometric and spirometric data, number of exacerbations in the previous year, use of O₂ at home, presence of anxiety and/or depression, mMRC, VAS and CAT results, as well as CRP, leukometry and differential leukogram^{16,17} were presented as mean \pm standard deviation, minimum-maximum, or number (percentage), n(%). Age, CAT, body mass index (BMI) and FEV₁ (pre-bd) were standardized to be grouped into a hierarchical cluster analysis using the Ward aggregation method and the square Euclidean distance as a measure of dissimilarity. As a decision criterion on the number of clusters to be retained, a visual inspection of the

dendrogram produced was done, choosing the solution with the lowest number of clusters. The classification of the retained clusters was later refined through a non-hierarchical K-means procedure. One-way ANOVA was used to compare the variables that formed the clusters. The association between categories and clusters that were formed was performed using Pearson's Chi-square and Fisher's exact test if necessary. The Kruskal-Wallis test was performed to identify differences in the quantitative variables among the clusters. All analyzes were performed in SPSS statistics v.21 software, adopting a significance level of $p < 0.05$.

RESULTS

During the study period, there were 639 hospitalizations in the pulmonology ward, of which 102 were initially diagnosed as eCOPD, according to the International Code of Diseases (ICD), while 537 received other diagnoses. Of the 102 patients, 57 patients were excluded: 19 did not have diagnostic confirmation of COPD, and 38 did not meet the inclusion criteria. Of the 537 patients initially admitted with other ICD codes, 30 ultimately had a diagnosis of exacerbation of COPD, i.e., there were 75 (12%) admissions for COPD (Figure 1), of which 27 were readmissions – 18 patients returned once and eight more than once, and of the total number of readmissions, nine were

early readmissions (less than 30 days after last hospital discharge for eCOPD) – and 48 were first-time admissions.

The sample was composed of the 48 patients admitted for the first time, who underwent anthropometric data verification and application of objective tests to assess dyspnea, symptoms (CAT), anxiety and depression, and laboratory parameters.

The duration of the first stay of each patient in the study period was 17 ± 16.5 (2-75) days. The outcomes of the 75 hospitalizations for eCOPD were: 28 (37%) for hospital discharge, 27 (36%) for discharge + readmission, and seven (9%) deaths. Of the seven deaths, five occurred in readmissions.

Table 1 shows that half of the individuals were male; 90% were white; the mean age was 73.5 ± 7.37 (51-94) years; smoking amounted to 44 ± 29 (10-155) pack-years; 37 (77%) were former smokers; 20 (42%) reported exposure to wood stoves; 8 (17%) had had bronchitis in childhood; 33 (69%) had ≥ 2 exacerbations in the previous year; mean follow-up time with a pulmonologist was 6 ± 5 (0.5-17) years; the number of spirometries per patient prior to admission was 3 ± 2 (1-9); pre-bd FEV_1 was 1.1 ± 0.4 (0.4-2.1) L and $44\% \pm 17\%$ (16-79) of the predicted value; 40 (92%) of the patients had a post-bd FEV_1 of 1.1 ± 0.4 (0.5-2.2) L and $46\% \pm 17\%$ (25-88) of the predicted, and 22 (46%) were oxygen dependent.

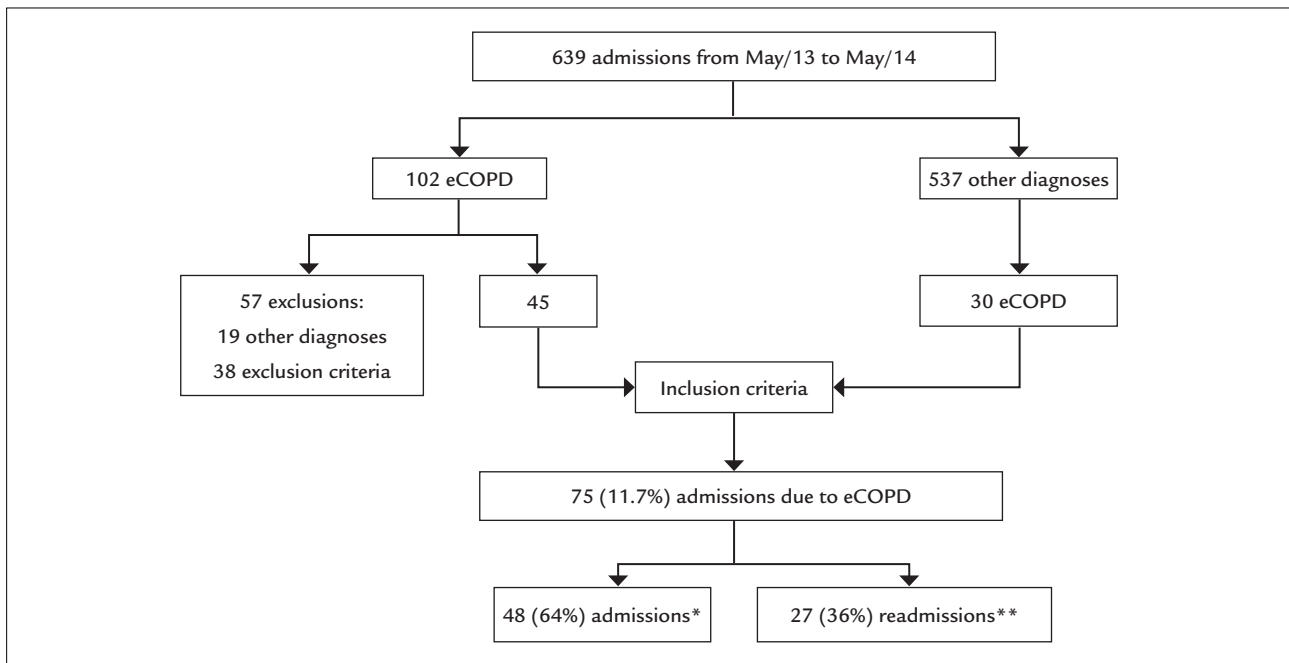


FIGURE 1 Flowchart study.

*First admission in the study period

**18 (37.5%) patients readmitted, 8 more than once, with a total of 27 readmissions, 9 early (≤ 30 days).

30 (62.5%) hospital discharges

7 deaths { 5 deaths occurred in readmissions
2 deaths in the first admission

TABLE 1 Characteristics of the 48 patients.

Results as n (%) or \pm SD (min-max):		
Male	24	50%
White	43	90%
Age	73 \pm 7.4	(51-94 years)
BMI	26 \pm 7	(15-56)
Years-pack	44 \pm 29	(10-155)
Former smokers	37	77%
Exposure to wood stoves	20	42%
Bronchitis in childhood	8	17%
\geq 2 exacerbations in the previous year	33	69%
n. of comorbidities in 48 (100%)*	4.2 \pm 2.2	(1-9)
Divo classification in 24 (50%)	0.8 \pm 0.9	(0-3)
COTE index in 22 (46%)	1.9 \pm 2.6	(0-8)
COTE index \geq 4	10	21%
Time of FUP	6.2 \pm 4.6	(0.5-17)
n. of spirometries/patient	3 \pm 2.1	(1-9)
FEV ₁ , pre-bd L	1.1 \pm 0.4	(0.4-2.1)
% predicted FEV ₁ , pre	44 \pm 17	(16-79)
FEV ₁ /FVC, pre	48 \pm 10	(27-69)
FEV ₁ , post-bd L**	1.1 \pm 0.4	(0.5-2.2)
% FEV ₁ , post**	46 \pm 17	(15-88)
FEV ₁ /FVC, post**	47 \pm 09	(23-65)
Home O ₂ therapy	22	46%

BMI: body mass index (kg/m²); FEV₁, pre or post: forced expiratory volume in one second, performed before or following bronchodilator administration; % predicted: percentage of the predicted value according to age and height; FVC: forced vital capacity; FUP: follow-up with a pulmonologist.

