BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

bjhbs.hupe.uerj.br

Vol. 21, número 1, janeiro-junho/2022

Editorial

Original articles

Review Article

BRAZILIAN JOURNAL BJHBS OF HEALTH AND BIOMEDICAL SCIENCES

Vol. 21, número 1, janeiro-junho/2022

Rio de Janeiro

Correspondence

Comissão Científica Pedro Ernesto (COCIPE)
Endereço: *Boulevard* 28 de Setembro, 77
Rio de Janeiro – RJ. CEP: 20551-030.

Telephone

(55 21) 2868 8586 | 2868 8108

Internet

bjhbs.hupe.uerj.br
E-mail: bjhbs.uerj@gmail.com

Editorial Assistant & Review:

Michelle Borges Rossi

Gabriela Dias Sucupira de Souza Linhares

Layout:

2ml design

Partially supported by

FAPERJ
Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro

Indexed in

Sistema Regional de Informação em Linha para Revistas Científicas da América Latina, Caribe, Espanha e Portugal (Latindex); Google Acadêmico (Scholar); Sistema Eletrônico de Editoração de Revistas (SEER); Associação Brasileira de Editores Científicos (ABEC); EBSCOhost Research Databases; National Geographic Learning; Cenage Learning; CrossRef.

CATALOG AT SOURCE
UERJ/REDE SIRIUS/CBA

Brazilian Journal of Health and Biomedical Sciences. – V. 21, n. 1 (jan.-jun.2022) . – Rio de Janeiro: HUPE, 2002-
v. : il. (some color.)

Semestral 2022-.
Available at: bjhbs.hupe.uerj.br
Previous title: Revista Hospital Universitário Pedro Ernesto.

1. Ciências médicas – Periódicos. 2. Saúde – Periódicos. I. Hospital Universitário Pedro Ernesto.

CDU 61

Librarian: Thais Ferreira Vieira - CRB - 5302

Universidade do Estado do Rio de Janeiro

Mario Sergio Alves Carneiro
Rector

Lincoln Tavares Silva
Undergraduate Pro-rectory – PR 1

Luís Antônio Campinho Pereira da Mota
Undergraduate Pro-rectory and Research – PR 2

Cláudia Gonçalves de Lima
Undergraduate Pro-rectory and Culture – PR 3

Catia Antonia da Silva
Undergraduate Student Support and Policy Pro-rectory - PR 4

Denizar Vianna
Health Pro-rectory - PR 5

Jorge José de Carvalho
Biomedical Center Director

Biomedical Center

University Hospital Pedro Ernesto

Ronaldo Damião
Director

José Luiz Muniz Bandeira Duarte
Vice-Director

Faculty of Medical Sciences

Mario Fritsch Toros Neves
Director

Alexandra Monteiro
Vice-Director

Nursing School

Luiza Mara Correia
Director

Ricardo Mattos Russo Rafael
Vice-Director

Institute of Biology Roberto Alcântara Gomes

Norma Albarello
Director

Alessandra Alves Thole
Vice-Director

Institute of Nutrition

Roberta Fontanive Miyahira
Director

Luciana Azevedo Maldonado
Vice-Director

Institute of Social Medicine

Claudia de Souza Lopes
Director

Rossano Cabral Lima
Vice-Director

Faculty of Dentistry

Ricardo Guimarães Fischer
Director

Angela Maria Vidal Moreira
Vice-Director

Brazilian Journal of Health and Biomedical Sciences
Editorial Board

Death in pandemic contemporaneity

The concept of death as an entity has existed in many societies since the beginning of our history. From the 15th century onwards, with the revival of Greco-Roman culture as a source of artistic inspiration, it came to be represented by a skeletal figure carrying a scythe and dressed in a hooded black robe. This was inspired by Hades, the Greek god of the underworld, and by Thanatos (Figure 1), the personification of death, and is an image with strong negative connotations. The theme of death can be approached from several perspectives, including positive ones. Regardless of the angle from which it is viewed, certainly in these times of pandemic, we all think or deepen our thinking about death. But what happens to humanity afterwards? Can we become better people? A socially better humankind? Can we produce really justifiable and sustainable health science? Transformations have taken place, but some were just repetitions of history disguised as contemporary innovation. As epidemiological data show the decline of the Covid-19 pandemic, life seems to be returning to "normality" in the concept of being as it was before. For those who think like this, we must not forget that what prevailed before is what brought us to where we are now and, therefore, a translational historical rescue becomes essential for survival with quality of life for both humans and humanity. Hope is still inside Pandora's box.

Figure 1. Septimius Severus, 193-211 A.D., AE16 of Nikopolis ad Istrum, Moesia. AY KAI CEYHPOC, laureate head right. / NIKOΠOΛIT ΠPOC ICTP, Eros (Thanatos) standing right, legs crossed, extinguishing a torch on an altar. Varbanov 2568

in memory of Professor Edna Ferreira da Cunha

Eloísio Alexsandro da Silva Ruellas

Editor In Chief

DOI: 10.12957/bjhbs.2022.68170

BRAZILIAN JOURNAL BJHBS OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Translation and cross-cultural adaptation of the air medical prehospital triage score for helicopter transport of trauma patients to brazilian portuguese

Roges Alvim-Oliveira,[1,2]* Camila L. Bernardes-Oliveira,[2,3] Aline S. Reis,[1,2] Joshua B. Brown,[4] Danúbia C. Sá-Caputo,[2,3,5] Mario Bernardo-Filho[2]

Abstract

Introduction: The transport of patients by airplanes or helicopters reduces treatment time, while improving the chances of survival and the quality of life. Due to its costly maintenance and operation service, the air transport of victims depends on appropriate triage criteria for patients eligible for this type of transport. The Air Medical Prehospital Triage (AMPT) Score for Helicopter Transport of Trauma Patients quickly classifies the likelihood of trauma victims benefiting or not from helicopter transport. Objectives: The aim of this study was to translate the AMPT Score and cross-culturally adapt it to Brazilian Portuguese. Methods: This study followed international guidelines for standardized translation processes and was developed from: translation, synthesis, back translation, assessment of equivalences by the expert committee, proposal of the previous version of AMPT Score, application of pre-test/post-test and proposition of the final version of the translated scale. Results: The Wilcoxon Test comparing the experts' assessment with the positive expected resulted in a *p*-value = 0.0625 (General) CI 95%. The Content Validity Index (CVI) of the experts committee was calculated as 0.9479. The pre-test data resulted in a Cronbach's Alpha of 0.920 ± 7.26. The free-marginal Kappa coefficient of pre-test data was 0.89 (95% CI for 0.86, 0.93). The post-test data resulted in a Cronbach's Alpha of 0.925 ± 5.36. The Wilcoxon Test comparing pre-test with post-test resulted in a p-value of 0.0942. Conclusions: The process resulted in a translation of the AMPT Score with the appropriate equivalences proposed by the literature that is statistically reliable and will be of great value to professionals who work with transporting trauma victims in helicopters.

Keywords: Prehospital care; Air ambulances; Helicopter; Triage; Translation.

1. Mestrado Profissional em Saúde, Medicina Laboratorial e Tecnologia Forense, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.
2. Laboratório de Vibrações Mecânicas e Práticas Integrativas, Instituto de Biologia Roberto Alcântara Gomes e Policlínica Piquet Carneiro, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.
3. Programa de Pós-Graduação em Ciências Médicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.
4. Division of General Surgery and Trauma, Department of Surgery, University of Pittsburgh Medical Center. Pittsburgh, Pennsylvania, USA.
5. Faculdade Bezerra de Araújo. Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
Rua Uberaba, 60/402
Rio de Janeiro, RJ, Brazil.
CEP 20561-240.
E-mail: roges.enf@gmail.com.
ORCID: https://orcid.org/0000-0003-3908-198X

BJHBS, Rio de Janeiro, 2022;21(1):11-20
DOI: 10.12957/bjhbs.2022.68176
Received on 30/06/21. Approved on 07/12/2021.

Introduction

The need to transport trauma victims, whether due to a lack of resources in a hospital unit or pre-hospital emergency care, means that movement by air is an important strategy. Helicopter Emergency Medical Services (HEMS) aim to take a highly specialized crew to an accident scene for triage, treatment and to provide a fast and efficient form of transport directly to a trauma center for definitive treatment.[1,2] When the location is difficult to access, HEMS can be the only viable means of transport for both rescuers and patients.[2,3] Currently, helicopter rescues cover the entire field of emergency medicine and are an important transport device for polytrauma victims and, in conjunction with ambulances, provide fast (even transregional) transport to specialized trauma centers. Transport by air using fixed-wing (airplanes) or rotary-wing (helicopters) aircraft provides a reduction in treatment time,[4] as well as benefits in terms of survivability[5] and quality of life.[6] Since it is a costly service to maintain and operate, the air transport of patients requires research to determine appropriate triage criteria for patients that stand to benefit from this type of transport.[7] Studies indicate that financial resources spent unnecessarily on air transport could be saved with appropriate triage.[7,8] On the other hand, if air transport is available and appropriate for a specific situation, the sooner the decision to call it in is

made during the evaluation process, the more likely it is for the victims to benefit from it.[9] On-board professionals working in pre-hospital rescue are expected to be able to confront problems and challenges in this area by seeking more knowledge, while developing skills for decision-making as supported by scientific evidence in any adverse situation.[10]

The Air Medical Prehospital Triage (AMPT) Score is a scale developed in the United States of America, validated nationally and internationally', that identifies trauma victims at the injury site who stand to benefit from helicopter transport.[11,12]

The AMPT Score has not been translated and cross-culturally adapted to the Portuguese language of Brazil according to the norms established for this purpose.[13,14] Using it through free translations can generate misinterpretations, which justified the need for the translation and cross-cultural adaptation of the AMPT Score. Its relevance is based on the need for a tool to assist health professionals who work with air transportation of trauma victims.

This study aimed to create a translation and cross-cultural adaptation of the AMPT Score for helicopter transportation of trauma victims, proposed by Brown and colleagues (2016),[11] into Brazilian Portuguese. This work is configured as a first step towards a future validation of this scale and its benefits are related to the improvement of the quality of the service provided by those who work with this type of transport. When using the AMPT Score, health professionals will have in their hand a tool to assist in determining whether air transport is justified or not, in addition to possible cost reductions, since unnecessary flights can be more easily triaged.

Methods

In Brazil, reports have arisen on the use of free translations of scales without carrying out cross-cultural adaptation, an essential step before conducting a study and applying its results.[15] The type of translation most used nowadays is based on the work of two independent translators, in which the back translation method is applied.[13,14,16,17] It was a cross-sectional methodological study with a quantitative and qualitative approach that deals with the process of translation and cross-cultural adaptation to Brazilian Portuguese of the AMPT Score. Equivalence will be assessed according to the stages proposed by Beaton and colleagues (1993 and 2000).[13,14]

All participants in this study provided their written informed consent. The study protocol was approved by the Research Ethics Committee of the *Hospital Universitário Pedro Ernesto* of the *Universidade do Estado do Rio de Janeiro* (UERJ) under the number CAAE 91960418.0.0000.5259, opinion number 2.751.679.

Dr. Joshua Brown, creator of the AMPT Score, authorized this study.

Translation and cross-cultural adaptation

- Stage 1: Translation – the translation of the AMPT Score from English to Portuguese was performed by two individuals proficient in the English language. One individual was informed about the purpose of the study, while the other did not receive any information. As a result, two translations were obtained (T1 and T2).

- Stage 2: Synthesis – T1 and T2 were evaluated for the general meaning of each item by consensus of translators and researchers, paying attention to the Brazilian cultural context. This meaning transcends the literalness of words, encompassing more subtle aspects, such as the impact of a term on the cultural context of the target population. This evaluation was necessary because the literal correspondence of a certain term does not imply similar interpretations in different cultures.[13] From this assessment and evaluation of T1 and T2, a joint Translation 12 (T-12) was generated.

- Stage 3: Back-translation – from the resulting document (T-12), a back-translation was performed by two other native speakers of the English language (BT1 and BT2). Again, only one individual was informed of the purpose of the work, while the other individual did not receive any information. BT1 and BT2 were analyzed and, by consensus among researchers and back-translators, gave rise to Back-translation 12 (BT12). BT12 was compared to the original document, and the creator of the Scale (Dr. Joshua Brown), was asked to assess the equivalence between them.

- Stage 4: Committee of Experts – following the guidelines of Beaton and colleagues, (2000),[14] the entire process of translation and back-translation, along with their respective reports, was analyzed by a committee formed by: a methodological health professional with English language proficiency, a bilingual health professional, a translator, a researcher with English language proficiency, a teacher with English language proficiency and a student with English language proficiency. These professionals, in addition to assessing the entire process through reports, evaluated the equivalences of each item by comparing the original

scale with the translated document (T12). They assigned scores for each item according to the semantic, idiomatic, cultural and conceptual equivalences.[14] The Wilcoxon Test and the Content Validity Index were used to assess the responses of these professionals and, by consensus of these assessments, an initial version translated into Brazilian Portuguese of the AMPT Score was proposed.

- Stage 5: Pre-test – from this initial version, a pre-test was applied to 44 health professionals who work with the air transport of patients in helicopters. The aim was to assess the level of understanding of the scale by these professionals. This pre-test was reapplied to the same professionals after an average interval of two weeks, being answered again by 32 professionals, and then submitted to the Wilcoxon Test, Kappa and Cronbach's Alpha in order to assess internal consistency and agreement, so as to determine operational equivalence and reliability.

The analysis was performed using Excel for Windows® software (Microsoft Office Professional Plus, 2016, Microsoft Corporation), Prism 6 for Windows® software (version 6.01, 2012, GraphPad Software Inc.) and Online Kappa Calculator software (Randolph Justus, 2008).

In stage 4 (experts committee) the Wilcoxon test and the Content Validation Index (CVI) were used. The Wilcoxon Test is a non-parametric hypothesis test used when comparing two related samples [18] and it was applied in stage 4 to compare the evaluation by the experts committee. The CVI, a proportion agreement procedure, allows two or more raters to independently review and evaluate the relevance of a sample of items to the domain of content represented in an instrument. It then determines the proportion of cases in which the raters agree and calculates the stability of their agreement.[19]

In stage 5 (pre-test and post-test), statistical tools were used to determine the internal consistency, agreement and equivalence (Cronbach's α, Kappa's Agreement Coefficient and Wilcoxon Test) as a way to assess the reliability of the construct.[20] In the pre-test, Cronbach's α and Kappa were used. Cronbach's α was used to assess the internal consistency of a construct.[21] The Kappa Agreement Coefficient is a measure used for interobserver evaluation, that is, a measure of agreement among evaluators. Values range from 0.00 to 1.00. The higher the Kappa value, the greater the agreement among observers.[22] Cronbach's α was utilized in the post-test. The Wilcoxon Test was used to compare the equivalence of the pre- and post-tests. The results are presented in absolute values and in terms of mean or standard deviation (confidence interval, CI).

Results

In first and second stage, two independent Brazilian translators, with proficiency in the English language, produced two documents in the stage of translating the original document into Brazilian Portuguese (T1 and T2). Translators and researchers evaluated T1 and T2 to perceive subtle aspects that, if free translation were used, might be non-equivalent. This assessment resulted in the T12 scale.

Table 1 shows sentences that illustrate the comparisons between the original sentence, variations in translation and the first version (synthesis) of the AMPT Score translation (T12).

In the third stage, two back-translators, North Americans fluent in Portuguese, performed the back-translation of this initial version of the Scale into English.

Table 1. Comparisons between the original sentence, translation variation and synthesis (T12) of the AMPT Score

AMPT Score	Translation variation	Synthesis (T12)
Respiratory rate	Ritmo Respiratório	Frequência Respiratória
Multisystem trauma	Traumas múltiplos	Trauma multissistêmico
Signs of tension physiology	Sinais de tensão fisiológica	Sinais de tensão/compressão (dispneia, distensão de jugular desvio de traqueia contralateral)
Mangled	Laceramento	Mutilada

Source: The authors (2021).

The BT12 scale was generated by consensus. BT12 was compared with the original scale and submitted to the assessment of the author of the AMPT, who rated it as very good in general ("Overall is a very good translation to the original") with only 2 caveats that were analyzed and accepted by the expert committee.

The Expert Committee (Stage 4) judged each item of the translated scale (T12) and compared them with the original scale. Each item received 4 marks between 1 and 4 (one for each equivalence judged: semantic, idiomatic, conceptual, cultural), being: 1 = unchanged; 2 = little changed; 3 = very changed; 4 = completely changed.

The evaluation data were submitted to the Wilcoxon Test comparing the expert assessments with the positive expected (completely equivalent) and the results of the equivalences are shown in Figure 1.

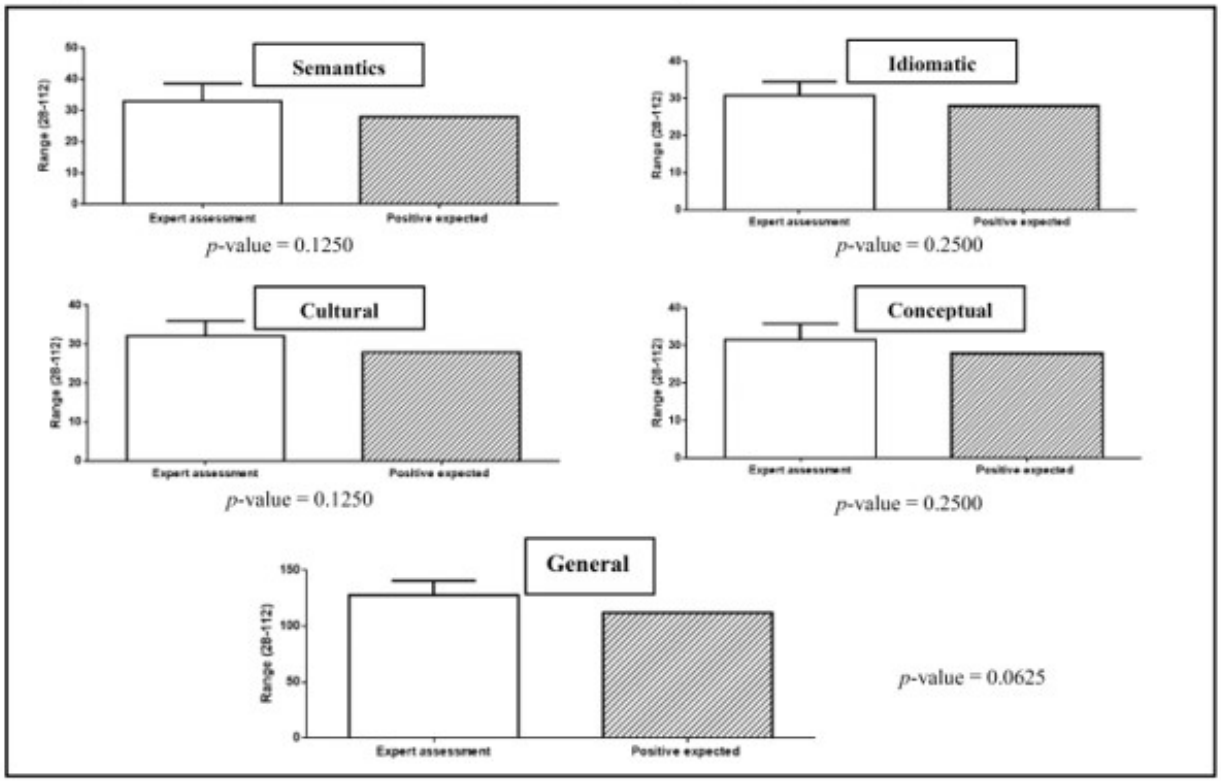

Figure 1. The Wilcoxon Test of Experts Committee
Source: The authors (2021).

The evaluations of the expert committee were also submitted to the CVI, by adding responses 1 and 2 of the participants and dividing the result of this sum by the total number of responses, with the calculated CVI being 0.9479.

In this fourth stage, after the placements and changes suggested by the expert committee discussed below, the final version of the translation of the AMPT Score into Brazilian Portuguese was then proposed.

Stage 5 consisted of an assessment by 44 health professionals with a higher education degree who work with the air transport of patients on their level of understanding of the items on the scale. The profile of these professionals is presented in Table 2.

These professionals were asked to assign values from 1 to 5 (1 – I did not understand anything at all; 2 – I understood very little; 3 – I do not know if I understood or did not understand; 4 – I understood, but with some

Table 2. Profile of professionals who responded to the pre-test

Characterization of the individuals		
Age (year old)	41.8 ‡ 5.75	
Gender	Male 32 (72.7%) Female 12 (27.3%)	
Work City	Rio de Janeiro RJ - 18 (40.8%) Curitiba PR - 4 (9.1%) Cascavel PR - 2 (4.5%) Blumenau SC - 1 (2.3%) Itaboraí RJ - 1 (2.3%) Maricá RJ - 1 (2.3%) São Paulo SP - 1 (2.3%)	Brasília DF - 6 (13.6%) Florianópolis SC - 4 (9.1%) Paranaguá PR - 2 (4.5%) Chapecó SC - 1 (2.3%) Itajaí SC - 1 (2.3%) Ponta Grossa PR - 1 (2.3%) Toledo PR - 1 (2.3%)
Scholarity	Doctorate degree - I (2.3%) Postgraduate - 31 (70.5%)	Master's degree - I (2.3%) Graduate - 6 (13.6%)
University Graduate	Nursing - 26 (59.2%)	Medicine - 18 (40.8%)
Post-graduation in Acrospace Medicine or Aerospace Nursing?	Yes - 17 (38.6%)	No - 27 (61.4%)
Use of a trauma patient triage scale for transport by helicopter?	Yes - 6 (13.7%)	No - 38 (86.3%)
Which scale do you use?	Glasgow - 2 (4.5%) Glasgow and RASS - 1 (2.3%) RTS - 1 (2.3%)	Glasgow and Aldrete - 1 (2.3%) SOP - 1 (2.3%) None - 38 (86.3%)

Source: The authors (2021).

doubts; 5 – I understood perfectly and have no doubts) for each item, according to the clarity and level of understanding of the information. As a way to facilitate understanding, four items analyzed separately by the Committee of Experts were grouped, totaling 24 items for this pre-test. The results were submitted to Cronbach's Alpha for assessment of internal consistency. Cronbach's Alpha was 0.920 ± 7.26.

The Kappa coefficient was applied to determine the level of agreement among the 44 professionals who answered the pre-test. For this calculation, the values of 4 and 5 (4 – I understood, but with some doubts; 5 – I understood perfectly and have no doubts) were considered a high level of understanding, whereas values 1, 2 and 3 (1 – I did not understand at all; 2 – I understood very little; 3 – I do not know if I understood or if I did not understand) were considered a low level of understanding. It results in free-marginal Kappa 0.89 [95% CI for free-marginal Kappa (0.86, 0.93)], percent overall agreement 94.65%.

Within 15±3 days after the pre-test, 32 of the 44 professionals answered a post-test, containing the same questions as the pre-test. Although this post-test is not provided for the guideline used (19), it was applied to determine whether the level of understanding of the professionals changed over time. The professionals were instructed not to consult their previous responses. Cronbach's Alpha was 0.925 ± 5.36 for these data.

The pre-test and post-test data were compared to determine pre-test – post-test reliability, and the Wilcoxon Test was calculated, resulting in a p-value of 0.0942 (Figure 2).

Discussion

The AMPT score represents the first attempt to develop a triage tool for the helicopter transport of trauma patients [11] and, in addition to internal validation, the AMPT has also been validated externally.[12]

Measurement instruments are used in clinical practice and research in different areas of knowledge in order to provide valid and reliable measures, requiring the evaluation of their quality during the selection of an instrument.[20] Therefore, reliability and validity are

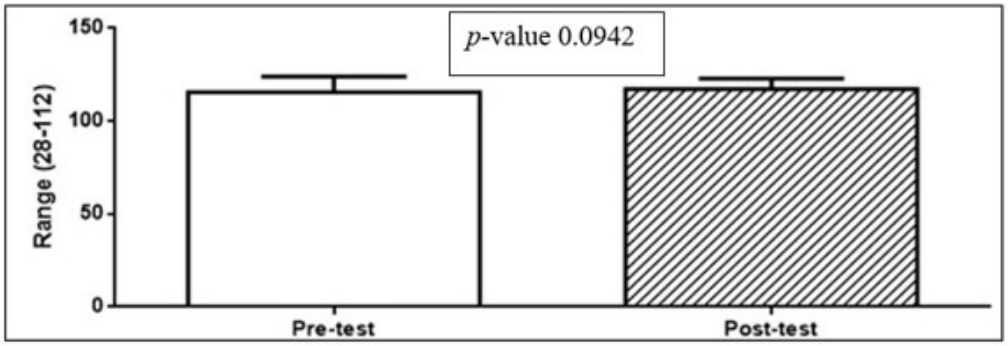

Figure 2. The Wilcoxon test of pre-test and post-test
Source: The authors (2021).

configured as the main measurement properties of such instruments.[23]

For necessary adaptation, even if an instrument is designed in English, using it in another country also in English requires adaptation to the local culture, which need is further increased when transported to a language other than the original.[13]

According to the recommendations,[14] additional comments were made to highlight challenging phrases or uncertainties and our reasoning for choices is also summarized in the written report.[14] Table 1 demonstrated the challenge of adapting literal translations to appropriate sentences.

The term "respiratory rate" would not be incorrect if translated as "*ritmo respiratório*", but the cross-cultural adaptation to Brazilian Portuguese shows a better perception if translated as "*frequência respiratória*". The expression "*ritmo respiratório*", refers to the sequence, form and amplitude of respiratory incursions[24] (for example: dyspnea, platypnea, orthopnea, trepopnea, Cheyne-stokes, among others). Therefore, it does not denote the number of respiratory incursions per minute, which is clearly the object evaluated in the AMPT Score and is more correctly translated as "*frequência respiratória*".

The term "multisystem trauma" could be understood as "*traumas múltiplos*" in a free translation, however the term "*trauma multissistêmico*" occurs frequently in the Brazilian scientific literature[25] and also in translated reference documents,[9] reflecting practicality and understanding for health professionals who use this triage object.

The term "signs of tension physiology", when translated as "*sinais de tensão fisiológica*", is a typical case of error due to free translation, because, in the context, it is clear that the term refers to physiological signs of compression. In order to confer greater simplicity and objectivity, it was decided to adapt the translation to "*sinais de tensão/compressão*" in addition to including examples of these signs: "*dispneia, distensão de jugular ou desvio de traqueia contralateral*",[9] in order to facilitate the evaluation by the persons who will use the scale.

During the translation of "mangled", the word "*laceramento*" came up, a word that does not exist in Brazilian Portuguese language because the correct one would be "*laceração*". However, it was observed that "mangled" is more widely used in the English language to denote "mutilation", which is why it has been translated as "*mutilada*". "Mangled" is defined as "to destroy something by twisting it with force or tearing it into pieces so that its original form is completely changed",[26] which is compatible with the meaning of "mutilated" in the Portuguese language: "Cut (any part of the body), eliminate part or parts of, unravel, distort, destroy part of."[24]

Based on the synthesis (T12), a back translation was performed by two other native speakers of the English language, who, by consensus, originated the back translation 12 (BT12).

The author of the AMPT received the reports on stages 1, 2 and 3 (translation, synthesis and back-translation) and considered the work up to that point to be very good. Two comments were made: in the expression "All penetrating injuries to head, neck, torso, and extremities proximal to elbow or knee" the RT12 back translation was "All injuries penetrating head, neck, torso, or extremities near elbow or knee", with

the author observing that the word "above" would be more precise than "near" compared to the original "proximal"; in the original expression "Amputation proximal to wrist or ankle" the RT12 was "Amputation near wrist or ankle", with the author again observing that the word "above" would be more precisely equivalent than "near".

In both cases, it was observed that the word "proximal" is used in the medical field to anatomically define a point closer to the center of the body (proximal - distal).[26] Thus, in order to avoid confusion between the words "proximal" and "near", the word "above/*acima*" was chosen.[27]

The expert committee recommended changing a preposition[27] that might cause confusion. They also recommended to change the term "*pressão sanguínea sistólica*" to "*pressão arterial sistólica*", a term used in the 7th Brazilian Guideline for Hypertension[28] and also widely used by academic and health professionals.

In relation to the term "wrist", the committee recommended replacing the translated term "*pulso*" by "*punho*", which is a better anatomical designation.[29]

The Wilcoxon test was applied to compare two related samples (34): the evaluation (by the expert committee) of the initial translated version of the AMPT under the best possible scenario, which would be the full equivalence (Figure 1), resulting in a p-value = 0.0625 (general); p-value = 0.1250 (semantics); p-value = 0.2500 (idiomatic); p-value = 0.1250 (conceptual); p-value = 0.2500 (cultural) demonstrating that the two results are not significantly different.

The CVI[30] was calculated at 0.9479, and a relevant CVI agreement between the members of the expert committee must be at least 0.80 and, preferably, greater than 0.90,[31] showing high agreement on the aspects of the instrument and its items.

After the deliberations and amendments suggested by the Committee of Experts, the final version of the translation into Brazilian Portuguese of the Air Medical Prehospital Triage (AMPT) Score for Helicopter Transport of Trauma Patients was written.

Health professionals with higher education degrees who work with the air transport of patients answered a questionnaire assessing the clarity of the scale items and their level of understanding. In the Table 2 it is possible to verify that there is a predominance of professionals from the Southeast (21/47.7%) over the South (17/38.6%) and Midwest (6/13.7%) regions of Brazil. The professional profile reveals 26/59.2% nurses and 18/40.8% physicians; the vast majority (31/70.5%) have undergraduate degrees', however, only 17 (38.6%) have a specialization in Aerospace Medicine or Nursing; the highest prevalence of time since graduation was 11 to 15 years (13/29.5%) and experience with air transportation of patients from 1 to 3 years (15/34.1%). Furthermore, only six professionals (13.7%) reported using any scale to triage trauma victims, mentioning the following (Table 2): Aldrete, Glasgow, RTS, RASS and SOP.

In an attempt to systematize the criteria of evolution in the post-anesthesia period, the Aldrete Scale was devised by Aldrete and Kroulik in 1970[32] to assess muscle activity, respiration, systemic circulation, conscience and oxygen saturation.

The Glasgow Coma Scale is a reliable and practical method of assessing the level of consciousness in patients suffering from head trauma through the sum of scores attributed to three independent measures: eye opening, motor response and verbal response.[33]

The Revised Trauma Score (RTS) is a tool for trauma triage and estimating initial severity that does not require sophisticated examination devices and is extremely useful in prehospital emergency care. This scoring system consists of the sum of values attributed to: Glasgow Coma Scale, systolic blood pressure and respiratory rate.[34]

The Richmond Agitation and Sedation Scale (RASS) is used for routine neurological assessments in intensive care units, especially in patients without traumatic brain injury.[35] It was initially developed to assist in the management of sedation and analgesia in ICUs and has been shown to be highly reliable and consistent in estimating the patient's level of consciousness. It can be assessed in less than a minute with a simple three-step sequence (observation, response to verbal stimulation and response to physical stimulation).[36]

Standard operating procedures (SOPs) are components of clinical use that were introduced to improve diagnosis and therapeutic management in medicine. They are based on current studies and recommendations for experts and professional organizations.[37] However, in certain situations, they are created internally based on the experiences and opinions of professionals.

It can be seen that the instruments mentioned by health professionals may have a predictive value for the severity of injury to the patient, but do not demonstrate any benefit relationship linked to helicopter transport.

In stage 5 (pre-test and post-test), statistical tools were used to determine the internal consistency, equivalence

and agreement (Cronbach's Alpha, Kappa's Agreement Coefficient and Wilcoxon Test), as a means to assess the reliability of the construct.[20]

Cronbach's Alpha demonstrated positive consistency rates, both when evaluating the pre-test and in post-test evaluation. The pre-test obtained a Cronbach's Alpha value of 0.920 with a standard deviation of 7.26. The post-test obtained a Cronbach's Alpha value of 0.925 ± 5.36. Values between 0.81 and 1.00 are considered to show "almost perfect" consistency.[38]

The Kappa Agreement Coefficient is a measure used for interobserver evaluation, that is, a measure of agreement among evaluators. Values range from 0.00 to 1.00. The higher the Kappa value, the greater the agreement among observers.[22] Applied to the pre-test, the calculated Kappa was 0.89 with an overall agreement percentage of 94.65%, which reflects an "almost perfect" agreement (from 0.81 to 1.00).