*High blood pressure, cardiovascular diseases, DM, dyslipidemia, hypothyroidism, rheumatic diseases, liver disease, non-dialytic renal insufficiency, cancer, osteoporosis, gastrointestinal diseases.

**40 patients.

The number of comorbidities found in 48 patients was 4.2 \pm 2.2 (1-9): high blood pressure, cardiovascular disease, diabetes mellitus, dyslipidemia, hypothyroidism, rheumatic diseases, liver diseases, non-dialytic kidney failure, cancer, osteoporosis and gastrointestinal diseases. According to the criteria by Divo,⁶ 24 (50%) had comorbidities that increased the risk of death. Ten patients (21%) had Cote score \geq 4, of whom two died.

The causes for the seven deaths were: respiratory failure in four patients who had advanced COPD and used O₂ at home, and cancer in three patients (lung, breast and undetermined primary site carcinomatosis).

The results of the dyspnea, CAT and HAD scales were: high/very high impact of exacerbation in the patient's life according to CAT in 25 (50%) patients, moderate impact in 15 (33%), and low impact in five (11%); degree of dyspnea from 0 (poor) to 100 (optimal) mm according to VAS at 48 \pm 29 (4-100) mm; and mMRC at 3 \pm 1 (1-4).

Anxiety was present in 15 (31%), depression in 17 (35%) and anxiety plus depression in seven (14.5%). Regarding laboratory tests at admission, CRP was increased in 38 (89%) patients; there was leukocytosis (leukocytes > 10,000) in 30 (62.5%); eosinophilia > 2% in eight (17%); and BNP > 100 in 16 (39%), ranging from 303 \pm 201 (112-809).

Age, FEV₁, BMI and CAT were variables correlated with disease severity and grouped for cluster analysis. This analysis was performed with 45 valid measures of CAT, age, pre-bd FEV₁ and BMI, whose values, in addition to the Z score, discriminated three clusters with p<0.05. The square Euclidean distances between patients generated a dendrogram, with three clusters on visual inspection. The classification of each individual in the three clusters was refined with the "K-means" method and is shown in Figure 2.

- Cluster no. 1 had eight (16.7%) patients, 75% female and 25% male with age close to the mean, higher CAT and BMI results, and lower FEV₁.
- Cluster no. 2 included 14 (31%) patients, who were older and had higher CAT results, BMI within normal range and also lower FEV₁.
- Cluster no. 3 had 23 (51%) patients who were younger than the average, with a lower CAT score, BMI compatible with overweight and higher values for FEV₁.

The hospitalization outcomes (discharge, readmission and death) and other characteristics of the sample, except for mMRC, did not present a statistically significant difference between the clusters. The mMRC presented a statistically significant difference among the clusters (p=0.001).

All patients with the exception of three had eCOPD due to infection. Antibiotics were prescribed for 45 (94%) of the patients, of whom 34 (75.5%) progressed well. However, 11 (24.4%) patients had an unfavorable outcome and there was a need for initial antibiotic therapy replacement. Tuberculosis was diagnosed in one of the patients in the study sample.

DISCUSSION

Admissions in the pulmonology ward of HSPE due to eCOPD accounted for 12% of the total number of admissions from May/2013 to May/2014. The rate of COPD underdiagnosis was 5% (30/537), while overdiagnosis occurred in 18% (19/102). The rate of COPD underdiagnosis in São Paulo is 14%.¹ In the US, this rate reaches 50%, and occurs due to several factors such as lack of knowledge about COPD or lack of suspicion for its diagnosis, which often occurs during the exacerbation.^{18,19}

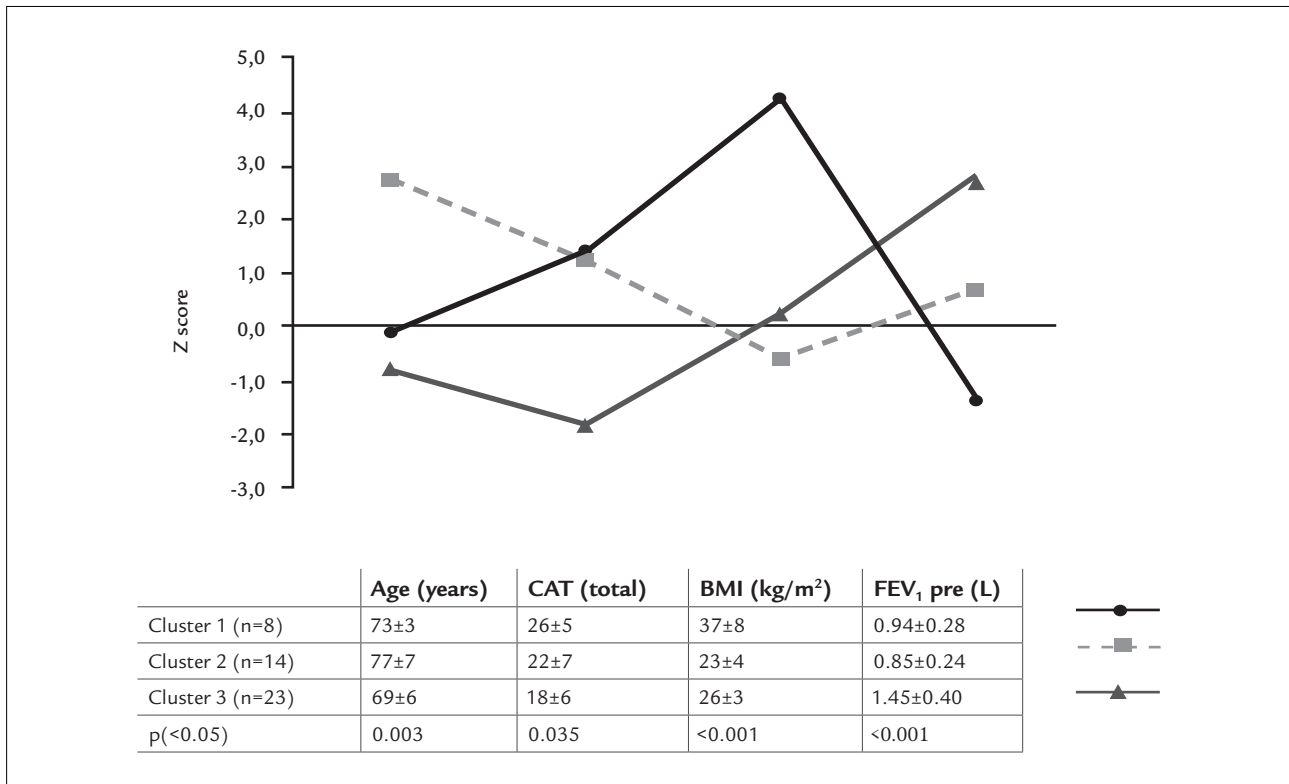


FIGURE 2 Standardized variables related to disease severity (age, CAT, FEV₁ and BMI) allowed grouping of patients into three clusters.

Table 1 shows that patients have a high average age and that in some the follow-up period with a pulmonologist was only 6 months, that is, the diagnosis was recent, and as a consequence, the number of spirometries performed was small. It is interesting to note that several patients (38) were not included in the study because they had never undergone spirometry (inclusion criteria), a fundamental exam for the diagnosis of COPD.¹⁸ COPD underdiagnosis results in late recognition of the disease and in later stages.^{19,20} Early detection of airflow limitation and smoking cessation intervention may delay the decline of lung function, reduce COPD symptoms, and improve the patient's quality of life.

In a retrospective study of COPD patients hospitalized for respiratory failure over a period of 8 years, only 31% had a diagnosis confirmed by spirometry despite having a clinical diagnosis of eCOPD,¹⁹ which characterizes overdiagnosis.

Patients with a smoking load ≥ 10 packs/year were included in this study. Smoking is the most frequent cause of COPD, although there are other risk factors such as exposure to occupational dust, air pollution and biomass burning.²⁰ We observed that 42% of our patients reported exposure to wood stoves.

Still in relation to the characteristics of the sample, 17% of the patients had a history of bronchitis in childhood. It is known that the prevalence of asthmatics who smoke is similar to that of the general population, and that many COPD patients may present a history of asthma prior to COPD. COPD is often confused with asthma.^{21,22} The co-existence of these conditions is called asma-COPD overlap syndrome.²³ With increasing age, there is an increase in the proportion of patients with this syndrome. Some studies found that 55% of COPD patients over 50 years of age had asthma, whereas in other studies the prevalence of asthma-COPD overlap syndrome ranged from 13 to 19%.²³

Patients hospitalized with eCOPD had 4.2±2.2 comorbidities, which is consistent with reports in the medical literature that these are more frequent in patients with COPD than in the general population.²⁴ Some comorbidities present in patients with COPD affect the prognosis, as described by Divo and Cote.⁶ In our study, the Cote score was higher than 4 for ten patients (21%), which means an increased risk of death. There is evidence that the specific management of COPD reduces the number of exacerbations leading to clinical stability for comorbidities with reduced mortality. The same happens with the treatment of comorbidities, which affects the stability of COPD.^{24,25}

Management of COPD aims to control symptoms and comorbidities, and prevent exacerbations.³ Hospitalization due to eCOPD does not necessarily occur in patients with more advanced disease²⁶ and, in our study, we found that the patients had different grades of severity, despite the fact that FEV₁ pre-bd was 44%±17%, and 22 (45%) patients used oxygen at home.

Mortality in eCOPD is high and we observed in our study frequent readmissions that correlated with the outcome of death, as described by Hurst,²⁷ Soriano,²⁸ and Teixeira,²⁹ the latter in Brazil. Teixeira says that 87.8% of the patients hospitalized with COPD had two or more comorbidities, and hospital mortality due to eCOPD was 37.7%.

The length of hospital stay was 18±17 days. We observed the heterogeneity of clinical manifestations in COPD patients through CAT variability and dyspnea as measured by mMRC and VAS.³⁰ There is a correlation between high CAT score and higher frequency of exacerbations, reflecting both severity and duration. CAT may assist in assessing the severity of the exacerbation.^{12,31}

The prevalence of depression found in the sample was 35%. Coexistence of anxiety and/or depression with COPD increases the number of exacerbations and hospitalizations.^{8,32}

Biomarkers are useful to monitor patients admitted with eCOPD. The presence of eosinophilia > 2% indicates a better response to steroid therapy,¹⁶ and it was found in 20% of the patients. CRP and BNP are useful biomarkers for monitoring, respectively, infectious exacerbations and cardiopathies.^{17,26,33}

The seven deaths reported in our study were due to respiratory failure (four patients) and cancer (three patients). Respiratory failure correlates with more severe COPD, whereas lung cancer affects 9% of COPD patients, regardless of staging.²⁸

The standardized analysis of age, CAT, FEV₁ and BMI allowed grouping of patients into three clusters (Figure 2), with different degrees of severity and no correlation with the outcomes of hospitalization. In the first group there were more women with lower FEV₁, higher BMI, and CAT displaying high scores. In the second group, there were older patients with high CAT; and in the third group, younger patients, with higher FEV₁ and lower CAT scores, which indicates less severe COPD in this group with a greater number of patients.³⁴

Readmissions due to eCOPD are a marker of poor prognosis. The number of readmissions was high in our study, which points to the need to adopt protocols for hospital discharge and appointment scheduling soon after discharge, with referral to a pulmonary rehabilitation program.³⁵

The small number of patients included in the sample was a limitation in our study, and was due to a high rate of readmissions and failure to meet the inclusion criteria.

COPD exacerbation is an event that often requires hospitalization and progresses with a high mortality rate. Many times, COPD is under- or overdiagnosed, and one reason is underutilization of spirometry. Thorough assessment of these patients on admission, using laboratory tests, comorbidities assessment, and objective instruments to quantify dyspnea and symptoms (mMRC, VAS and CAT) is essential to reduce hospital stay, prevent readmission and decrease mortality.^{36,37}

Patients admitted due to eCOPD are a heterogeneous group that can be grouped into three clusters as described, although we did not find an association between these clusters and the outcomes of hospitalization. Studies with a larger sample of patients are needed to confirm the findings reported here and to relate them to the outcomes of hospitalizations due to eCOPD.

RESUMO

Hospitalização por exacerbação da DPOC: desfechos da “vida real”

Introdução: As hospitalizações por exacerbação da doença pulmonar obstrutiva crônica (eDPOC) podem indicar um pior prognóstico. É importante conhecer o perfil dos pacientes internados e os desfechos das internações para personalizar e otimizar seu tratamento.

Método: Avaliação dos pacientes hospitalizados por eDPOC, com ≥ 10 anos/maços e ≥ 1 espirometria prévia com obstrução ao fluxo aéreo no período de um ano em um serviço de pneumologia de um hospital geral. Foram utilizados: teste de avaliação da DPOC (CAT); mMRC e Escala Analógica Visual (EAV) para aferição da dispneia; escala hospitalar de ansiedade e depressão (HAD); comorbidades pelos critérios de Divo e índice de Cote; espirometria; e exames laboratoriais, eosinófilos no sangue, proteína C reativa (PCR), brain natriuretic peptide (BNP). Observamos evolução dos pacientes, duração da internação e desfechos da hospitalização.

Resultados: Ocorreram 75 (12%) internações por eDPOC, sendo 27 reinternações, nove das quais com menos de 30 dias após a alta. Os principais desfechos foram: duração da internação de 17±16,5 (2-75) dias; 30 (62,5%) altas hospitalares; 18 (37,5%) altas/reinternações, oito pacientes reinternaram mais de uma vez; e sete (14,5%) óbitos, cinco durante as reinternações. Analisamos 48 pacientes em sua primeira internação. A amostra era um grupo heterogêneo

que ordenamos em três *clusters* de acordo com idade, VEF₁, índice de massa corporal (IMC) e CAT. Os *clusters* não se correlacionaram com os principais desfechos.

Conclusão: A eDPOC é causa frequente de internações. Foram frequentes as reinternações e estas se correlacionaram com o desfecho óbito. Os pacientes internados por eDPOC formaram um grupo heterogêneo, que pôde ser agrupado em três *clusters* com diferentes graus de gravidade e sem correlação com os desfechos das hospitalizações.

Keywords: hospitalização por exacerbação da DPOC, exacerbação da DPOC, teste de avaliação da DPOC, Escala Analógica Visual, morte por DPOC.