Test-retest reliability is assessed by applying the same instrument to the same professionals after an average interval of two weeks.[39,40] The average time between pre-test and post-test applications was 15±3 days. Several tests can be used as a statistical measure,[39] and we performed the Wilcoxon Test (Figure 3), which showed no statistically significant difference between the samples (*p*-value = 0.0942).

The limitations of the study are related to: i) lack of comparison of the performance of the scale with another (gold standard), because the AMPT Score represents the first attempt to develop a triage tool for the helicopter transport of trauma victims;[11] ii) psychometric variables of construct validity, item response theory were not evaluated, since they will be the subject of further work to validate the scale, even though the document has been properly translated and adapted to Brazilian Portuguese, psychometric properties must be checked in order to validate the reliability of the data when applied in Brazilian territory; iii) the evaluation did not cover professionals from all regions of Brazil, only the South, Southeast and Midwest regions, and this need should be taken into account in a future validation study.

The Brazilian Portuguese version of the AMPT Score presented in this study is a short and specific questionnaire that assesses, through objective criteria, which trauma patients stand to benefit from air transport by helicopter.

It was observed that few professionals who work with air transport report using any patient triage scale to evaluate the use of a helicopter. Additionally, they reported that, in most cases, the scales used reflect the severity of the victim's injuries, but have no direct relationship to possible benefits of air transport. Thus, the AMPT Score qualifies as an important tool in guiding and assisting healthcare professionals in triage trauma patients who stand to benefit from helicopter transport. In view of the completion of all stages of the translation and cross-cultural adaptation process and positive statistical results, we consider the Air Medical Prehospital Triage Score for Helicopter Transport of Trauma Patients to have been translated and culturally adapted to Brazilian Portuguese (Figure 3), thus qualifying this material for future validation studies.

AMPT Brasil – Versão em Português Brasileiro do Air Medical Prehospital Triage (AMPT) Score for Helicopter Transporte of Trauma Patients

Critério	Pontos
Escala de Coma de Glasgow <14	1
Frequência Respiratória <10 ou >29	1
Fraturas instáveis na parede torácica[1]	1
Suspeita de hemotórax ou pneumotórax[2]	1
Paralisia	1
Trauma multissistêmico[3]	1
1 Critério Fisiológico + 1 critério anatômico[4]	2
Considerar transporte por helicóptero se pontuação total ≥ 2	

[1]Qualquer instabilidade ou deformidade da parede torácica, incluindo tórax instável ou múltiplas fraturas de costelas ao exame físico;

[2]Ausência de sons respiratórios no hemitórax acometido MAIS sinais objetivos de distúrbio respiratório [cianose, SpO2<92%, sinais de tensão/compressão (dispneia, distensão de jugular ou desvio de traqueia contralateral)];

[3]Ferimentos em 3 ou mais regiões anatômicas;

[4]Qualquer 1 **critério fisiológico** + qualquer 1 **critério anatômico** presente nas orientações nacionais de triagem do *American College of Surgeons Committee on Trauma*:

Critérios Fisiológicos
* Escala de Coma de Glasgow ≤ 13
* Pressão arterial sistólica < 90 mmHg
* Frequência Respiratória <10 ou >29 respirações/minuto (<20 em crianças <1 ano) ou necessidade de suporte ventilatório

Critérios Anatômicos
* Todo ferimento penetrante na cabeça, pescoço, tronco ou extremidades acima do cotovelo ou joelho
* Instabilidade ou deformidade da parede torácica (por exemplo, tórax instável).
* Amputação acima do punho ou tornozelo
* Duas ou mais fraturas de ossos longos proximais (por exemplo, fêmur e úmero)
* Extremidade esmagada, desenluvada, mutilada ou sem pulso
* Fraturas Pélvicas
* Fratura do crânio aberta ou com depressão
* Paralisia

Figure 3. The Wilcoxon test of pre-test and post-test
Source: The authors (2021).

Acknowledgments

The corresponding author of AMPT Dr. Joshua Brown.

Declaration of interest statement

The authors declare no conflict of interest.

References

1. Butler DP, Anwar I, Willett K. Is it the H or the EMS in HEMS that has an impact on trauma patient mortality? A systematic review of the evidence. Emerg Med J. 2010;27(9):692–701. doi: 10.1136/emj.2009.087486
2. Assa A, Landau DA, Barenboim E, et al. Role of air-medical evacuation in mass-casualty incidents-A train collision experience. Prehosp Disaster Med. 2009;24(3):271–6. doi: 10.1017/S1049023X00006920
3. Lyon RM, Sanders J. The Swiss bus accident on 13 March 2012: Lessons for pre-hospital care. Crit Care. 2012;16(4):2010–1. doi: 10.1186/cc11370
4. Phillips M, Arthur AO, Chandwaney R, et al. Helicopter transport effectiveness of patients for primary percutaneous coronary intervention. Air Med J. 2013;32(3):144–52. doi: 10.1016/j.amj.2012.08.007
5. Gearhart PA, Wuerz R, Localio AR. Cost-effectiveness analysis of helicopter ems for trauma patients. J Trauma Nurs. 1998;5(1):18–9. doi: 10.1097/00043860-199801000-00006
6. Silbergleit R, Scott PA, Lowell MJ, et al. Cost-effectiveness of helicopter transport of stroke patients for thrombolysis. Acad Emerg Med. 2003;10(9):966–72. doi: 10.1197/S1069-6563(03)00316-6
7. Englum BR, Rialon KL, Kim J, et al. Current use and outcomes of helicopter transport in pediatric trauma: a review of 18,291 transports. J Pediatr Surg. 2017;52(1):140–4. doi: 10.1016/j.jpedsurg.2016.10.030
8. Grantham W, To P, Watson J, et al. Retrospective Review of Air Transportation Use for Upper Extremity Amputations at a Level-1 Trauma Center. J Hand Microsurg. 2016;08(02):086–90. doi: 10.1055/s-0036-1583299
9. Wai AKC. Prehospital Trauma Life Support. Eur J Emerg Med. 8a ed. 2012 Dec;19(6):412. doi: 10.1097/MEJ.0b013e32835538b8
10. Morais ÊM de, Agostini FCAD, Oliveira NA de. Role of aerospace care nursing in Brazil: Integrative review. Brazilian J Heal Biomed Sci. 2021;20(1):63–72. doi: 10.12957/bjhbs.2021.59747
11. Brown JJB, Gestring ML, Guyette FX, et al. Development and validation of the air medical prehospital triage score. Ann Surg. 2016;264(2):378–85. doi: 10.1097/SLA.0000000000001496
12. Brown JB, Gestring ML, Guyette FX, et al. External validation of the Air Medical Prehospital Triage score for identifying trauma patients likely to benefit from scene helicopter transport. J Trauma Acute Care Surg. 2017;82(2):270–9. doi: 10.1097/TA.0000000000001326
13. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. J Clin Épidemiology. 1993;46(12):1417–32. doi: 10.1016/0895-4356(93)90142-N
14. Beaton DE, Bombardier C, Guillemin F, et al. Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures. Spine (Phila Pa 1976). 2000;25(24):3186–91. doi: 0362-2436
15. Lino VTS, Pereira SRM, Camacho LAB, et al. Adaptação transcultural da Escala de Independência em Atividades da Vida Diária (Escala de Katz). Cad Saude Publica. 2008;24(1):103–12. doi: 10.1590/s0102-311x2008000100010
16. Hilton A, Skrutowski M. Translating instruments into other lnguages: development and testing processes. Cancer Nurs. 2002;25(1):1–7. doi: 10.1097/00002820-200202000-00001
17. Reichenheim ME, Moraes CL, Hasselmannb MH. Equivalencia semantica da versão em português do instrumento Abuse Assessment Screen para rastrear a violência contra a mulher grávida. Rev Saude Publica. 2000;34(6):610–6. doi: 10.1590/S0034-89102000000600008
18. Society IB. Probability Tables for Individual Comparisons by Ranking Methods Author (s): Frank Wilcoxon Published by: International Biometric Society Stable [Internet]. [cited 2019 Jan 15]. Available from: http://www.jstor.org/stable/3001946. 2010;3(3):119–22
19. Lynn MR. Determination and quantification of content validity. Nurs Res. 1986;35:382–5. doi: 10.1097/00006199-198611000-00017
20. Souza AC de, Alexandre NMC, Guirardello E de B. Propriedades psicométricas na avaliação de instrumentos: avaliação da confiabilidade e da validade. Epidemiol e Serv saude Rev do Sist Unico Saude do Bras. 2017;26(3):649–59. doi: 10.5123/S1679-49742017000300022
21. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;33(1):159-74. doi: 10.2307/2529310. Available from: http://www.jstor.org/stable/2529310
22. Salmond SS. Evaluating the Reliability and Validity of Measurement Instruments. Orthop Nurs. 2008;27(1):28–30. doi: 10.1097/01.NOR.0000310608.00743.54
23. Cook DA, Beckman TJ. Current concepts in validity and reliability for psychometric instruments: Theory and application. Am J Med. 2006;119(2):166.e7-166.e16. doi: 10.1016/j.amjmed.2005.10.036
24. Dicionário Aurélio [Internet]. [cited 2019 Jan 15]. Available from: https://dicionariodoaurelio.com/mutilada
25. Gentile JK de A, Himuro HS, Rojas SSO, et al. Condutas no paciente com trauma crânioencefálico. [Internet]. Rev Bras Clin Med. 2011;9(jan-fev):74–82. [cited 2019 Dez 28]. Available from: https://pesquisa.bvsalud.org/portal/resource/pt/lil-577701
26. Cambridge Dictionary [Internet]. [cited 2019 Jan 15]. Available from: https://dictionary.cambridge.org/pt/dicionario/ingles/mangled
27. Michaelis. Michaelis Dicionário Escolar Língua Portuguesa. São Paulo: Editora Melhoramentos; 2016
28. Malachias M, Plavnik FL, Machado CA, et al. 7th Brazilian Guideline of Arterial Hypertension: Chapter 1 - Concept, Epidemiology and Primary Prevention. Arq Bras Cardiol. 2016;107(3 Suppl 3):1–6. doi: 10.5935/abc.2013s010
29. Netter FH. Atlas de Anatomia Humana. 6a Ed. Rio de Janeiro: Elsevier; 2014
30. Alexandre NMC, Coluci MZO. Validade de conteúdo nos processos de construção e adaptação de instrumentos de medidas. Cienc e Saude Coletiva. 2011;16(7):3061–8. doi: 10.1590/S1413-81232011000800006
31. Polit DF, Beck CT. The content validity index: are you know what's being reported? Critique and recommendations. Res

Nurs Health. 2006;29:489–97. doi: 10.1002/nur.20147
32. Aldrete JA, Kroulik D. A postanesthetic recovery score. Anesth Analg. 1970;49(6):924–34. doi: 10.1213/00000539-197011000-00020
33. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974 Jul 13;2(7872):81-4. doi: 10.1016/s0140-6736(74)91639-0
34. Champion H, Sacco W, Copes W, et al. A revision of the trauma score. J Trauma. 1989;29:623–9. doi: 10.1097/00005373-198905000-00017
35. Trivedi V, Iyer VN. Utility of the Richmond Agitation-Sedation Scale in evaluation of acute neurologic dysfunction in the intensive care unit. J Thorac Dis. 2016;8(5):E292–4. doi: 10.21037/jtd.2016.03.71
36. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44. doi: 10.1164/rccm.2107138
37. Zausig YA, Bayer Y, Hacke N, et al. Simulation as an additional tool for investigating the performance of standard operating procedures in anaesthesia. Br J Anaesth. 2007;99(5):673–8. doi: 10.1093/bja/aem240
38. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;33(1):159. doi: 10.2307/2529310
39. Arafat S, Chowdhury H, Qusar M, et al. Cross Cultural Adaptation and Psychometric Validation of Research Instruments: a Methodological Review. J Behav Heal. 2016;5(3):129. doi: 10.5455/jbh.20160615121755
40. Arafat S. Validation study can be a separate study design. Int J Med Sci Public Heal. 2016;5(11):2421. doi: 10.5455/ijmsph.2016.19042016471

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Apoptosis in myelodysplasia: association with patient age, bone marrow cellularity and karyotypes

Daiane C. de Souza,[1] Adriana C. Camargo,[2] Eliane F. Rodrigues,[1] Mércia M. Campos,[3] Tatiana F. Alvarenga,[4] Cecília de S. Fernandez,[5] Elaine S. da Costa,[6] Teresa de S. Fernandez[1]*

Abstract

Background: Myelodysplastic syndrome (MDS) comprises a heterogeneous group of clonal hematopoietic stem cell diseases, characterized by dysplasias and apoptosis in bone marrow (BM) and cytopenias in peripheral blood. In this study, we analyzed apoptosis in MDS to verify associations with patient age, bone marrow cellularity and karyotypes and to investigate the role of apoptosis in MDS pathogenesis. Methods: Bone marrow cells were collected from 81 patients with primary MDS, of which 60 were adults and 21 children. BM cells were also collected from 10 healthy donors for bone marrow transplants, 5 adults and 5 children, as controls. The patients and controls came from public onco-hematology institutions in Rio de Janeiro. The percentage of apoptotic BM cells was assessed by flow cytometry using two combinations: annexin V-FITC/CD34PE/CD45PerCP and annexin V-FITC/CD14PE/CD45PerCP in BM cells. Cytogenetic analysis was performed by G-banding. Results: The comparison between adult and pediatric patients showed that these patients show a similar behavior with regard to apoptotic cells percentages in BM samples. Apoptosis occurs independently of BM cellularity, being more prominent in patients with hyper/normocellular BM. Patients with normal karyotypes, del(5q), del(17p) had higher apoptosis rates than patients with del(11q) and complex karyotypes. Cells committed to a differentiation program were associated with high rates of apoptosis, suggesting that apoptosis may be a consequence of inefficient hematopoiesis, such that the hematopoietic system may eliminate dysplastic cells at the beginning of the disease. Conclusions: Our results suggest that apoptosis is an important characteristic of BM cells from adult and pediatric MDS patients and may be a consequence of inefficient hematopoiesis. In addition, we suggest that apoptosis is not the main mechanism associated with hypocellular MDS, and it occurs preferentially in MDS cases of hyper/normocellular BM and is associated with a good prognosis.

Keywords: Myelodysplastic syndrome; Apoptosis; Patient age; Bone marrow cellularity; Karyotypes.

1. Laboratório de Citogenética, Centro de Transplante de Medula Óssea, Instituto Nacional de Câncer (INCA). Rio de Janeiro, RJ, Brazil.
2. Instituto de Hematologia Arthur Siqueira Cavalcanti (Hemorio). Rio de Janeiro, RJ, Brazil.
3. Laboratório de Imunologia, Centro de Transplante de Medula Óssea, Instituto Nacional de Câncer (INCA). Rio de Janeiro, RJ, Brazil.
4. Departamento de Patologia, Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brazil.
5. Instituto de Matemática e Estatística da Universidade Federal Fluminense (UFF). Niterói, RJ, Brazil.
6. Instituto de Pediatria e Puericultura Martagão Gesteira, Universidade Federal do Rio de Janeiro (UFRJ). Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
Centro de Transplante de Medula Óssea, Laboratório de Citogenética
Praça Cruz Vermelha, 23, 6º andar
Rio de Janeiro, RJ, Brazil.
CEP: 20230-130.
E-mail: teresafernandez@inca.gov.br
ORCID: https://orcid.org/0000-0003-1299-4666

BJHBS, Rio de Janeiro, 2022;21(1):21-30
DOI: 10.12957/bjhbs.2022.68177
Received on 17/05/2021. Approved on 22/02/2022.