REFERENCES

- Projeto Latino-Americano de Investigação e Obstrução Pulmonar. PLATINO. Brasil. Available from: <http://www.platino-alat.org>.
- Moreira GL, Manzano BM, Gazzotti MR, Nascimento OA, Perez-Padill R, Menezes AMB et al. PLATINO, a nine-year follow-up study of COPD in the city of São Paulo, Brazil: the problem of underdiagnosis. *J Bras Pneumol*. 2014; 40(1):30-7.
- Global Initiative for Chronic Obstructive Lung Disease (Updated 2015). Available from: http://goldcopd.it/wp-content/uploads/materiali/2015/Gold_Pocket_DEF_2015.pdf
- Toyoshima MTK, Ito GM, Gouveia N. Morbidades por doenças respiratórias em pacientes hospitalizados em São Paulo/SP. *Rev Assoc Med Bras*. 2005; 51(4):209-13.
- Brasil. Ministério da Saúde. Departamento de Informática do SUS. Brasília (DF): DATASUS; 2010. Available from: <http://www2.datasus.gov.br/DATASUS/index.php>. Cited in "Protocolo Clínico e Diretrizes Terapêuticas (PCDT) – Doença Pulmonar Obstrutiva Crônica", regulamentado pela PORTARIA Nº 609, 6 de junho de 2013, do Ministério da Saúde Secretaria de Atenção à Saúde. CONITEC Comissão Nacional de Incorporação de Tecnologias ao SUS.
- Divo M, Cote C, Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012; 186(2):155-61.
- Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest*. 2011; 139(1):165-73.
- Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. *Chest*. 2008; 134(4 Suppl):43s-56s.
- Botea NJ, Bio MR, Zomignani MA, Garcia Jr C, Pereira WAB. Transtornos do humor em enfermária de clínica médica e validação de escala de medida (HAD) de ansiedade e depressão. *Rev Saúde Pública*. 1999; 29(5):355-63.
- Camargo LACR, Pereira CAC. Dispneia em DPOC: além da escala modified Medical Research Council. *J Bras Pneumol*. 2010; 36(5):571-8.
- Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy NK. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009; 34(4):648-54.
- Mackay AJ, Donaldson GC, Patel ARC, Jones PW, Hurst JR, Wedzicha JA. Usefulness of the Chronic Obstructive Pulmonary Disease Assessment Test to evaluate severity of COPD exacerbations. *Am J Respir Crit Care Med*. 2012; 185(11):1218-24.
- Silva GPF, Morano MTAP, Viana CMS, Magalhães CBA, Pereira EDB. Portuguese-language version of the COPD Assessment Test: validation for use in Brazil. *J Bras Pneumol*. 2013; 39(4):402-8.
- Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*. 2008; 133(3):756-66.
- Marchiori RC, Susin CF, Dal Lago L, Felice CD, Brandão da Silva D, Severo MD. Diagnóstico e tratamento da DPOC exacerbada na emergência. *AMRIGS (Porto Alegre)*. 2010; 54(2):214-23.
- Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Veng P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med*. 2012; 186(1):48-55.
- Chen YW, Leung JM, Sin DD. A systematic review of diagnostic biomarkers of COPD exacerbation. *PLoS One*. 2016; 11(7):e0158843.
- Price D, Crockett A, Arne M, Garbe B, Jones R, Kaplan A, et al. Spirometry in primary care case-identification, diagnosis and management of COPD. *Prim Care Respir J*. 2009; 18(3):216-23.
- Fromer L. Diagnosing and treating COPD: understanding the challenges and finding solutions. *Int J Gen Med*. 2011; 4:729-39.
- Tan WC, Sin DD, Bourbeau J, Hernandez P, Chapman KR, Cowie R, et al.; CanCOLD Collaborative Research Group. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. *Thorax*. 2015; 70(9):822-9.
- Fu JJ, Gibson PG, Simpson JL, McDonald VM. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD Overlap Syndrome. *Respiration*. 2014; 87(1):63-74.
- Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). A joint project of GINA and GOLD 2014. This chapter is excerpted from the Global Strategy for Asthma Management and Prevention, 2014. Available from: <http://www.ginasthma.org>.
- Turner AM, Tamasi L, Schleich F, Hoxha M, Horvath I, Louis R, et al. Clinically relevant subgroups in COPD and asthma. *Eur Respir Rev*. 2015; 24(136):283-98.
- Echave-Sustaeta JM, Comeche Casanova L, Cosio BG, Soler-Cataluña JJ, García-Lujan R, Ribera X. Comorbidity in chronic obstructive pulmonary disease. Related to disease severity? *Int J Chron Obstruct Pulmon Dis*. 2014; 9:1307-14.
- Jeong SH, Lee H, Carriere KC, Shin SE, Moon SM, Jeong BH, et al. Comorbidity as a contributor to frequent severe acute exacerbation in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2016; 11:1857-65.
- Miravittles M, Moragas A, Hernández S, Bayona C, Llor C. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest*. 2013; 144(5):1571-7.
- Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010; 363(12):1128-38.
- Ortiz JBS, Almagro P, Sauleda Roig J. Causas de mortalidad en la EPOC. *Arch Bronconeumol*. 2009; 45(Supl 4):8-13.
- Teixeira C, Cabral CR, Hass JS, Oliveira RP, Vargas MAO, Freitas APR, et al. Exacerbação aguda da DPOC: mortalidade e estado funcional dois anos após a alta da UTI. *J Bras Pneumol*. 2011; 37(3):334-40.
- Csiksz NG, Gartman EJ. New developments in the assessment of COPD: early diagnosis is key. *Int J Chron Obstruct Pulmon Dis*. 2014; 9:277-86.
- Chetta A, Olivieri D. The COPD Assessment Test in the evaluation of chronic obstructive pulmonary disease exacerbations. *Expert Rev Resp Med*. 2012; 6(4):373-5.
- Pooler A, Beech R. Examining the relationship between anxiety and depression and exacerbations of COPD which result in hospital admission: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2014; 9:315-30.
- Patel AR, Hurst JR, Wedzicha JA. The potential value of biomarkers in diagnosis and staging of COPD and exacerbations. *Semin Respir Crit Care Med*. 2010; 31(3):267-75.
- Burgel PR, Paillasseur JL, Caillaud D, Tillie-Leblond I, Chanez P, Escamilla R, et al. Longitudinal validation of clinical COPD phenotypes identified by cluster analysis. *Eur Respir J*. 2010; 36:531-9.
- Hurst JR, Wedzicha JA. Management and prevention of chronic obstructive pulmonary disease exacerbations: a state of the art review. *BMC Med*. 2009; 7:40.
- Müllerova H, Maselli DJ, Locantore N, Vestbo J, Hurst JR, Wedzicha JA, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. *Chest*. 2015; 147(4):999-1007.
- Santibáñez M, Garrastazu R, Ruiz-Núñez M, Helguera JM, Arenal S, Bonnardoux C, et al. Predictors of hospitalized exacerbations and mortality in chronic obstructive disease. *PLoS One*. 2016; 11(6):e0158727.

Association between physical activity and vitamin D: A narrative literature review

MARCOS RASSI FERNANDES^{1*}, WALDIVINO DOS REIS BARRETO JUNIOR²

¹PhD in Health Sciences, Lecturer Advisor of the Graduate Program in Health Sciences, Faculdade de Medicina da Universidade Federal de Goiás (FM-UFG), Goiânia, GO, Brazil

²MSc. Student of the Graduate Program in Health Sciences, FM-UFG, Goiânia, GO, Brazil

SUMMARY

This narrative review of the medical literature assessed whether outdoor and indoor physical activity would increase the plasma levels of vitamin D. Synthesis of this liposoluble vitamin is mainly mediated by sunlight on the skin, where it is activated to perform its main action, which is to control the serum levels of calcium as soon as the element is absorbed in the intestines, assisting in the regulation of bone metabolism. Physical activity is any body movement that results in energy expenditure, while outdoor physical activity refers to physical activity carried out at public parks or other open spaces, as is the case of the popular practice of taking walks. Exercising outdoors would have both the benefits of physical activity and of sun exposure, namely the synthesis of vitamin D. However, according to the studies analyzed, increased plasma concentration of vitamin D occurs with physical activity both indoors and outdoors.

Keywords: vitamin D, physical activity, environmental exposure, sunlight, external work environment.

Study conducted by Graduate Program in Health Sciences, Faculdade de Medicina da Universidade Federal de Goiás (FM-UFG), Goiânia, GO, Brazil

Article received: 10/13/2016

Accepted for publication: 11/20/2016

*Correspondence:

Address: Av. Azaleias, Qd 10, Lt 20

Aparecida de Goiânia, GO – Brazil

Postal code: 74935-187

marcosombro@ig.com.br

<http://dx.doi.org/10.1590/1806-9282.63.06.550>

INTRODUCTION

Vitamin D is a liposoluble compound with antioxidant properties, essential for maintaining the body's mineral balance. It can be acquired from an exogenous source (feed) or endogenously synthesized from the incidence of the sun's ultraviolet rays on the skin. Although it is a vitamin, it is also considered a hormone, since its activation is made by means of chemical reactions inside the organism.¹

Vitamin D occurs in the form of two biologically inert precursors or prohormones, vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Ergocalciferol is of vegetable origin, whereas cholecalciferol is of animal origin, being formed by ultraviolet B radiation on 7-dehydrocholesterol.² Vitamin D in these forms must be converted into active hormone to be able to exert biological influence on mineral metabolism and other physiological functions.¹

Physical activity is any movement of the body produced by skeletal muscles that results in greater energy expenditure than that of rest levels. Performing physical activity in an outdoor environment, with sun exposure,

would provide benefits both from the physical work itself and from vitamin D synthesis and action in the body.³ Based on current evidence, our narrative review of the literature aimed to answer whether physical activity performed both outdoors (with sun exposure) and indoors (without sun exposure) would increase vitamin D plasma levels.

HISTORICAL ASPECTS

Elmer V. McCollum at the end of the 19th century, in experiments on fats associated with the cure of certain diseases (rickets), observed how this process took place in the organism and its relation in the interruption of inadequate bone mineralization during growth due to lack of sun exposure. Today, this substance is called vitamin D.⁴

Physical activity has always existed throughout history, both indoors (Figure 1) and outdoors⁵ (Figure 2). Millennial accounts of Greeks, Chinese and Indians in relation to the practice of physical activity affirm the idea that a stimulated body becomes strong regardless of variation in the environment. The important thing is for the individual to become an adept of this practice.^{6,7}



FIGURE 1 Indoor physical activity.



FIGURE 2 Outdoor physical activity.

VITAMIN D

The needs of the human body, in relation to vitamin D, are supplied to a lesser extent by the exogenous absorption of dietary sources: vitamin D₂, found in vegetables and called ergocalciferol, and vitamin D₃, of animal origin, found in fish and called cholecalciferol. But most of it is endogenously synthesized.⁸

Both participate in the same metabolic process. These forms of vitamin D are produced in the epidermis by 7-dehydrocholesterol photolysis action/reaction.⁹ After synthesis, vitamin D remains inactive, mainly bound to a vitamin D binding protein and, to a lesser extent, albumin, and circulates through the bloodstream until it reaches the liver. There, it undergoes hydroxylation at carbon 25, generating 25-hydroxyvitamin D or calcidiol. It is a rapid process that undergoes little regulation, and the product is deposited in the reservoir of adipose tissue. To be active, this vitamin requires participation of the kidneys and 1-hydroxylase enzyme. Then, vitamin D₃ goes back into the bloodstream to the kidneys and, mediated by the enzyme hydroxylase, forms 1,25-dihydroxyvitamin D or calcitriol. This renal action is controlled by several factors, unlike the previous stage, in the liver, which is poorly regulated^{10,11} (Figure 3).

Vitamin D acts in the control of plasma calcium levels, after its absorption in the intestinal tract, aiding in the regulation of bone metabolism. It also acts in non-calcemic effects, such as strengthening the immune system, improving balance and preventing premature aging.⁴

Researchers' interest in vitamin D has been enhanced by recent advances related to biology, as it plays an important role far beyond calcium metabolism in various extra-skeletal tissues such as adipocytes, skeletal striated muscle, and pancreatic tissue. It also participates in the modulation of immunity and inflammation, which shows its therapeutic potential in diseases such as multiple sclerosis, type 1

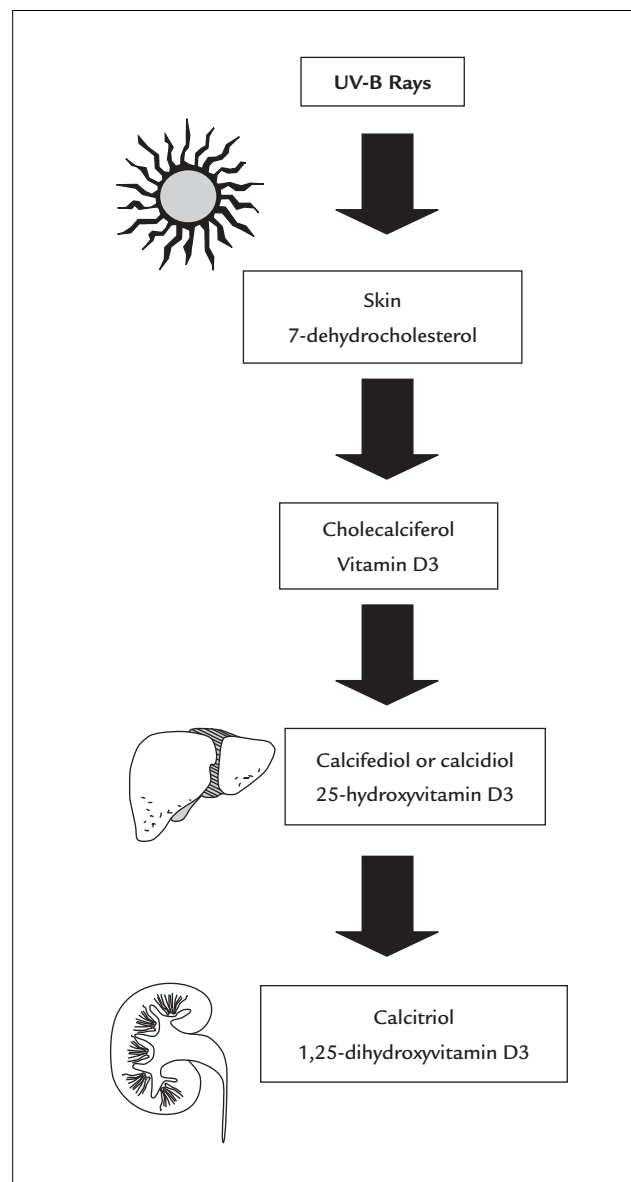


FIGURE 3 Scheme of vitamin D formation.

and 2 diabetes, and autoimmune dermatological and thyroid diseases. Obesity has a negative correlation with plasma vitamin D levels, and vitamin D deficiency causes an increased risk for the development of metabolic syndrome, as well as increased oxidative burden.⁴

PHYSICAL ACTIVITY

Although physical activity is thought to be synonymous with physical exercise, it is actually any movement caused by a muscle contraction resulting in increased energy expenditure than at rest.³ Physical exercise is defined as well-structured, planned and repetitive physical activity, aiming at improving health, well-being, and maintaining physical fitness.¹² The purpose of their use is what sets them apart. Physical activity is therapeutic and its purpose is treatment, while physical exercise improves physical fitness.^{13,14}

Physical fitness, in turn, is defined by the amount of energy that a person has while performing physical work, according to physical valences, and involves flexibility, strength, endurance and motor coordination.¹⁵ From a physical point of view, an inactive individual is one who does not practice physical activity for at least 150 minutes per week.¹⁶

There is a type of exercise called green, which is given to activity practiced in nature, with behavioral results in stress relief in acute exercise sessions.¹⁷

Outdoor physical activity would be its accomplishment in squares, parks and field environments.¹⁸ The most popular of these activities is walking, practiced by the elderly with the goal of improving health and preventing diseases.¹⁹

Studies show that some cities joined the creation of outdoor fitness centers, with the incorporation and adaptation of gymnastics and bodybuilding equipment, with a view to physical, mental and social improvement²⁰ (Figure 4).