Introduction

Apoptosis or programmed cell death is an essential physiological process that plays a critical role in development and tissue homeostasis. Apoptotic cells may be characterized by specific morphological and biochemical changes, including cell shrinkage, chromatin condensation and internucleosomal cleavage of genomic DNA.[1] Apoptosis is involved in a wide range of pathological conditions. Cancer is one of the scenarios where little apoptosis occurs. The apoptosis signaling pathway plays an important role in the treatment of cancer because it is a target of many treatment strategies.[2,3]

Myelodysplasia or myelodysplastic syndrome (MDS) encompasses a group of clonal stem cell disorders characterized by dysplasias and apoptosis in bone marrow (BM), which lead to cytopenias in peripheral blood and a risk of progression to acute myeloid leukemia (AML). Peripheral cytopenias are known hallmark of MDS and they are associated with ineffective hematopoiesis, a condition in which the

BM is unable to produce and deliver adequate numbers of mature cells to the peripheral blood. Cumulative evidence indicates that this apparent paradox is caused by premature intramedullary cell death via apoptosis.[4] Some studies consider apoptosis in MDS as a defect that causes cytopenias in the peripheral blood, and apoptosis to be deregulated.[4-8] However, other studies point to apoptosis as a mechanism whereby the hematopoietic system is able to abrogate defective and/or potentially harmful clones.[9,10] Apoptosis in MDS remains unclear.[11]

MDS is viewed as a disease of adults, particularly the elderly. Pediatric MDS is an uncommon disorder, comprising less than 5% of hematopoietic malignancies.[12,13] In children, MDS appears with distinct clinical and laboratory characteristics when compared with adults, which may reflect specific biological issues related to MDS during childhood.[14] However, studies do not show the frequency of apoptosis in pediatric patients or if this process is similar when compared with BM cells from adult MDS patients. Another important point, focusing on apoptosis, concerns BM cellularity in MDS patients. The BM in primary MDS patients is usually hypercellular or normocellular. Nevertheless, between 10% and 20% of patients can present hypocellular BM.[15-17] Many studies involving apoptosis in MDS have been conducted in patients with hypercellular BM. In hypocellular MDS, it is unclear if apoptosis has some influence in this low cellularity. Goal and colleagues[18] suggested that hypocellularity in MDS could be explained by excessive apoptosis, but they also suggested that there is another sub-group of patients who may have a stem-cell failure defect since they show no evidence of apoptosis.

In primary MDS, independently of cellularity in the BM, the cytogenetic pattern is characterized mainly by partial or total loss of chromosomes.[19] Few studies show an association between apoptosis and karyotypes. The presence of del(5q) and trisomy 8 have been associated with a reduction in the rate of apoptosis in MDS.[20,21] The aim of this study was to analyze apoptosis in primary MDS in order to verify if there are associations with patient age, bone marrow cellularity and karyotypes and to investigate the role of apoptosis in MDS pathogenesis.

Materials and methods

Patients and controls

Bone marrow cells were collected from 81 patients with primary MDS. These patients included 34 males and 47 females. There were 60 adult patients, with the mean age of 54 years, ranging from 21-86 years, and 21 pediatric patients, with the mean age of 10 years, ranging from 5 months to 18 years. The patients were diagnosed at the following public hematology/oncology centers in Rio de Janeiro, Brazil: Bone Marrow Transplant Center (in Portuguese, Centro de Transplante de Medula Óssea, CEMO-INCA), Hematology Service (in Portuguese, Instituto Nacional do Câncer, INCA), Arthur Siqueira Cavalcanti Hematology Institute (in Portuguese, HEMORIO) and Martagão Gesteira Pediatric and Puericulture Institute (IPPMG). The criteria for inclusion of the patients were the presence of dysplastic cells and the percentage of blasts according to the bone marrow analysis and immunophenotyping. The diagnosis was based on clinical history, morphological, cytochemical studies, immunophenotypic and cytogenetic analyses. None of the patients had been previously treated for a malignancy. The pediatric patients included individuals aged 18 years or less, while adult patients were those aged 19 years or more. The pediatric patients were classified according to Hasle and colleagues.[22] Seventeen pediatric patients were classified as having refractory cytopenia (RC) and four as having refractory anemia with excess of blasts (RAEB). The classification of adult patients was in accordance with the French-American British (FAB) Co-operative Group.[23] Forty-six adult patients were classified as having refractory anemia (RA), eleven patients as RAEB and three as RAEB in transformation (RAEB-t). The cellularity of the bone marrow was analyzed by means of biopsy. The age-related normal values of bone marrow cellularity (%) were: infant (1 month to 1 year): 80-90%; child: 60-80%; adult: 40-70%; and ≥70 years: 30-40%.[24-26] The bone marrow samples from pediatric and adult MDS patients were sent to the Cytogenetic and Immunology Laboratories of CEMO-INCA, at the time of diagnosis. The cytogenetic analyses were conducted at the Cytogenetic Laboratory (CEMO-INCA) and the immunophenotyping and apoptosis experiments were conducted at the Immunology Laboratory (CEMO-INCA). The interpretation and discussion of apoptosis were performed at IPPMG-UFRJ, using the Infinicyt software program (Cytognos, Salamanca, Spain). Bone marrow samples from 10 healthy individuals, donors for hematopoietic stem cell transplantation (HSCT), were used as a control group for apoptosis experiments. The controls included 5 healthy pediatric donors and 5 healthy adult donors. This study was

reviewed and approved by the Ethics Committees of the National Cancer Institute (CEP#3401739), the Arthur Siqueira Cavalcanti Hematology Institute (HEMORIO) (CEP#063/05) and the IPPMG-UFRJ (CEP#08926213.9.0000.5264), and was conducted in conformity with the Declaration of Helsinki.

Apoptosis analysis by flow cytometry

To determine the percentage of apoptotic cells, we used fresh bone marrow cells from MDS patients and healthy individuals. Initially, it was used red blood lysis solution (RBC) for 5 minutes. After centrifugation, the supernatant was withdrawn. The bone marrow cells were washed in phosphate-buffered saline (PBS). Next, cells were divided into two aliquots ($1x10^6$) and stained with two different antibody combinations: CD34-PE/CD45-PerCP and CD14-PE/CD45-PerCP (BD Biosciences) for 15 minutes in the dark. In the following step, PBS was added and cells were centrifuged during 5 minutes. Finally, the cells were incubated with annexin-V-FITC and propidium iodide (PI) (Apoptosis Detection Kit II, BD Biosciences) for 20 minutes at room temperature protected from light, according to manufacturer's instructions. A total of 200,000 events were acquired using a FACSCalibur Flow Cytometer (Becton Dickinson, USA) and analyzed using the Infinicyt software program (Cytognos, Salamanca, Spain).

Cytogenetic study

Karyotypes of bone marrow cells were obtained from cultures in RPMI 1640, with 20% fetal calf serum (GIBCO) at 37 °C for 24 hours. Cell cultures were pulsed with colcemid to a final concentration of 0.05 µg/mL for the final hour of incubation. Cells were subsequently harvested by standard procedures (hypotonic shock: 0,075M) and fixed in methanol: acetic acid (3:1). GTG banding was performed. Chromosomes were identified and arranged according to the International System for Cytogenetic Nomenclature, 2016.[27]

Statistical analysis

The associations of the percentage of apoptosis between healthy individuals and MDS patients, patient age (adult and pediatric patients), bone marrow cellularity, disease subtype, cell populations (considering immature cells, $CD34^+$, and mature, $CD34^-$) and karyotypes were performed using the Mann-Whitney test. Our sample was considered statistically significant at $p<0.05$.

Results

Apoptosis analysis in bone marrow cells of primary MDS patients

The percentage of apoptotic cells in total BM cells from MDS patients (median: 9.9%; range 1.7%-55.4%, 81 patients) was significantly higher than the percentage from healthy BM donors (4.3%; 2.6%-5.7%, 10 individuals), $p<0.0001$ (Figure 1A). Considering age, rates of apoptosis in BM cells were similar in MDS adults (9.9%; range 1.7%-55.4%) and pediatric patients (9.5%; 2.9%-36%), $p<0.9$ (Figure 1B). Taking into account MDS BM cellularity, cases with hyper/normocellular BM had increased percentages of apoptotic cells (12.2%, range 1.7% to 55.4%) compared to healthy donors 4.3% (range 2.6%-5.7%), $p<0.0001$. Interestingly, MDS patients with hypocellular BM also had more apoptotic cells (8.6%; 2.9%-25.8%) than healthy donors, $p<0.0004$. Our results showed an increased rate of apoptosis in patients with MDS, independently of the cellularity of the BM. Furthermore, MDS patients with hyper/normocellular BM had a higher apoptosis rate than MDS cases with hypocellular BM ($p<0.01$) (Figure 1C).

Analysis of apoptosis and MDS subtypes

In our sample, of the 81 patients analyzed, 63 patients were classified as RA/RC, 15 as RAEB and 3 as RAEB-t. Analyzing the apoptosis according to each subtype of disease, it was observed that patients in early-stages (RA/RC) had significantly higher rates of apoptosis (11.3%; 2.8%-55.4%) than patients in more advanced stages (RAEB and RAEB-t), with a median percentage of apoptosis of 7.2% (range 1.7%-18.9%), $p<0.006$ (Figure 2A).

In patients in the early stages of the disease (RA/RC), cases with hyper/normocellular BM had a higher median percentage of apoptosis (14.2%; range 2.8%-55.4%) than patients with hypocellular BM (8.6%; range 3.2%-25.8%), ($p<0.007$) (Figure 2B). In the later stages of the disease (RAEB and RAEB-t), patients with hyper/normocellular BM had a similar median percentage of apoptosis (6.5%; range 1.7%-18.9%) to hypocellular BM cases (7.8% apoptosis, range 2.9%-13.6%), $p<0.9$ (Figure 2C).

Apoptosis on bone marrow hematopoietic progenitor cells ($CD34^+$cells) and bone marrow cells committed to differentiate lineages ($CD34^-$ cells)

An apoptosis analysis was performed on different cell populations to determine whether the pluripotent

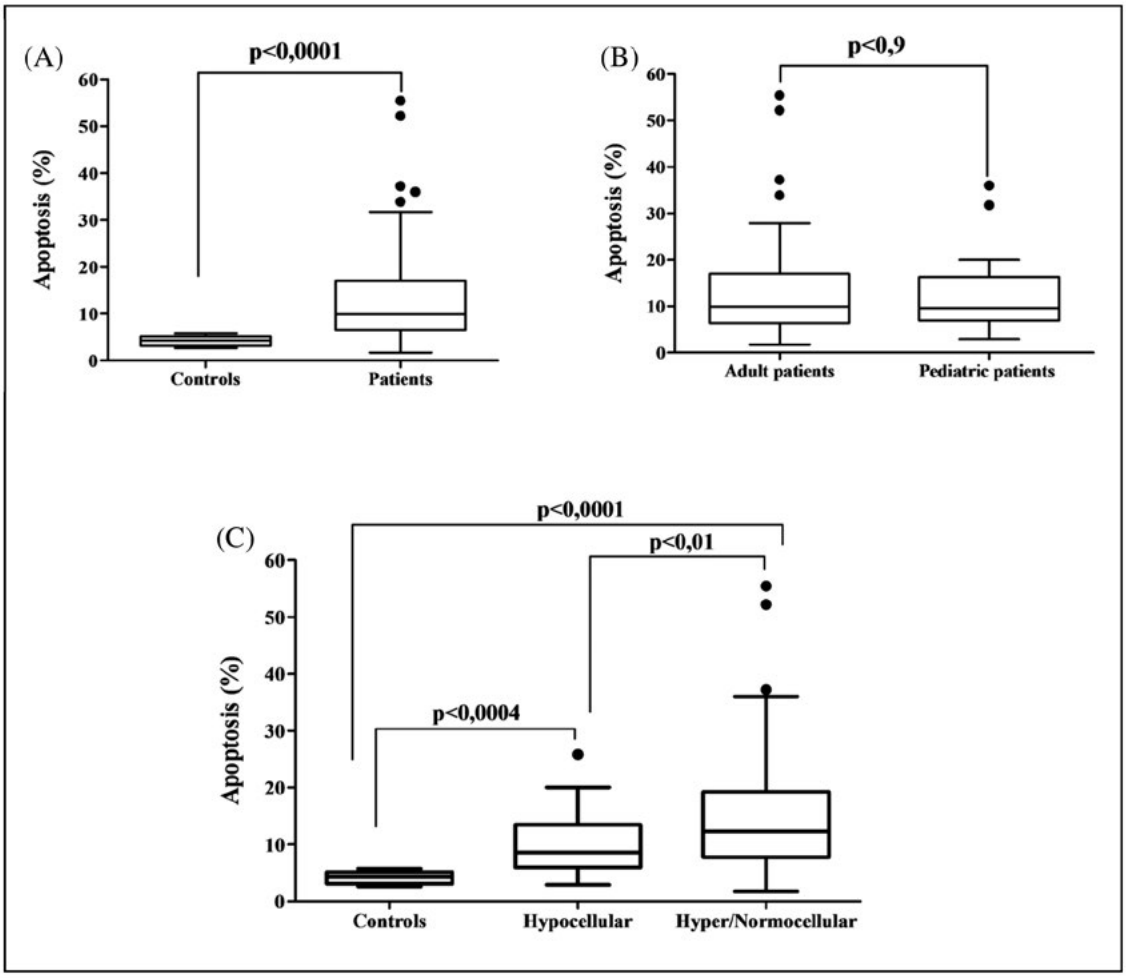

Figure 1. (A) Percentage of apoptotic cells: controls versus MDS patients; (B) Percentage of apoptotic cells: adults MDS patients versus pediatric MDS patients. (C) Percentage of apoptotic cells: controls versus hypocellular BM, controls versus hyper/normocellular BM, hypocellular BM versus hyper/normocellular BM. The results are shown in box-plot graphics in linear scale, showing the median, range, and the dots represent outliers

Source: The authors (2022).

stem cells ($CD34^+$ cells) or the cells already committed to differentiation were in apoptosis. This analysis showed that apoptosis occurs in $CD34^+$ cells. However, the percentage of apoptosis is higher in cells already involved in a cell differentiation program. This can be seen in the healthy individuals and patients, independent of BM cellularity. We observed that more mature cells had a median percentage value of apoptosis equal to 9.6% (range 1.7%-53.6%), while progenitor cells ($CD34^+$) showed a median percentage of apoptosis equal to 0.14% (range 0%-1.9%). Thus, the cells already committed to the program of cell differentiation had a higher percentage of apoptosis ($p<0.0001$) (Figure 3).

We used flow cytometry to analyze the percentage of apoptosis in specific hematopoietic cell populations according to the cellularity of bone marrow. We observed that lymphocytes are the cells with the lowest percentage of apoptosis compared with other hematopoietic cell populations, with median percentage value of apoptosis equal to 5.47% (range 0.37%-50.03%) in cases of hypocellular BM and 10.7% (range 0%-46.96%) in hyper/normocellular BM. Nucleated red blood cells (NRBC), granulocytic and monocytic cells showed higher apoptosis rates compared with both $CD34^+$ cells and lymphocytes. NRBC showed a median percentage value of apoptosis

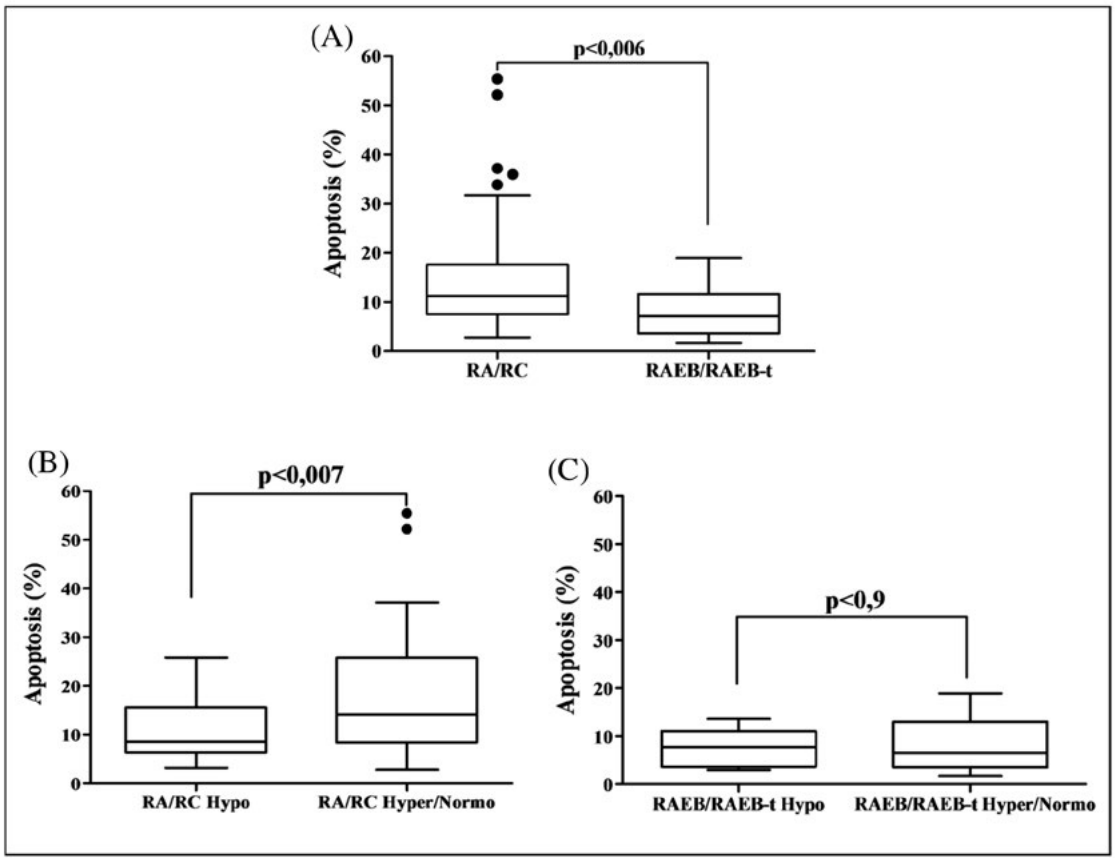

Figure 2. Analysis of apoptosis in bone marrow cells in different MDS subtypes. (A) Percentage of apoptosis: early stages (RA/RC) versus advanced stages (RAEB and RAEB-t). (B) Percentage of apoptosis: RA/RC Hypocellular BM versus RA/RC hyper/normocellular BM. (C) Percentage of apoptosis RAEB/RAEB-t Hypocellular BM versus RAEB/RAEB-t hyper/normocellular BM. The results are shown in box-plot graphics in linear scale, showing the median, range, and the dots represent outliers

Source: The authors (2022).

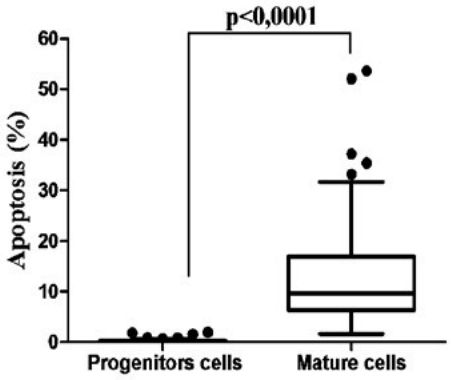

Figure 3. Percentage of apoptosis in progenitor cells versus mature cells from MDS patients. The results are shown in box-plot graphic in linear scale, showing the median, range, and the dots represent outliers

Source: The authors (2022).

of 43.1% (range 2.26%-87.17%) in hypocellular BM and 28.6% (range 0-91%) in hyper/normocellular BM. The granulocyte population had a median percentage value of apoptosis of 8.24% (range 3%-71.8%) in hypocellular BM and a median percentage value of apoptosis 12% (range 1.45%-90.71%) in hyper/normocellular BM. Monocytic populations showed a median percentage value of apoptosis of 24% (range 2%-100%) and 50.33% (range 1.78%-95.9%) in hypocellular and hyper/normocellular BM, respectively (Figure 4).

Comparison of the percentage of apoptotic bone marrow cells according to karyotypes

The analysis of the percentage of apoptosis and the karyotypes showed: the median percentage of apoptosis in normal karyotypes (n=34) was 9.1% (range 1.7%-55.4%); the median percentage of apoptosis in del(5q) (n=5) was 16.9% (range 2%-19.3%); in the case of patients with del(11q) (n=4) the median percentage of apoptosis was 6.4% (range 3.2%-8.2%); the del(17p) (n=8) had a median percentage of apoptosis of 12% (range 2.9%-15.6%) and patients with complex karyotypes (n=3) presented a median percentage of apoptosis of 3.7% (range 2.8%-4.9%). Patients with normal karyotypes, del(5q) and del(17p), presented higher apoptosis rates. Patients with del(11q) and complex karyotypes showed a decrease in apoptosis (Figure 5). The comparison of apoptosis in these two karyotype groups was statistically significant, $p<0.004$.

Discussion

Apoptosis has been presented as part of primary MDS pathogenesis.[28-30] Although many studies focus on MDS apoptosis, a review of the literature showed that little is known about apoptosis in pediatric primary MDS and about the difference in apoptosis between pediatric and adult patients.[9,28,31,32] In our study, we initially compared the presence of apoptosis in patients with primary MDS versus healthy individuals, which showed an increase of apoptosis in MDS patients. Then, we compared apoptosis rates in BM samples from adult and pediatric MDS patients, which were found to be similar, suggesting that MDS-related apoptosis is a process that is independent of the age. In relation to the apoptosis rate according to the BM cellularity in MDS patients, we observed a higher apoptosis in hyper/normocellular BM cases. Our results suggest that, despite having an increased percentage of apoptosis when compared to healthy individuals, the hypocellular BM of some MDS patients is probably not caused solely by apoptosis, and that other factors may be associated, such as, for example, alterations in the cell proliferation program of hematopoietic stem cells, in which the presence of a molecular alteration could induce silencing or decrease of the expression in one or more genes related to the cell proliferation program. The cause of hypocellular MDS is not completely understood. Serio and colleagues[33] reported that hypocellular MDS patients showed a severe deficit of immature hematopoietic progenitor cells, measured as secondary colony-forming cells (CFC), compared to healthy individuals, which would imply that immature hematopoietic stem cell compartment is affected by disease processes in hypocellular MDS. The damage to marrow hematopoietic progenitors occurring in hypocellular MDS may be explained by different immune-mediated mechanisms. Clinically, the strongest evidence for immune-mediated hematopoietic suppression in some hypocellular MDS is the response to immunosuppression, including mainly cyclosporine and anti-thymocyte globulin.

The high incidence of apoptosis is a remarkable feature observed in early stage of the MDS, while a decrease in apoptosis is observed in more advanced subtypes.[7,29] In our study, patients with RA/RC, independently of BM cellularity, showed a higher percentage of apoptosis when compared with patients with RAEB/RAEB-t. Some studies attributed the decrease in apoptosis rates of patients in advanced stages to increased levels of BCL2 protein and other anti-apoptotic proteins.[27,28] Increased expression of BCL2 protein has also been associated with increased resistance to apoptosis and leukemic transformation, and therefore a poor prognosis.[32]

The literature contains discussions on which cells would be entering in the apoptosis program, whether the progenitor cells or cells already committed to a cell differentiation program.[7,29] In our study, we observed a significant difference between apoptosis in cells already committed to a cell differentiation program and progenitor cells. Our results suggest that apoptosis is more intense in cells already committed to a cell differentiation program, maybe as an attempt of patients' own BM to remove dysplastic cells at beginning of the disease, as cited by Corey and colleagues.[7] According to Raza and colleagues[23] the immature $CD34^+$ cells are stimulated to proliferate, while their later differentiated daughters are induced to undergo apoptosis accounting for the clinical syndrome of pancytopenia.

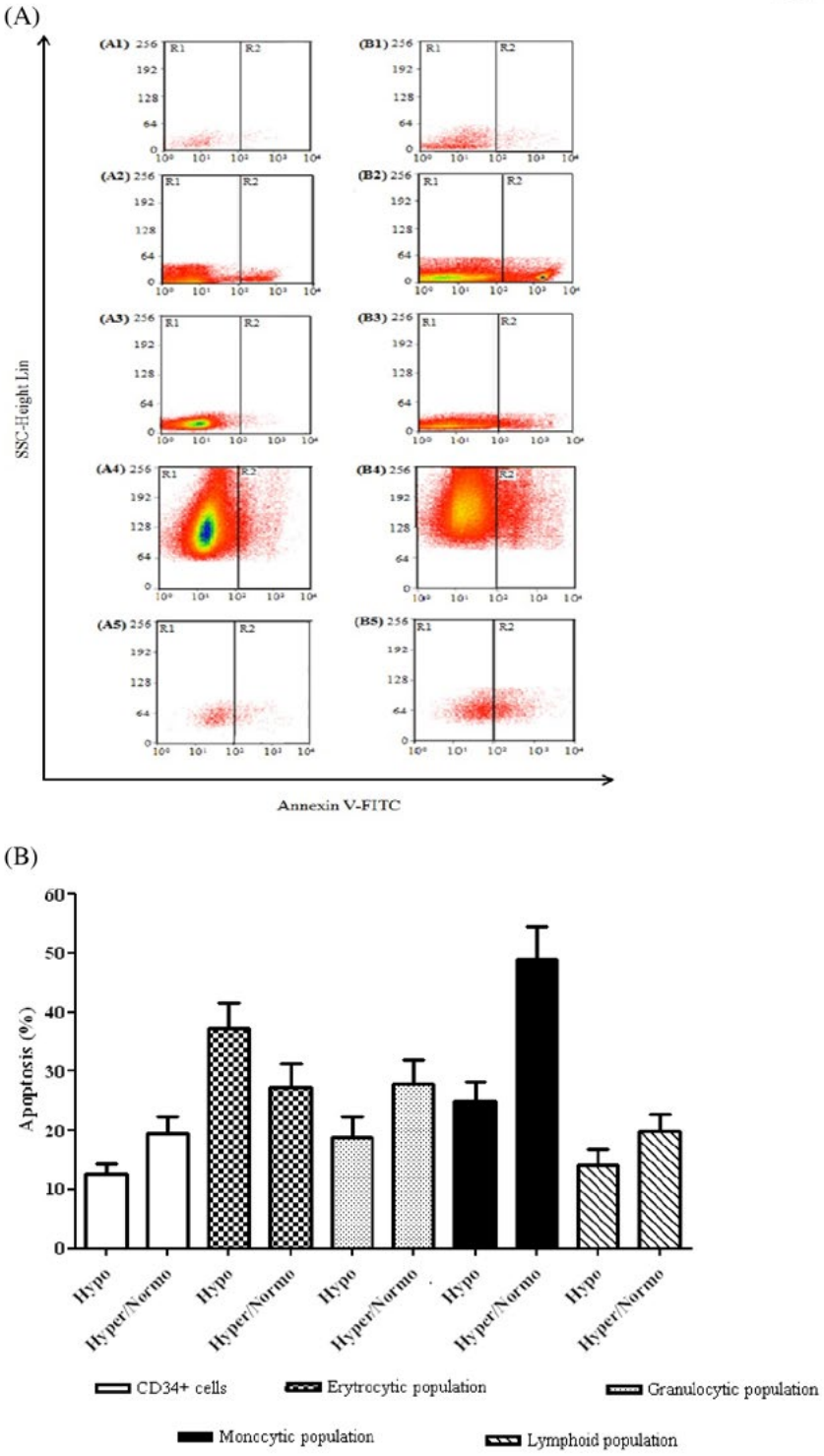

Figure 4. (A) Apoptosis analysis in specific hematopoietic cell populations in MDS patients by flow cytometry. In column A, sample of hypocellular BM MDS and in column B, sample of hypercellular BM MIDS. Apoptotic cells are in gate R2. Al and B1 are CD34* cells; A2 and B2 erytrocytic population; A3 and B3 lymphoid population; A4 and B4 granulocytic population; A5 and B5 monocytic population. (B) Comparison of apoptosis between specific hematopoietic cell populations in BM of hypocellular and hyper/normocellular MDS patients

Source: The authors (2022).

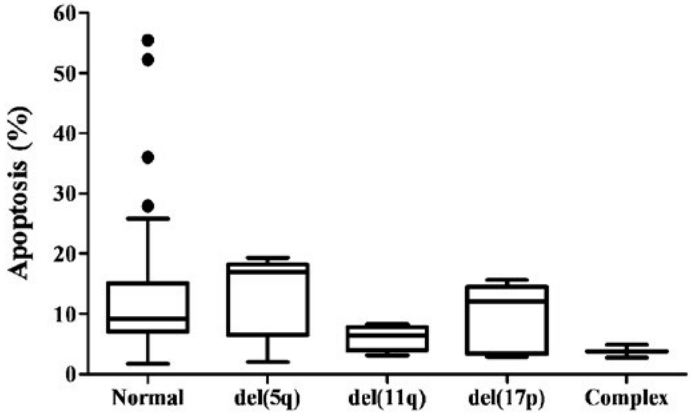

Figure 5. Association between the percentage of apoptosis and the karyotype in MDS patients. The results are shown in box-plot graphic in linear scale, showing the median, range, and the dots represent outliers

Source: The authors (2022).

Few studies have been conducted to try to identify an association between apoptosis and karyotypes of MDS patients. Washington and colleagues[20] and Sloand and colleagues[21] associated the presence of del(5q) and trisomy 8 with a reduction in the rate of apoptosis in MDS. In our study, MDS patients with normal karyotypes, del(5q) and del(17p) had significantly higher apoptosis rates than MDS cases with del(11q) and complex karyotypes.

An intriguing question related to apoptosis in MDS is a possible association with the paradox of the disease (BM usually hypercellular with peripheral blood cytopenias), in which apoptosis was the cause of ineffective hematopoiesis[8,34,35] or apoptosis would be related to the paradigm of the disease, where the presence of dysplasias (failure of maturation of hematopoietic cells) would lead to apoptosis as a physiological process, where the hematopoietic system would be trying to eliminate clones with dysplastic defects in early stages of the disease.[10,36,37] Thus, in this latter case, defects in differentiation or in maturation would be the cause of ineffective hematopoiesis, not apoptosis. Our results suggest that apoptosis may be a consequence of inefficient hematopoiesis. Therefore, apoptosis in primary MDS is related to the disease paradigm. In addition, we suggest that apoptosis is not the main mechanism associated with hypocellular MDS, and occurs preferentially in primary MDS cases of hyper/normocellular that are associated with a good prognosis. To our knowledge, this is the first study analyzing the percentage of apoptosis in BM of patients with primary MDS and their associations with patient age, BM cellularity and different karyotypic patterns.

Conclusions

The BM cells committed to differentiate ($CD34^-$ cells) had a higher percentage of apoptosis than BM hematopoietic progenitor cells ($CD34^+$ cells). Patients with normal karyotypes, del(5q) and del(17p) had higher apoptosis rates in comparison to patients with del(11q) and complex karyotypes. Apoptosis is an important characteristic of BM cells in adult and pediatric MDS patients, where the hematopoietic system would be trying to eliminate cells with dysplastic defects in the early stage of the disease.

~~Conflict of interest~~

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by Brazilian Ministry of Health (National Institute of Cancer, INCA, Brazil). The authors thank the pathologist, Dr. Cristiane Milito, from UFRJ, for her contribution to the revision of the MDS diagnosis.