ASSOCIATION BETWEEN PHYSICAL ACTIVITY AND VITAMIN D

Regular practice of physical activity has several benefits to the human being, but it is regulated by innumerable demographic, social, physical, environmental, economic and psychological factors that can be both stimulating and inhibiting.²¹

Vitamin D, important in the absorption of calcium at the intestinal level, also acts in the immune, cardiovascular and musculoskeletal systems. Solar exposure in outdoor environment allows the synthesis of this vitamin, with a consequent process of gain of bone tissue through its mineralization. According to current knowledge, the skin is the only organ capable of producing vitamin D, which is also absorbed from dietary intake.²²



FIGURE 4 Outdoor fitness Center.

There is research indicating the practice of physical activity in outdoor settings, but they do not mention the importance of vitamin D.^{17,23} Similarly, there are studies on the synthesis of vitamin D from the incidence of sun rays on the skin, but they do not mention physical activity with sun exposure.²⁴ Why not consider outdoor physical activity in view of the benefits of such activity along with the possibility of vitamin D synthesis from skin exposure to ultraviolet B? It is important to establish if this type of activity, in outdoor environment, would be the only one capable of increasing vitamin D plasma levels (Figure 2).

Sela and Sela identified the beneficial results of outdoor sports, with elderly individuals having better disposition for this activity, as well as less depression, and a reduction in body weight and medication intake, favoring their quality of life.²⁵ A systematic review by Mochcovitch et al. also demonstrated that regular physical activity may be effective for the improvement of anxiety symptoms in older adults; however, they concluded that more research would be necessary to identify the modality, frequency, duration and intensity to optimize the positive effects of this activity on anxiety in the study population.²⁶ The authors did not mention physical activity with sun exposure for vitamin D synthesis, as seen in the study by Al-Eisa et al., who reported the improvement of the individual's physical performance associated with vitamin D and calcium levels as factors to prevent muscle fatigue.²⁷

Vitamin D sufficiency related to physical activity provides better neuromuscular performance, including with increased type II muscle fibers, and also improves the regulatory role of the immune system. Indoor environments, more pigmented skin and excessive use of sports equipment favor vitamin D deficiency.²⁸

Pagels et al. compared indoor and outdoor physical activity among 179 children aged 7 to 14 years from schools in Sweden, and found that outdoor physical activity led to a moderate and vigorous increase in physical activity, during all seasons of the year.²² This strong correlation between the variables of moderate/vigorous physical activity and outdoor environment was also found in the studies by Sallis et al.²⁹ and Cooper et al.³⁰ These authors did not, however, study the association with serum levels of vitamin D.^{22,29,30}

Pagels et al., in another recent study, report that outdoor environment, due to suberythral exposure to the sun even at high latitudes, has a favorable health impact, helping students to acquire vitamin D.³¹ Therefore, moderate exposure to ultraviolet rays in outdoor environment during school days in northern European countries has a positive impact on the immune system, bone mineralization and, possibly, mental health.²²

Florez et al. conducted a cross-sectional study and found an association between vitamin D levels, body mass index and outdoor physical activity in white Hispanic, and non-Hispanic patients. In Hispanics, there was a high prevalence of hypovitaminosis D among the obese compared to non-obese individuals. The practice of outdoor physical activity decreased the prevalence of hypovitaminosis D, with individuals 47% less likely to have this condition.³²

Valtueña et al. investigated 408 Spanish athletes from 34 different modalities, both male and female, and concluded that 82% had suboptimal levels of plasma vitamin D concentration, demonstrating that outdoor physical training is the appropriate way to increase this concentration in athletes.³³

Some studies, however, mention high levels of physical activity associated with increases in vitamin D levels in older adults over the years, regardless of outdoor practice. This, because indoor physical practice would also result in increased levels of vitamin D, suggesting that the concentration of vitamin D is not only attributed to high sun exposure.³⁴⁻³⁷

The findings of the analysis based on data from the US National Health and Nutrition Examination Survey (NHANES) indicate that physical activity is associated with high serum levels of vitamin D, regardless of indoor or outdoor practice.³⁸ Scragg and Camargo conducted an earlier study using the same database (NHANES III), and found that the association between physical activity and vitamin D was stronger in outdoor compared with indoor environments.³⁹ Therefore, even though both studies have reported associations between physical activity and vita-

min D in older individuals, and despite the fact that the ability of vitamin D synthesis from sun exposure decreases with age, the results were not replicated.^{38,39}

Independent effects on sun exposure during physical activity may be associated with increased plasma concentrations of vitamin D. A French study by Touvier et al. supports this claim, with findings of association between physical activity and vitamin D after adjusting for sun exposure and outdoor sports.⁴⁰ Maimoun and Sultan also corroborate the hypothesis that other factors, which are known and altered by physical activity, may contribute to elevated levels of vitamin D metabolites in athletes, such as decreased serum phosphate and ionized calcium.^{41,42}

In addition, Kimlin et al., in an Australian study, reported that exposure to ultraviolet rays was responsible for only 8% of the variation found in vitamin D concentration, while the largest contribution was clothing coverage (27%), followed by location (20%), season (17%), supplementation (7%) and body mass index/physical activity, with 4% each. These results suggest that modifiable factors related to sun exposure could help maintain the healthy state of vitamin D, such as decreased clothing coverage, rather than increasing the duration of exposure to ultraviolet rays.⁴³

Van den Heuvel et al. evaluated the contribution of different physical activity characteristics, such as duration, intensity and location, in relation to plasma levels of vitamin D and concluded that physical activity performed at high intensity had the strongest positive association with vitamin D levels.⁴⁴

It is important to emphasize that exposure of the body to the sun during physical activity should have some particularities in order to raise the plasma concentrations of vitamin D, since it depends on the amount of melanin present in the skin, the type of clothing and the use of sunscreen, as well as hour of the day, season of the year, latitude of the place and age of the individual.^{28,45,46}

The studies included in our narrative review are presented in Table 1 (outdoor physical activity and vitamin D synthesis) and Table 2 (indoor physical activity and vitamin D synthesis), and show sample size, study design and their main findings.

Directed attention plays a fundamental role in cognitive functions, but once it is weakened, the individual's ability to concentrate for certain tasks is reduced, leading to mental fatigue.⁴⁷ The practice of physical activity interacting with nature may be important for recovery of this directed attention, which is closely linked to the process of regaining balance.⁴⁸⁻⁵¹

TABLE 1 Summary of studies in the narrative review: Outdoor physical activity and synthesis of vitamin D.

Studies	Year	Sample	Study design	Main findings
Pagels et al. ³¹	2016	196	Cross-sectional	Suberythral exposure to the sun contributed to the synthesis of vitamin D
Florez et al. ³²	2007	291	Cross-sectional	The practice of outdoor physical activity decreased the prevalence of hypovitaminosis D
Valtueña et al. ³³	2014	408	Cross-sectional	Outdoor physical training is the appropriate way to increase the plasma concentration of vitamin D in athletes
Scragg and Camargo ³⁹	2008	15,148	Cross-sectional	The association between physical activity and vitamin D was stronger outdoors compared to indoor environments

TABLE 2 Summary of studies in the narrative review: Indoor physical activity and synthesis of vitamin D.