References

1. Zimmermann KC, Bonzon C, Green DR. The machinery of programmed cell death. Pharmacol Ther 2001;92:57-70. doi: 10.1016/s0163-7258(01)00159-0
2. Wong RSY. Apoptosis in cancer: from pathogenesis to treatment. J Exp Clin Cancer Res. 2011;30:1-14. doi: 10.1186/1756-9966-30-87
3. Koff JL, Ramachandiran S, Bernal-Mizrachi L. A time to kill: targeting apoptosis in cancer. Int J Mol Sci. 2015;16:2942-55. doi: 10.3390/ijms16022942
4. Yoshida Y. A new look at apoptosis in MDS; an uneasy neighbor. Leuk Res 2007; 31:1617-19. doi: 10.1016/j.leukres.2007.06.003
5. Invernizzi R. The role of apoptosis in myelodysplastic syndrome. Haematologica. 2002;87:337-339.
6. Candelaria M, Dueñas-Gonzalez A. Therapy-related myelodysplastic syndrome. Expert Opin Drug Saf. 2015;12:1-11. doi: 10.1517/14740338.2015.1014340
7. Corey SJ, Minden MD, Barber DL, et al. Myelodysplastic syndromes: the complexity of stem-cell diseases. Nat Rev Cancer. 2007;7:118-29. doi: 10.1038/nrc2047
8. Boudard D, Vasselon C, Berthéas MF, et al. Expression and prognostic significance of Bcl-2 family proteins in myelodysplastic syndromes. Am J Hematol. 2002;70:115-25. doi: 10.1002/ajh.10108
9. Parker JE, Mufti GJ, Rasool F, et al. The role of apoptosis, proliferation, and the Bcl-2-related proteins in the myelodysplastic syndromes and acute myeloid leukemia secondary to MDS. Blood. 2000;96:3932-3938. doi: 10.1182/blood.V96.12.3932
10. List AF. New approaches to the treatment of myelodysplasia. Oncologist. 2002;7(Suppl 1):39-49. doi: 10.1634/theoncologist.7-suppl_1-39
11. Pleyer L, Valent P, Greil R. Mesenchymal Stem and Progenitor Cells in normal and dysplastic hematopoiesis-masters of survival and clonality? Int J Mol Sci. 2016;17(7):1009. doi: 10.3390/ijms17071009
12. Niemeyer CM, Baumann I. Myelodysplastic Syndrome in Children and Adolescents. Semin Hematol. 2008;45:60-70. doi: 10.1053/j.seminhematol.2007.10.006
13. Elghetany MT. Myelodysplastic Syndromes in Children: A Critical Review of Issues in the Diagnosis and Classification of 887 Cases from 13 Published Series. Arch Pathol Lab Med. 2007;131:1110-1116. doi: 10.5858/2007-131-1110-MSICAC
14. Polychronopoulou S, Panagiotou JP, Kossiva L, et al. Clinical and morphological features of paediatric myelodysplastic syndromes: a review of 34 cases. Acta Paediatric. 2004;93:1015-1023. doi: 10.1111/j.1651-2227.2004.tb02708.x
15. Tuzuner N, Cox C, Rowe JM, et al. Hypocellular myelodysplastic syndromes (MDS): new proposals. Br J Haematol.1995;91:612-617. doi: 10.1111/j.1365-2141.1995.tb05356.x
16. Tomonaga M, Nagai K. Hypocellular Myelodysplastic Syndromes and Hypocellular Acute Myeloid Leukemia: Relationship to Aplastic Anemia. In: The Myelodysplastic Syndromes: Pathobiology and Clinical management, USA: Marcel Dekker Inc;2002. p.121-138
17. Yue G, Hao S, Fadare O, et al. Hypocellularity in myelodysplastic syndrome is an independent factor which predicts a favorable outcome. Leuk Res. 2008;32:553-58. doi: 10.1016/j.leukres.2007.08.006
18. Goyal R, Qawi H, Ali I, et al. Biologic characteristics of patients with hypocellular myelodysplstic syndromes. Leuk Res. 1999;23:357-364. doi: 10.1016/s0145-2126(98)00187-8
19. de Souza DC, Fernandez CS, Camargo A, et al. Cytogenetic as an important tool for diagnosis and prognosis for patients syndrome. Biomed Res Int. 2014;2014:542395. doi: 10.1155/2014/542395
20. Washington LT, Jilani I, Estey E, et al. Less apoptosis in patients with 5q-syndrome than in patients with refractory anemia. Leuk Res. 2002;26: 899-902. doi: 10.1016/s0145-2126(02)00039-5
21. Sloand EM, Pfannes L, Chen G, et al. CD34 cells from patients with trisomy 8 myelodysplastic syndrome (MDS) express early apoptotic markers but avoid programmed cell death by up-regulation of antiapoptotic proteins. Blood. 2007;109:2399-2405. doi: 10.1182/blood-2006-01-030643
22. Hasle H, Niemeyer CM, Chessels JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia. 2003;17:277-282. doi: 10.1038/sj.leu.2402765
23. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the Classification of the Myelodysplastic Syndrome. Br J Haematol. 1982;51:189-199. doi: 10.1111/j.1365-2141.1982.tb02771.x
24. Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128–32.
25. Proytcheva M. Bone marrow evaluation for pediatric patients. International Journal of Laboratory Hematology. 2013;35: 283-289. doi: 10.1111/ijlh.12073
26. Foucar K. Bone Marrow Pathology. 2nd ed. ASCP Press, Chicago. 2001
27. McGowan-Jordan J, Simons A, Schmid M, editors. ISCN 2016: an international system for human cytogenetic nomenclature. Basel: Kager; 2016.
28. Raza A, Mundle S, Shetty V, et al. Novel insights into the biology of myelodysplastic syndromes: excessive apoptosis and the role of cytokines. Int J Hematol. 1996;63:265-278. doi: 10.1016/0925-5710(96)00455-0
29. Ogata K. Myelodysplastic syndromes: recent progress in diagnosis and understanding of their pathophysiology. J Nippon Med Sch. 2006;73:300-307. doi: 10.1272/jnms.73.300
30. Tormo, M., Marugán, I. & Calabuig, M. Myelodysplastic syndromes: an update on molecular pathology. Clin Transl Oncol. 2010;12:652-661. doi: 10.1007/s12094-010-0574-9
31. Davis RE, Greenberg PL. Bcl-2 expression by myeloid precursors in myelodysplastic syndromes: relation to disease progression. Leuk Res. 1998;22:767-777. doi: 10.1016/s0145-2126(98)00051-4
32. Raza A, Galili N. The genetic basis of phenotypic heterogeneneity in myelodysplastic syndromes. Nat Rev Cancer. 2012;12:849-59. doi: 10.1038/nrc3321
33. Serio B, Risitano AM, Giudice V, et al. Immunological Derangement in Hypocellular Myelodysplastic Syndromes. Transl Med UniSa. 2014;8:31-42.
34. Parcharidou A, Raza A, Economopoulos T, et al. Extensive apoptosis of bone marrow cells as evaluated by the in situ end-labelling (ISEL) technique may be the basis for ineffective haematopoiesis in patients with myelodysplastic syndromes. Eur J Haematol. 1999;62:19-26. doi: 10.1111/j.1600-0609.1999.tb01109.x
35. Boudard D, Sordet O, Vasselon C, et al. Expression and activity of caspases 1 and 3 in myelodysplastic syndromes. Leukemia. 2000;14:2045-2051. doi: 10.1038/sj.leu.2401959

36. Yoshida Y, Anzai N, Kawabata H. Apoptosis in myelodysplasia: a paradox or paradigm. Leuk Res. 1995;19: 887-891. doi: 10.1016/0145-2126(95)00100-x

37. Parker JE, Fishlock KL, Mijovic A, et al. “Low-risk” myelodysplastic syndrome is associated with excessive apoptosis and an increased ratio of pro-versus anti-apoptotic bcl-2-related proteins. Br J Haematol. 1998;103:1075-82. doi: 10.1046/j.1365-2141.1998.01114.x

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Original article

Evaluation of the serum level of C-reactive protein for diagnosing acute periprosthetic infection after total knee arthroplasty

Rafael E. de Paula,[1]* Fabrício B. Loures,[2] Fernando Rondon,[1] Rodrigo Pires e Albuquerque,[1] Phelippe V. Maia,[1] João Maurício Barreto[3]

Abstract

Objective: To determine the serum level of C-reactive protein (CRP) with greater accuracy for diagnosing acute periprosthetic infection after total knee arthroplasty (TKA). Method: Case-control study evaluating serum levels of CRP after TKA in infected and uninfected groups. The serum levels of CRP were assessed in patients submitted to TKA who had been readmitted in the acute phase for surgical debridement with implant retention and had their diagnosis of periprosthetic infection confirmed. These values were compared with a control group, which did not present infectious complications. Results: Between March 2014 and March 2016, 1,373 TKAs were performed in the institution, and 28 patients (0.49%) were readmitted in the acute phase with a diagnosis of periprosthetic infection. Sixteen patients met the inclusion criteria. Gender, skin color, age, and body mass index (BMI) were similar between the groups. The patients in the acute periprosthetic infection group had significantly higher mean serum levels of CRP than the control group ($p<0.001$). For CRP levels = 30.615, the test's highest sensitivity (75%) and specificity (77%) were achieved, with an accuracy of 77.3% for the diagnosis of infection. The area under the 0.762 Receiver Operating Characteristics (ROC) curve showed satisfactory performance of the proposed test. Conclusion: Serum levels of CRP greater than 30.615 mg/L in the third week after TKA associated with clinical signs are highly suggestive of acute periprosthetic infection.

Keywords: Knee; Osteoarthritis; Arthroplasty; Infection; CRP.

1. Centro de Cirurgia de Joelho, Instituto Nacional de Traumatologia e Ortopedia (INTO), Rio de Janeiro, RJ, Brazil.
2. Unidade Docente Assistencial de Ortopedia, Universidade do Estado do Rio de Janeiro, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.
3. Serviço de Ortopedia e Ciurgia do Joelho, Hospital São Vicente da Gávea, Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
Estrada Francisco da Cruz Nunes, 7465, Casa 16
Condomínio Ubá Piratininga, Niterói, RJ, Brazil.
CEP: 24350-310.
E-mail: erthalortopedia@gmail.com
ORCID: https://orcid.org/0000-0003-2112-7652

BJHBS, Rio de Janeiro, 2022;21(1):31-38
DOI: 10.12957/bjhbs.2022.68178
Received on 17/01/2022. Approved on 25/04/2022.

Introduction

Total knee arthroplasty (TKA) is a surgical procedure to treat advanced cases of osteoarthritis, from refractory to conservative treatment. Its effectiveness and safety are widely proven in the literature.[1-5]

Increases in life expectancy[6] and the growth of obesity[7] have exponentially increased the demand for TKAs. Since the end of the 1980s, the number of surgeries performed in the United States (USA) rose by up to 10% per year.[4] As a result, between 1990 and 2002, the number of TKA per 100,000 inhabitants tripled.[4]

In 2019, more than 13,000 knee prostheses were implanted in Brazil, and this number is expected to increase exponentially, driven by increased longevity and growth of obesity.[3] Although the clinical satisfaction rate can reach up to 92% of operated patients,[1-3], complications occur in between 0.4%[8] and 7% of cases.[3,9,10] Among the difficulties, infection is the most frequent and feared, accounting for up to 25.2% of revisions and reaching mortality rates of 18%.[11] In addition, the cost of treating a prosthesis-associated infection is about three to four times the value of a primary arthroplasty.[11]

The diagnosis of infection after TKA is difficult in the immediate postoperative period since clinical signs, such as edema and erythema, can occur even in a normal postoperative period.[12] In addition, laboratory tests traditionally used to diagnose periprosthetic infections, such as C-reactive protein (CRP) and serum erythrocyte sedimentation rate (ESR), are usually elevated in the immediate postoperative period.[13] Early diagnosis allows treatment with surgical debridement and implant retention (D+R), a less aggressive strategy, with lower cost and a success rate of up to 36%,[14] as long as it is performed until the third week.[15] Although serum

CRP is part of the periprosthetic infection protocol,[16] its level may be altered without any relation to infection in up to two-thirds of patients.[17]

The objective of this study was to determine the serum value of CRP with greater accuracy to assist in the diagnosis of acute periprosthetic infection after TKA.

Materials and methods

After the approval by the institution Ethics and Research Committee under number 804.216, the medical records of all hospitalized patients diagnosed with acute periprosthetic infection between March 2014 and March 2016 were evaluated retrospectively and for convenience.

The study included all patients submitted to TKA who evolved to acute postoperative infection within 30 days after surgery and required surgical intervention. The diagnosis of periprosthetic infection was confirmed according to the criteria established by the Center for Disease Control (CDC).[18]

Patients who did not have a diagnosis of infection confirmed by the results of the cultures obtained intraoperatively, who had been diagnosed for over 30 days, or with incomplete data in the medical record were excluded.

A control group was created, consisting of 103 patients submitted to TKA, with the same pre- and postoperative protocol, the same surgical technique, and who did not present infectious complications.

Data on age, gender, BMI, and ethnicity were obtained from all patients. In the "case" group, both the CRP value and the postoperative interval to collect the CRP that led to reoperation were recorded. In addition, preoperative CRPs on the third and 21st postoperative days were evaluated in the control group.

Quantitative CRP, evaluated in a 2 mL sample of venous blood, was used for analysis, which was performed in the institution's laboratory. The turbidimetric method was used in the BT3000 *Plus* ® biochemistry analyzer (Wiener Lab – Rosario, Santa Fe, Argentina), with reference levels in adults of 5 mg/L for infectious diseases.

The data collected were analyzed using the Statistical Package for the Social Science (SPSS) program, version 22.0, and Microsoft Excel 2011. The data were synthesized for sample characterization and descriptive analysis of the variables' behavior by calculating descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation, proportions of interest), distributions of simple frequencies, and cross tables and descriptive graphs.

The Receiver Operating Characteristics (ROC) curve was used to identify an optimal CRP cutoff point for diagnosing the infection. The performance measure of the diagnostic test proposed using this cutoff point was the area under the ROC curve, and the significance of this area was evaluated by the test that judges the null hypothesis H0: the area under the ROC curve is equal to 50. Under the null hypothesis, the proposed test has no power to discriminate between infected and uninfected individuals and is therefore expected to reject H0. In addition to the significance test, an asymptotic confidence interval was obtained for the area under the ROC curve, which was expected not to contain the value of 0.5. The data were analyzed considering a maximum significance level of 5%.

Results

Between March 2014 and March 2016, 1,373 primary knee TKAs were performed. Twenty-eight readmissions (0.49%) occurred with a diagnosis of acute periprosthetic infection and indication for surgical debridement and implant retention. After the application of inclusion and exclusion criteria, 16 patients were selected for the study.

The statistical analysis showed that the case and control groups were similar in gender ($p = 0.535$), age ($p = 0.833$), skin color ($p = 0.264$), and BMI ($p = 0.453$) (Figures 1 and 2).

Table 1 shows the main CRP statistics of infected and uninfected patients. Both groups show a high variability of values, as shown by the sample amplitude and coefficients of variation. However, the mean and median values of the infected group are higher ($p = 0.001$) (Figure 3).

The ROC curve identified as the optimal cutoff point the CRP level equal to 30.615 mg/L, where sensitivity and specificity simultaneously reach their highest level (Figure 4).

The test based on the proposed cutoff point has sensitivity equal to 0.75 and specificity equal to 0.777. Therefore, the accuracy of the proposed test is 77.3%. In addition, the proportion of false negatives is equal to 25.0%.

In this analysis, the area under the ROC curve was 0.762, showing satisfactory performance of the proposed test with the new CRP cutoff point. Table 2 shows the significance analysis of this area under the curve.

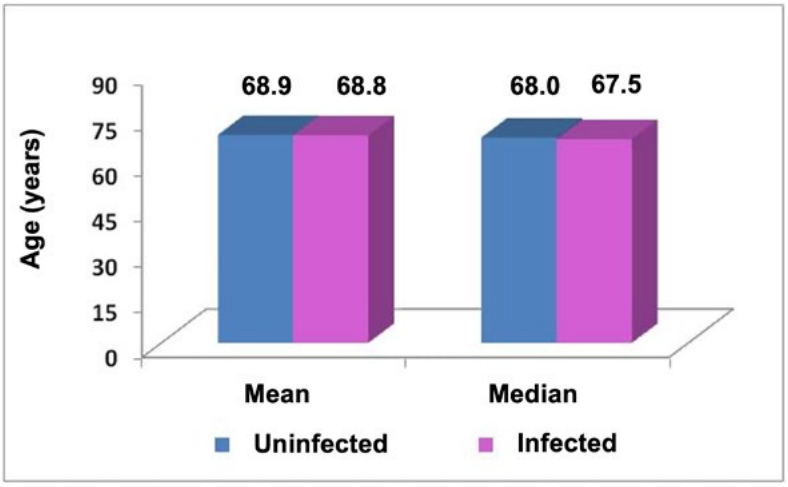

Figure 1. Mean and median ages of uninfected and infected patients
Source: The authors (2022).