Studies	Year	Sample	Study design	Main findings
Scott et al. ³⁴	2015	615	Cohort	Exercising indoors would also result in increased levels of vitamin D, suggesting that vitamin D concentration is not only attributed to high sun exposure
Gerdhem et al. ³⁵	2005	986	Cohort	
Scott et al. ³⁶	2010	686	Cohort	
Bell et al. ³⁷	1988	28	Cohort	
Touvier et al. ⁴⁰	2015	1,828	Cross-sectional	There was an association between physical activity and vitamin D, even after adjusting for exposure to the sun and outdoor sports
Maimoun and Sultan ⁴¹	2009	24	Systematic review	Other factors, which are known and altered by physical activity, may contribute to elevated vitamin D levels in athletes
Kimlin et al. ⁴³	2014	1,002	Cross-sectional	Modifiable factors related to sun exposure could help maintain healthy vitamin D status, such as decreased clothing coverage, rather than increasing the duration of exposure to ultraviolet rays
Van den Heuvel et al. ⁴⁴	2013	1,255	Cross-sectional	High-intensity physical activity had the strongest positive association with vitamin D levels
Wanner et al. ³⁸	2015	6,370	Cross-sectional	Physical activity is associated with high serum levels of vitamin D, regardless of the practice environment, outdoors or indoors

The sufficiency of vitamin D has been related to the mental health of the individuals due to the presence of receptors of this vitamin in cells inside the brain,⁵²⁻⁵⁴ also favoring their cognitive performance.^{55,56} 25(OH)D, in a cross-sectional analysis, was associated with the cognitive decline of subjects over 65 years.⁵⁷ Therefore, both the practice of physical activity and the status of vitamin D are relevant to the reduction of common mental illnesses.⁵²⁻⁵⁸

CONCLUSION

According to the studies included in our narrative review, there is an elevation of the plasma concentration of vitamin D both with physical activity indoors and outdoors. However, randomized controlled trials are needed to compare the synthesis of vitamin D (serum level) associated with physical activity in both settings, so that the difference between the groups would be the incidence or absence of sunlight alone.

RESUMO

Associação entre atividade física e vitamina D: revisão narrativa da literatura

Esta revisão narrativa da literatura avaliou se tanto a atividade física realizada ao ar livre quanto aquela em ambiente interno aumentariam os níveis plasmáticos da vitamina D. A síntese dessa vitamina lipossolúvel ocorre, principalmente, por meio da radiação solar na pele, que, após sofrer processo de ativação no organismo, estabelece sua principal ação no controle dos níveis séricos do cálcio, assim que é absorvido no trato intestinal, auxiliando na regulação do metabolismo ósseo. Atividade física é qualquer movimento corporal que resulte em gasto energético, enquanto atividade física ao ar livre é aquela realizada em parques ou praças, cuja prática mais popular é a caminhada. Esse ambiente externo teria os benefícios propriamente ditos da atividade física, além da exposição solar com a

síntese da vitamina D. Entretanto, segundo os estudos apresentados, há elevação da concentração plasmática da vitamina D na realização de atividade física tanto em ambiente interno quanto ao ar livre.

Palavras-chave: vitamina D, atividade física, exposição ambiental, luz solar, ambiente externo de trabalho.

REFERENCES

- Inda Filho AJ, Melamed ML. Vitamina D e doença renal: o que nós sabemos e o que nós não sabemos. *J Bras Nefrol.* 2013; 35(4):323-31.
- Kich DM, Vieira FAS, Bassuino M, Linden R. Determinação de 25-hidroxitamina D2 e D3 em plasma por CLAE-DAD. *J Bras Patol Med Lab.* 2012; 48(5):329-36.
- Björger K. Physical activity in light of affordances in outdoor environments: qualitative observation studies of 3-5 years old in kindergarten. *Springerplus.* 2016; 5(1):950.
- Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. *Eat Weight Disord.* 2017; 22(1):27-41.
- Antunes HKM, Santos RF, Cassilhas R, Santos RVT, Bueno OFA, Mello MT. Exercício físico e função cognitiva: uma revisão. *Rev Bras Med Esporte.* 2006; 12(2):108-14.
- Nahas MV, Garcia LMT. Um pouco de história, desenvolvimentos recentes e perspectivas para a pesquisa em atividade física e saúde no Brasil. *Rev Bras Educ Fis Esporte.* 2010; 24(1):135-48.
- Araújo DSMS, Araújo CGS. Aptidão física, saúde e qualidade de vida relacionada à saúde em adultos. *Rev Bras Med Esporte.* 2000; 6(5):194-203.
- Premaor MO, Furlanetto TW. Hipovitaminose D em adultos: entendendo melhor a apresentação de uma velha doença. *Arq Bras Endocrinol Metab.* 2006; 50(1):25-37.
- Barral D, Barros AC, Araújo RPC. Vitamina D: uma abordagem molecular. *Pesq Bras Odontoped Clin Integr.* 2007; 7(3):309-15.
- Pedrosa MAC, Castro ML. Papel da vitamina D na função neuro-muscular. *Arq Bras Endocrinol Metab.* 2005; 49(4):495-502.
- Marques CDL, Dantas AT, Fragoso TS, Duarte ALBP. A importância dos níveis de vitamina D nas doenças autoimunes. *Rev Bras Reumatol.* 2010; 50(1):73-80.
- Thomaz PMD, Costa THM, Silva EF, Hallal PC. Fatores associados à atividade física em adultos, Brasília, DF. *Rev Saúde Pública.* 2010; 44(5):894-900.
- Matsudo SM, Matsudo VKR, Barros Neto TL. Atividade física e envelhecimento: aspectos epidemiológicos. *Rev Bras Med Esporte.* 2001; 7(1):2-13.
- Ribeiro RR, Santos KD, Carvalho WRG, Gonçalves EM, Roman EP, Minatto G. Aerobic fitness and biological and sociodemographic indicators in female school children. *Rev Bras Cineantropom Desempenho Hum.* 2013; 15(4):448-57.
- Campos ALP, Del Ponte LS, Cavalli AS, Afonso MR, Schild JFG, Reichert FF. Efeitos do treinamento concorrente sobre aspectos da saúde de idosas. *Rev Bras Cineantropom Desemp Hum.* 2013; 15(4):437-47.
- Alves C, Lima RVB. Impacto da atividade física e esportes sobre o crescimento e puberdade de crianças e adolescentes. *Rev Paul Pediatr.* 2008; 26(4):383-91.
- Rogerson M, Gladwell VF, Gallagher DJ, Barton JL. Influences of green outdoors versus indoors environmental settings on psychological and social outcomes of controlled exercise. *Int J Environ Res Public Health.* 2016; 13(4):363.
- Silva DAS, Petroski EL, Reis RS. Barreiras e facilitadores de atividades físicas em frequentadores de parques públicos. *Motriz Rev Educ Fis.* 2009; 15(2):219-27.
- Ory MG, Towne Jr SD, Won J, Forjuoh SN, Lee C. Social and environmental predictors of walking among older adults. *BMC Geriatr.* 2016; 16(1):155.
- Martins LS, Ovando RGM. Benefícios dos exercícios resistidos ao ar livre para terceira idade de Campo Grande. *Rev Cient JOPEF.* 2012; 13(1):27-35.
- Jesus GM, Jesus EFA. Nível de atividade física e barreiras percebidas para a prática de atividades físicas entre policiais militares. *Rev Bras Ciênc Esporte.* 2012; 34(2):433-48.
- Pagels P, Raustorp A, Guban P, Fröberg A, Boldemann C. Compulsory school in- and outdoors-implications for school children's physical activity and health during one academic year. *Int J Environ Res Public Health.* 2016; 13(7):699.
- Ceci R, Hassmén P. Self-monitored exercise at three different RPE intensities in treadmill vs field running. *Med Sci Sports Exerc.* 1991; 23(6):732-8.
- Wintermeyer E, Ihle C, Ehnert S, Stöckle U, Ochs G, De Zwart P, et al. Crucial role of vitamin D in the musculoskeletal system. *Nutrients.* 2016; 8(6):319.
- Sela VM, Sela FER. A academia da terceira idade como um projeto do governo municipal de Maringá-PR para solucionar as falhas de mercado. *Caderno Administração.* 2012; 20(1):82-90.
- Mochcovitch MD, Deslandes AC, Freire RC, Garcia RF, Nardi AE. The effects of regular physical activity on anxiety symptoms in healthy older adults: a systematic review. *Rev Bras Psiquiatr.* 2016; 38(3):255-61.
- Al-Eisa ES, Alghadir AH, Gabr SA. Correlation between vitamin D levels and muscle fatigue risk factors based on physical activity in healthy older adults. *Clin Interv Aging.* 2016; 11:513-22.
- Borges N, Teixeira VH. Vitamina D'atleta. *Rev Med Desp.* 2011; 2(4):6-8.
- Sallis JF, Prochaska JJ, Taylor WC. A review of correlates of physical activity of children and adolescents. *Med Sci Sports Exerc.* 2000; 32(5):963-75.
- Cooper AR, Page AS, Wheeler BW, Hillsdon M, Griev P, Jago R. Patterns of GPS measured time outdoors after school and objective physical activity in English children: The PEACH project. *Int J Behav Nutr Phys Act.* 2010; 7:31.
- Pagels P, Wester U, Soderström M, Lindelof B, Boldemann C. Suberythral sun exposures at Swedish schools depend on sky views of the outdoor environments - Possible implications for pupils' health. *Photochem Photobiol.* 2016; 92(1):201-7.
- Florez H, Martinez R, Chacra W, Strickman-Stein N, Levis S. Outdoor exercise reduces the risk of hypovitaminosis D in the obese. *J Steroid Biochem Mol Biol.* 2007; 103(3-5):679-81.
- Valtueña J, Dominguez D, Til L, González-Gross M, Drobic F. High prevalence of vitamin D insufficiency among elite Spanish athletes: the importance of outdoor training adaptation. *Nutr Hosp.* 2014; 30(1):124-31.
- Scott D, Ebeling PR, Sanders KM, Aitken D, Winzenberg T, Jones G. Vitamin D and physical activity status: associations with five-year changes in body composition and muscle function in community-dwelling older adults. *J Clin Endocrinol Metab.* 2015; 100(2):670-8.
- Gerdhem P, Ringsberg KAM, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA study of elderly women. *Osteoporos Int.* 2005; 16(11):1425-31.
- Scott D, Blizzard L, Fell J, Ding C, Winzenberg T, Jones G. A prospective study of the associations between 25-hydroxyvitamin D, sarcopenia progression, and physical activity in older adults. *Clin Endocrinol (Oxf).* 2010; 73(5):581-7.
- Bell NH, Godsen RN, Henry DP, Shary J, Epstein S. The effects of muscle-building exercise on vitamin D and mineral metabolism. *J Bone Miner Res.* 1988; 3(4):369-73.
- Wanner M, Richard A, Martin B, Linseisen J, Rohrmann S. Associations between objective and self-reported physical activity and vitamin D serum levels in the US population. *Cancer Causes Control.* 2015; 26(6):881-91.
- Scragg R, Camargo Jr CA. Frequency of leisure-time physical activity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 2008; 168(6):577-86.
- Touvier M, Deschasaux M, Montourcy M, Sutton A, Charnaux N, Kesse-Guyot, et al. Determinants of vitamin D status in Caucasian adults: influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors. *J Invest Dermatol.* 2015; 135(2):378-88.
- Maimoun L, Sultan C. Effect of physical activity on calcium homeostasis and calciotropic hormones: a review. *Calcif Tissue Int.* 2009; 85(4):277-86.
- Fukumoto S. Phosphate metabolism and vitamin D. *Bonekey Rep.* 2014; 3:497.
- Kimlin MG, Lucas RM, Harrison SL, Van der Mei I, Armstrong BK, Whiteman DC, et al. The contributions of solar ultraviolet radiation exposure and other determinants to serum 25-hydroxyvitamin D concentrations in Australian adults: the AusD Study. *Am J Epidemiol.* 2014; 179(7):864-74.
- Van den Heuvel E, Van Schoor N, De Jongh R, Visser M, Lips P. Cross sectional study on different characteristics of physical activity as determinants of vitamin D status; inadequate in half of the population. *Eur J Clin Nutr.* 2013; 67(4):360-5.