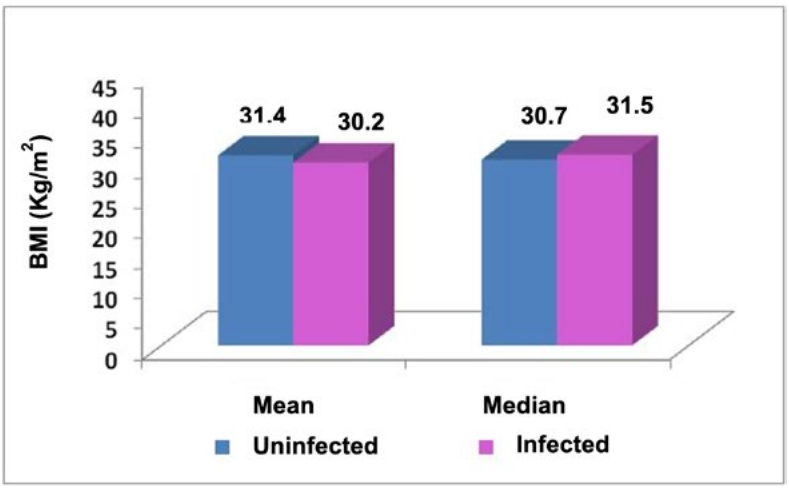

Figure 2. Mean and median BMI of uninfected and infected patients
Source: The authors (2022).

Table 3 shows, for different values of CRP cutoff points, the measures of false positive, sensitivity, and specificity, resulting in tests with stricter and less strict criteria. The serum level of CRP of 30.615 mg/L is the one that presented the greatest balance between sensitivity and specificity.

Discussion

Increased life expectancy and the desire for greater activity, associated with favorable results, have motivated the increased demand for TKA surgeries in recent years. Unfortunately, however, the number of complications continues to rise in equal proportion.

The diagnosis of infection after knee arthroplasty in the immediate postoperative period is particularly difficult since clinical signs can occur even in the normal postoperative period.[13] The laboratory tests traditionally used for diagnostic of periprosthetic infections, such as CRP, are usually elevated in the immediate postoperative period.[12]

The definition and performance of studies on this subject in Brazil are important in order to adopt

Table 1. Main CRP statistics in the infected and uninfected groups

CRP Statistics	Uninfected	Infected
Mean	27.4	57.3
Median	15.4	39.1
Standard deviation	36.9	49.4
Minimum	0.7	5.4
Maximum	263.9	154.0
Sample amplitude (Range)	263.2	148.6
CV	1.4	0.9
p-value of KS test	0.000	0.029
p-value of SW test	0.000	0.003
p-value of Mann Whitney test	0.001	

Legend: CV: Coefficient of variation. KS test: Kolmogorov–Smirnov test. SW test: Shapiro-Wilk test.
Source: The authors (2022).

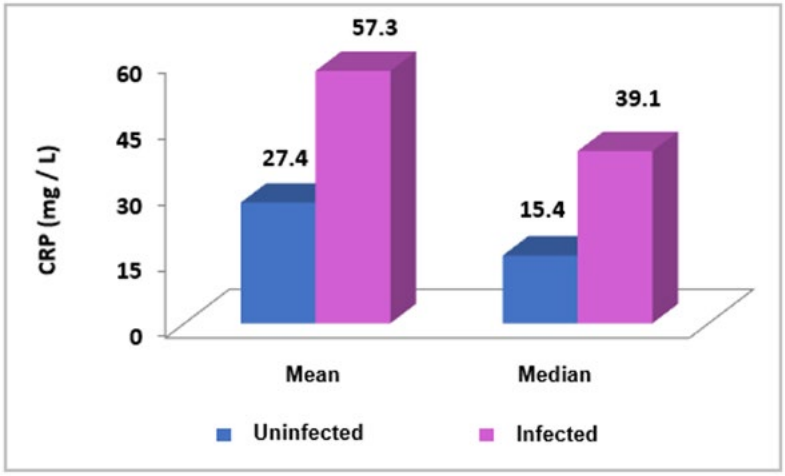

Figure 3. Mean and median CRP dosages in uninfected and infected patients
Source: The authors (2022).

specific protocols for diagnosing and treating acute postoperative infections after TKA.

Barreto and colleagues[17] evaluated CRP levels in 103 patients undergoing primary TKA. Serum CRP was measured on the day before surgery, as well as on the third and 21st days after the procedure. There was a sudden increase on the third day after surgery, reaching a mean value of 111.9 mg/L, with a median of 75.9 mg/L. Two-thirds of the patients maintained above normal values of serum CRP at the end of the third week. This alteration was not related to infectious complications but to surgical trauma. As this is a quantitative examination, it is important to define a value that presents greater safety for diagnosing acute periprosthetic infection and helps to indicate the need for a new surgical intervention. Our results showed that the value of 36.615 mg/L would be the most reliable for suspecting periprosthetic infection.

Greidanus and colleagues[19] suggest that the serum level of CRP is a good test for establishing the presence

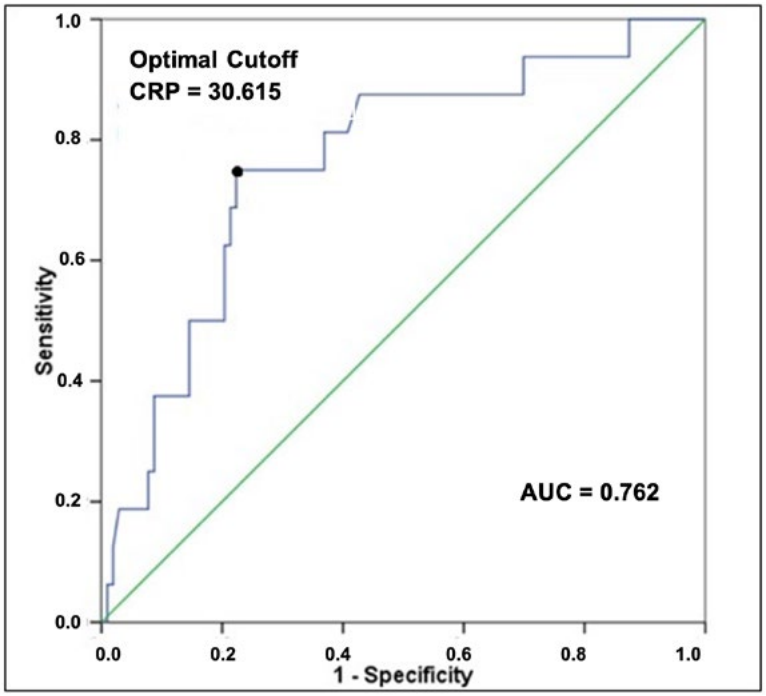

Figure 4. Mean and median CRP dosages in uninfected and infected patients
Source: The authors (2022).

Table 2. Significance analysis of the area under the ROC curve

Area under the ROC curve	Standard error	Asymptotic p-value	Asymptotic confidence interval for the area under the curve	
			Inferior limit	Upper limit
0.762	0.065	0.001	0.636	0.889

Source: The authors (2022).

or absence of infection before surgical intervention in patients with pain at the site of knee arthroplasty. However, this study evaluated the role of CRP in chronic infections and not in the acute scenario, as in our study.

Paul and colleagues[20] evaluated the ideal CRP cutoff point after arthroplasties in the immediate postoperative period (within six weeks of surgery). They showed that adopting a CRP cutoff point of 93 mg/L has ideal sensitivity. However, their study evaluated patients undergoing total hip arthroplasty and not TKA, as in our study. Since these surgeries are different, it is to be expected that the specific level for postoperative follow-up of knee arthroplasty will have a different cutoff point.

Bedair and colleagues[12] established guidelines for diagnosing infection after TKA in the immediate postoperative period (first six weeks after surgery). In addition, they demonstrated that adopting a CRP cutoff point of 95 mg/L has ideal sensitivity, being substantially higher than those previously published for late periprosthetic infections.[13,21-23]

Cipriano and colleagues[24] suggested a lower CRP cutoff point in patients who underwent knee prosthesis that evolved into periprosthetic infection. The levels found were 15 and 17 mg/L for non-inflammatory and inflammatory arthritis, respectively, with an area under the curve of 88.5% and 85.1%. Unlike our study, these authors did not investigate CRP cutoff levels specific

Table 3. CRP cutoff points for tests with stricter and less strict criteria

	CRP cutoff point	Specificity	Sensitivity	Specificity
Less strict criteria →	0.000	1.000	1.000	0.000
	3.780	0.942	1.000	0.058
	5.060	0.883	1.000	0.117
	6.355	0.825	0.938	0.175
	7.410	0.767	0.938	0.233
	9.730	0,709	0.938	0.291
	11.275	0.660	0.875	0.340
	13.085	0.602	0.875	0.398
	15.000	0.524	0.875	0.476
	17.510	0.456	0.875	0.544
	19.560	0.388	0.813	0.612
	22.860	0.340	0.750	0.660
	26.165	0.282	0.750	0.718
Optimal point	30.615	0.223	0.750	0.777
← Stricter criteria	35.080	0.204	0.500	0.796
	43.000	0.146	0.500	0.854
	55.070	0.107	0.375	0.893
	75.010	0.078	0.188	0.922
	148.000	0.019	0.125	0.981
	264.900	0.000	0.000	1.000

Legend: CRP: C-reactive protein.
Source: The authors (2022).

to acute or chronic infection cases, which may explain the differences between the studies.

Glehr and colleagues,[25] using a CRP cutoff of 23.65 mg/L to diagnose acute infections after knee or hip prostheses, found 80% sensitivity and 79% specificity for the test. The same study suggests that other tests, such as the serum dosage of procalcitonin and IL-6, may help to detect infection in arthroplasty revisions.

In their cohort, Kim and colleagues[26] reported that 13% of patients undergoing primary TKA evolved with a so-called bimodal pattern of increased serum CRP (elevation-depression-elevation) in the first four weeks after operation. However, they concluded that this increase might occur in similar proportions for causes other than periprosthetic infection, so it is necessary to investigate them in a scenario of acute infection after TKA.

Early diagnosis of a periprosthetic infection increases the chances of successful treatment. The performance of the implant debridement and retention procedure (D+R) with polyethylene replacement has a probability of success between 38 and 48%. In addition, if a two-stage revision is necessary, the earlier the diagnosis, the better the result, as demonstrated by Olubsola and colleagues.[26] They showed that the success rate after the two-stage revision procedure in patients submitted to D+R is significantly higher than in those submitted to sequential revision, with failures of 8.7% in the first group versus 17.5% in the second.

This is the first Brazilian study on the subject. A positive aspect of our research is the significant number

of patients, since it addresses a specific and relatively uncommon complication. In addition, the aid of an objective criterion in diagnosing acute infection is extremely desired and awaited by surgeons who perform arthroplasties. The limitations of the research are related to the fact that it is a retrospective study, since the approach protocols have been changed over time, leading to a high rate of exclusion. Nevertheless, we believe that these results can consistently assist in creating future algorithms that increase the reliability of the use of serum CRP in diagnosing acute periprosthetic infection.

Conclusion

Serum levels of CRP higher than 30.615 mg/L in the third week after TKA associated with clinical signs are highly suggestive of acute periprosthetic infection.

Acknowledgments

Study performed at the *Centro de Cirurgia do Joelho, Instituto Nacional de Traumatologia e Ortopedia* (INTO), Rio de Janeiro, RJ, Brazil.

References

1. Berger RA, Rosenberg AG, Barden RM, et al. Long-Term Followup of the Miller-Galante Total Knee Replacement. Clinical Orthopaedics & Related Research. 2001;388:58–67.
2. Indelli PF, Aglietti P, Buzzi R, et al. The Insall-Burstein II prosthesis: A 5- to 9-year follow-up study in osteoarthritic knees. Journal of Arthroplasty. 2002;17:544–549. doi: 10.1054/arth.2002.32186. PMID: 12168167
3. Bozic KJ, Kurtz SM, Lau E, et al. The epidemiology of revision total knee arthroplasty in the United States. Clinical Orthopaedics and Related Research. 2010;468:45–51. doi: 10.1007/s11999-009-0945-0. PMID: 19554385
4. CDC - Arthritis - Basics - Definition - Osteoarthritis [Internet]. [cited 2014 Apr 24]. Available from: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm.
5. Kurtz S, Ong K, Lau E, et al. Projections of Primary and Revision Hip and Knee Arthroplasty in the United States from 2005 to 2030. The Journal of Bone and Joint Surgery (American). 2007;89:780. doi: 10.2106/JBJS.F.00222. PMID: 17403800
6. Loures FB, Góes RF de A, da Palma IM, et al. Anthropometric study of the knee and its correlation with the size of three implants available for arthroplasty. Revista Brasileira de Ortopedia. 2016;51:282–289. doi: 10.1016/j.rboe.2015.07.009. PMID: 27274481
7. Loures FB, Góes RF de A, Labronici PJ, et al. Evaluation of body mass index as a prognostic factor in osteoarthrosis of the knee. Revista Brasileira de Ortopedia (English Edition). 2016;51:400–404. doi: 10.1016/j.rboe.2016.05.002. PMID: 27517017
8. de Carvalho Júnior LH, Temponi EF, Badet R. Infection after total knee replacement: diagnosis and treatment. Revista Brasileira de Ortopedia (English Edition). 2013;48:389–396. doi: 10.1016/j.rboe.2013.01.003
9. Illingworth KD, Mihalko WM, Parvizi J, et al. How to Minimize Infection and Thereby Maximize Patient Outcomes in Total Joint Arthroplasty: A Multicenter Approach. the Journal of Bone and Joint Surgery. 2013;95:1–13. doi: 10.2106/JBJS.L.00596
10. Lentino JR. Prosthetic Joint Infections: Bane of Orthopedists, Challenge for Infectious Disease Specialists. Clinical Infectious Diseases. 2003;36:1157–1161. doi: 10.1086/374554. PMID: 12715311
11. Matar WY, Jafari SM, Restrepo C, et al. Preventing Infection in Total Joint Arthroplasty. The Journal of Bone and Joint Surgery-American Volume. 2010;92:36–46. doi: 10.2106/JBJS.J.01046. PMID: 21123590
12. Bedair H, Ting N, Jacovides C, et al. The Mark Coventry Award: Diagnosis of early postoperative TKA infection using synovial fluid analysis. Clinical Orthopaedics and Related Research. 2011;469:34–40. doi: 10.1007/s11999-010-1433-2. PMID: 20585914
13. Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: From the workgroup of the musculoskeletal infection society. Clinical Orthopaedics and Related Research. 2011;469:2992–2994. doi: 10.1007/s11999-011-2102-9. PMID: 21938532
14. Odum SM, Fehring TK, Lombardi A V, et al. Irrigation and debridement for periprosthetic infections: Does the organism matter? Journal of Arthroplasty. 2011;26:114–118. doi: 10.1016/j.arth.2011.03.031. PMID: 21621955
15. Scott WN. Insaal & Scott Surgery of the knee. 5th ed. Philadelphia: Elsevier/Churchill Livingstone; 2012.
16. Parvizi J, Gehrke T. Consenso internacional em infecções articulares periprotéticas. Revista Brasileira de Ortopedia. 2016
17. Barreto JM. Centro de Cirurgia de Joelho. 10th ed. Rio de Janeiro: LTC; 2008.
18. Garner J, Jarvis W, Emori T, et al. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128–140.
19. Greidanus N, Masri B, Garbuz D, et al. Use of Erythrocyte Sedimentation Rate and C-Reactive Protein Level to Diagnose Infection Before Revision Total Knee Arthroplasty: A Prospective Evaluation. J Bone Joint Surg Am. 2007;89:1409–1416.
20. Yi PH, Cross MB, Moric M, et al. The 2013 Frank Stinchfield Award: Diagnosis of infection in the early postoperative period after total hip arthroplasty. Clinical Orthopaedics and Related Research. 2014;472:424–429. doi: 10.1007/s11999-013-3089-1. PMID: 23884798
21. Ghanem E, Parvizi J, Burnett RSJ, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. Journal of Bone and Joint Surgery - Series A. 2008;90:1637–1643. doi: 10.2106/JBJS.G.00470. PMID: 18676892
22. Schinsky M, Della Valle C, Sporer S, et al. Perioperative Testing for Joint Infection in Patients Undergoig Revision Total Hip Arthroplasty. J Bone Joint Surg Am. 2008;90:1869–1875.
23. Spangehl MJ, Masri BA, O'Connell JX, et al. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision

total hip arthroplasties. The Journal of Bone and Joint Surgery American volume. 1999;81:672–683. doi: 10.1097/00003086-197209000-00020. PMID: 10360695

24. Cipriano CA, Brown NM, Michael AM, et al. Serum and synovial fluid analysis for diagnosing chronic periprosthetic infection in patients with inflammatory arthritis. The Journal of Bone and Joint Surgery American volume. 2012;94:594–600. doi: 10.2106/JBJS.J.01318. PMID: 22488615
25. Glehr M, Friesenbichler J, Hofmann G, et al. Novel biomarkers to detect infection in revision hip and knee arthroplasties. Clinical Orthopaedics and Related Research. 2013;471:2621–2628. doi: 10.1007/s11999-013-2998-3. PMID: 23609811
26. Brimmo O, Ramanathan D, Schiltz NK, et al. Irrigation and Debridement Prior to a Two-Stage Revision Total Knee Arthroplasty Does Not Increase Risk of Failure. J Arthroplasty. 2016;31:461–464. doi: 10.1002/nbm.3369.Three. PMID: 24655651

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Expenditures on the treatment of encephalon malignant neoplasia by the Brazilian public health system (2008-2017)

Carlos G. Garcia,[1]* Joice Nespoli[2]

Abstract

Introduction: Encephalon malignant neoplasia (EMN) is a harmful type of cancer and its most aggressive phenotypes lead to the demise of patients in 12-18 months despite the use of state-of-the-art therapies, which remain inefficient and expensive for patients, families and health systems. The aim of this work was to analyze the expenditures of the Brazilian Sistema Único de Saúde (SUS), the national public health system, on EMN patients compared to all neoplasia patients over a span of ten years (2008 to 2017). Methodology and resources: Monthly data were collected from the SUS data base DATASUS from 2008 to 2017 and analyzed with regard to EMN and general neoplasia for the following categories: value of total expenditures; number of hospitalizations; mean value of hospitalizations; mean of monthly permanence time and death rate. Results: More than 0.3% of SUS costs were directed to EMN patients, although they represented 0.1% of total hospitalizations. The mean value of hospitalization of EMN patients was almost 80% that of general neoplasia patients and hospitalization time was twice that of general neoplasia patients. Moreover, EMN patients had a death rate almost four times higher than that of general neoplasia patients. Discussion and conclusion: EMN therapies remained expensive and lacked efficacy in the time period under analysis, with a disproportionate share of SUS expenditure being dedicated to these patients. Improving the effectiveness of treatment requires drug repurposing and adjuvant chemotherapy—in addition to radiotherapy and the use of monoclonal antibodies.