45. Oliveira V, Lara GM, Lourenço ED, Boff BD, Stauder GZ. Influência da vitamina D na saúde humana. *Acta Bioquím Clin Latinoam*. 2014; 48(3):339-47.
46. Cargill J, Lucas RM, Gies P, King K, Swaminathan A, Allen MW, et al. Validation of brief questionnaire measures of sun exposure and skin pigmentation against detailed and objective measures including vitamin D status. *Photochem Photobiol*. 2013; 89(1):219-26.
47. Castro LCG. O sistema endocrinológico vitamina D. *Arq Bras Endocrinol Metab*. 2011; 55(8):566-75.
48. Keniger LE, Gaston KJ, Irvine KN, Fuller RA. What are the benefits of interacting with nature? *Int J Environ Res Public Health*. 2013; 10(3):913-35.
49. Dias CAG, Melo VA, Alves Júnior ED. Os estudos dos esportes na natureza: desafios teóricos e conceituais. *Rev Port Cien Desp*. 2007; 7(3):358-67.
50. Flowers EP, Freeman P, Gladwell VF. A cross-sectional study examining predictors of visit frequency to local green space and the impact this has on physical activity levels. *BMC Public Health*. 2016; 16:420.
51. Calogiuri G, Evensen K, Weydahl A, Andersson K, Patil G, Ihlebæk C, et al. Green exercise as a workplace intervention to reduce job stress. Results from a pilot study. *Work*. 2015; 53(1):99-111.
52. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab*. 2012; 13(3):100-5.
53. Schäfer TK, Herrmann-Lingen C, Meyer T. Association of circulating 25-hydroxyvitamin D with mental well-being in a population-based, nationally representative sample of German adolescents. *Qual Life Res*. 2016; 25(12):3077-86.
54. Callegari ET, Reavley N, Garland SM, Gorelik A, Wark JD. Vitamin D status, bone mineral density and mental health in young Australian women: the Safe-D study. *J Public Health Res*. 2015; 4(3):594.
55. Maddock J, Berry DJ, Geoffroy MC, Power C, Hyppönen E. Vitamin D and common mental disorders in mid-life: cross-sectional and prospective findings. *Clin Nutr*. 2013; 32(5):758-64.
56. Maddock J, Geoffroy MC, Power C, Hyppönen E. 25-hydroxyvitamin D and cognitive performance in mid-life. *Br J Nutr*. 2014; 111(5):904-14.
57. Llewellyn DJ, Langa KM, Lang IA. Serum 25-hydroxyvitamin D concentration and cognitive impairment. *J Geriatr Psychiatry Neurol* 2009; 22(3):188-95.
58. Cherrie MPC, Wheeler BW, White MP, Sarran CE, Osborne NJ. Coastal climate is associated with elevated solar irradiance and higher 25(OH)D level. *Environ Int*. 2015; 77:76-84.



ASSOCIADOS RECEBEM A CBHPM GRATUITAMENTE*

CBHPM 2016 BROCHURA (LIVRO)

NÃO SÓCIO
R\$ 250,00

PESSOA JURÍDICA
R\$ 400,00

CBHPM 2016 CD (DADOS TABULADOS)

NÃO SÓCIO / PESSOA JURÍDICA
R\$ 650,00



*Para associados serão cobrados apenas valores de manuseio e envio: R\$ 35,00 para versão impressa e R\$ 70,00 para versão digital. Restrição de uma compra por CPF. Para demais aquisições será cobrado o valor de médico não sócio.

Para adquirir e mais informações, consulte nosso site:
amb.org.br/cbhpm



AS ELEIÇÕES DA AMB ESTÃO CHEGANDO!



Mantenha seu cadastro de Associado atualizado para garantir seu direito de votar

Acesse:

<https://recadastramento.amb.org.br/>