Keywords: Encephalon malignant neoplasia; Cancer treatment costs; SUS.

1. Centro Universitário Anhanguera de Niterói, Biomedical sciences graduate course, Niterói, Rio de Janeiro, Brazil.
2. Centro Universitário Anhanguera de Niterói, Biomedical sciences graduate course, Niterói, Rio de Janeiro, Brazil.

***Correspondence address:**
Avenida Visconde do Rio Branco, 123
Niterói, RJ, Brazil.
CEP: 24020-005.
E-mail: cg_garcia@id.uff.br.
ORCID: https://orcid.org/0000-0002-1247-2967

BJHBS, Rio de Janeiro, 2022;21(1):39-46
DOI: 10.12957/bjhbs.2022.68180
Recebido em 15/07/2021. Aprovado em 25/04/2022.

Introduction

Primary central nervous system (CNS) tumors, such as encephalon malignant neoplasia (EMN), account for around 2% of all adult human neoplasia. They involve many types of tumor, such as astocytomas—the most common EMNs—, ependymomas, oligodendrogliomas, neuroblastomas and others.[1,2] Considering all EMNs, Ostrom and colleagues (2018) showed that the incidence of new cases in the USA varies from 5 (children) to 50 (elders above 60 years old)/100.000 habitants per year, with variations depending on the age group.[3,4] One of the most classic symptoms of EMNs are associated convulsions in peritumoral area.[5] It is well known in the literature that the most common adult EMN is grade IV astrocytoma, known as human multiform glioblastoma (GB). GB is a WHO-IV grade tumor that exhibits nuclear atypia and genetic heterogeneity; it can induce neoangiogenesis and exhibit large necrosis in central tumor areas.[3,6-8] In Brazil, Werneck de Carvalho and colleagues (2017) showed that neuroepithelial CNS tumors accounted for almost 50% of all CN-diagnosed tumors in the population of a certain region in the state of Pará, Brazil, from 1997 to 2014.[9] Another recent study[10] showed that the greatest incidence of these neuroepithelial CNS tumors in Brazil occurs in the 40-59 year-old age group with no distinction between the sexes.

EMN diagnosis is identified through magnetic resonance imaging (MRI) in order to evaluate the location of the tumoral mass inside the encephalon and is followed by neurosurgery for the removal of the largest possible area of the tumoral mass. With regard to GB, even after neurosurgery and radio/chemotherapy protocols using the DNA alkylating agent temozolomide (TMZ) for many sessions, tumoral recurrence transpires in the vast majority of the cases.[6,11,12] It is well known that the overall 5-year survival rate of GB patients is 5%, despite the use of all available therapeutic tools, due to the capacity of GB to deregulate diverse

signaling pathways, which makes the establishment of a therapeutic protocol extremely difficult.[4,13,14]

Even with this evident problem, significantly more than 700 clinical trials related to GB exist, using different therapeutic protocols and interventions in an attempt to enhance the overall survival rate of patients.[15] This fact calls into question current therapies for GB and highlights the need to find therapeutic alternatives for treatment of this type of tumor and other EMNs, such as neuroblastomas, oligodendrogliomas and even lower-level (II and III) astrocytomas. One of the explanations for this myriad of protocols is the attempt to act, mainly pharmacologically, on many deregulated signaling pathways in EMN cells. The literature highlights the fact that GB and neuroblastoma cells, for example, exhibit enhanced phosphoinositide 3-kinase/RAC-alpha serine-threonine protein kinase/mammalian target of Rapamycin (PI3 kinase/Akt/mTOR) activation as well as Rat sarcoma virus (Ras), epidermal/vascular endothelial growth factor (EGF/VEGF), glycogen synthase kinase 3 beta (GSK-3β) and protein kinase C (PKC) downstream pathway triggering.[13,16-19] Since many of these pathways interact in tumoral cells, it is clear that no simple therapeutic approach can be easily found.

The literature widely describes that diagnosing and treating EMNs, especially GBs, is a costly process that involves a significant amount of time and is also very expensive for patients and health systems around the globe, while leading to no significant results in its clinical management.[20-22] Considering these factors, the aim of this work was to evaluate how the Brazilian public health system (Sistema Único de Saúde, SUS) managed certain aspects related to EMN, especially treatment costs, hospitalization time and death rates, over a decade (2008-2017).

Materials and methods

Data collect and table generation: Data from the Brazilian "Banco de Dados do Sistema Único de Saúde" (DATASUS) (http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sih/cnv/niuf.def) were used for the 2008-2017 period, year by year, concerning: a) Total value per month, Total value for the ICD-10-Neoplasia category and Total value for EMN (Table 1); b) Number of hospitalizations per month, Number of hospitalizations for the ICD-10-Neoplasia category and Number of hospitalizations for EMN (Table 2); c) Mean value of hospitalizations per month, Mean value of hospitalization for the ICD-10-Neoplasia category and Mean value of hospitalizations for EMN (Table 3); d) Mean time of permanence per month, Mean time of permanence for the ICD-10-

Table 1. SUS expenditures percentage from 2008 to 2017

Year	A) SUS expenditures with all neoplasia (%)	B) SUS expenditures with EMN (%)	C) EMN expenditures/ all neoplasia expenditures (%)
2008	7.15	0.269514	3.76
2009	7.21632	0.282442	3.916286
2010	7.318336	0.26667	3.645068
2011	7.515978	0.28	3.787532
2012	7.907894	0.296386	3.748988
2013	10.13073	0.294075	2.922765
2014	10.83456	0.306753	2.833148
2015	11.2412	0.321342	2.859452
2016	11.51003	0.344574	2.995991
2017	11.59962	0.337538	2.9101
Mean ± SEM	9.24±1.97	0.30±0.02	3.34±0.46

Legend: SUS: Sistema Único de Saúde. EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) total net expenditures (in Brazilian Real): 12,049,220,951.00.

Source: The authors (2022).

Table 2. SUS hospitalization percentage

Year	A) Hospitalizations due to general neoplasia (%)	B) Hospitalizations due to EMN (%)	C) EMN hospitalizations/ General neoplasia hospitalizations (%)
2008	5,05	0.09	1.841264
2009	5.166218	0.099831	1.934264
2010	5.323121	0.099351	1.867213
2011	5.531869	0.107138	1.93862
2012	5.949984	0.112836	1.897055
2013	6.199764	0.115381	1.861056
2014	6.410482	0.113681	1.773359
2015	6.640472	0.118143	1.779139
2016	7.382037	0.137936	1.868537
2017	6.933717	0.125973	1.816812
Mean ± SEM	6.06±0.79	0.11±0.01	1.86±0.05

Legend: SUS: Sistema Único de Saúde. EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean of total net hospitalizations/year: 11,041,635.00.

Source: The authors (2022).

Table 3. Mean hospitalization value percentage

Year	A) Mean hospitalization value for general neoplasia (%)	B) Mean hospitalization value for EMN (%)	C) Mean EMN value/ mean general neoplasia value (%)
2008	141.71	289.90	204.5576
2009	139.7482896	283.0601	202.5259
2010	137.5134631	268.2042	195.0322
2011	135.8815229	265.5436	195.4642
2012	132.9390426	262.8976	197.7258
2013	164.5797878	256.0027	155.5493
2014	169.0813648	269.8476	159.5963
2015	169.3457882	271.9947	160.6149
2016	169.2704299	271.1682	160.1982
2017	167.5050954	267.8203	159.8879
Mean± SEM	152.76±16.23	270.64±9.67	179.12±21.26

Legend: EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) hospitalization values (Brazilian Real): 1070.29

Source: The authors (2022).

Neoplasia category per month and Mean time of permanence for EMN (Table 4); and e) Death rate for the ICD-10-Neoplasia category and Death rate for EMN (Table 5).

The data were then organized in tables and shown as a percentage of each given year's value/number. Mean values of the studied period regarding the following parameters were included in the captions of the respective

Table 4. Mean hospitalization time percentage

Year	A) Mean hospitalization time for general neoplasia (%SUS mean)	B)Mean hospitalization time for EMN ((%SUS mean)	C) Mean hospitalization time for EMN (% mean general neoplasia value)
2008	101.72	213.7931	210.1695
2009	101.7241	208.6207	205.0847
2010	100	208.7719	208.7719
2011	98.24561	207.0175	210.7143
2012	96.49123	205.2632	212.7273
2013	96.49123	207.0175	214.5455
2014	96.42857	201.7857	209.2593
2015	96.42857	201.7857	209.2593
2016	92.85714	196.4286	211.5385
2017	94.44444	194.4444	205.8824
Mean± SEM	97.48±2.93	204.49±5.92	209.80±2.87

Legend: EMN: Encephalon malignant neoplasia. Last line: mean ± standard error of the mean. Mean: Sistema Único de Saúde (SUS) hospitalization time (days): 5.66.
Source: The authors (2022).

Table 5. Death rate

Year	A) Death rate by general neoplasia	B) Death rate by EMN
2008	3.28	13.72
2009	3.48	13.63
2010	3.61	14.09
2011	3.71	13.82
2012	3.8	13.5
2013	3.94	13.4
2014	3.97	14.1
2015	4.18	13.67
2016	4.38	13.7
2017	4.29	13.59
Mean ± SEM	3.86±0.35	13.72±0.22

Legend: Last line: mean ± standard error of the mean.
Source: The authors (2022).

tables: Total value per month, Total hospitalizations per month, Mean value of hospitalization and Mean time of permanence per month.

Results

At first, we wanted to identify the overall sum of SUS expenditures—that is, including all ICD-10 identified pathologies—and the share of this sum dedicated to all neoplasia and to EMNs specifically. As shown in column A of Table 1, a mean of 9.24±1.97% of SUS expenses were allocated to neoplasia patients during the 10 years analyzed. Specifically verifying SUS expenditures on EMN patients during the same period, we found that 0.3±0.02% of overall disbursements were dedicated to them (Table 1, column B). Using a more specific comparison parameter, we found that only 3.34±0.46% of total SUS expenditures on neoplasia were allocated to EMN patients (Table 1, column C).

Following the initial identification of mean general expenditures, we decided to evaluate the percentage of SUS hospitalizations related to neoplasia (Table 2, column A) as well as to EMN (Table 2, column B). We observed that 6.06±0.79% of hospitalizations were due to neoplasia, but only 0.11±0.01% corresponded to EMN in the period. We also verified that these hospitalizations accounted for 1.86±0.05% of the total number of neoplasia hospitalizations. This highlights the low number of patients hospitalized in SUS due to EMN during the years under analysis.

Next, we decided to evaluate differences in the cost of hospitalization between neoplasia and EMN patients. Table 3 shows SUS outcomes per hospitalization for neoplasia (column A) and we verified that these were 52.76±16.23% higher than the mean overall cost of hospitalization. Specifically for EMN, we observed that these patients exhibit a higher mean cost of hospitalization compared to the same parameter (170.64±9.67%) (column B). Moreover, we observed that the value for EMN was 79.12±21.26% higher than that of neoplasia in general (column C). In summary, EMN patients generate more costs for the SUS than other neoplasia patients, even though they are fewer in number.

In light of the data presented, we wondered if the high cost of EMN patients could be justified by a reduction in their hospitalization time or else in their death rates. To study this hypothesis, Table 4 was generated and shows that neoplasia patients are hospitalized for roughly the same time as the general mean of the SUS (column A, 97.48±2.93%). On the other hand, EMN patients presented a doubled hospitalization time compared to neoplasia in general (column C, 209.8±2.87%) or the mean of the SUS (column B, 204.49±5.92%). Even after the costly treatment allocated to a very small number of SUS patients, EMN patients clearly remained hospitalized for a longer time.

Last, we sought to evaluate the death rate of EMN patients compared to neoplasia patients (Table 5). We observed that death rate for neoplasia is around 3.86±0.35%, while for EMN this rate is three times higher, reaching 13.72±0.22%. It is noteworthy that the EMN death rate showed only a small variation over the 10 years under analysis, while total neoplasia grew gradually during the same period. In summary, EMN patients spent more time hospitalized and exhibited a higher death rate.

Discussion

A study showed that annual cost for treatment of CNS tumors in the USA in 2010 was the highest among all tumor types evaluated in the study.[20] The same study projected that the total cost with the treatment of cerebral tumors in the USA would increase by more than 20% from 2010 to 2020.

Despite the small number of patients compared to other neoplasia types, the direct and indirect economic impacts caused by high EMN treatment costs and mortality are substantial.[22,23] As an example, Tykocki and Eltayeb[24] published a meta-analysis identifying the 10-year survival rate in GB-diagnosed groups involving more than 30 studies between 1950 and 2010. The authors observed that this percentage was less than 1% even after the use of the entire available therapeutic arsenal in the respective decades. In Brazil the reality is the same. Regarding patient mortality, a study by Monteiro and Koifman[21] revealed that, in Brazil, the mortality rate due to cerebral tumors, whether malignant or not, increased by almost 50% from 1980 to 1998, mainly in the adult and elderly population groups.

In the present study we observed that EMN treatment costs are high and directed to a small number of patients. Additionally, we evaluated that the death rates related to EMN were three times higher than those of other neoplasia in the decade under analysis, despite the use of the entire therapeutic arsenal.

Back in the 1990s, Silverstein and colleagues[25] published a work analyzing grade III astrocytoma or GB

patients between 1987 and 1992, which showed that the cost per patient at that time exceeded US$67,000, taking in account the entire therapeutic process. More recently, a study from the first decade of this century showed that each temozolomide (TMZ) cycle for recurrent glioma treatment cost more than €2,000/month per patient at that time. In a critical and elucidative review, Raizer and colleagues[23] compared direct medical costs and other encephalic neoplasia treatment-related factors among ten works in the literature. The authors confirmed that adjuvant therapies, such as the use of irinotecan and bevacizumab, increased the cost of treatment greatly. As an example, treatment with only bevacizumab cost up to US$240,000/year for a 70kg patient. Comparatively, our study showed that EMN patients exhibited almost double the costs for the SUS in comparison with other neoplasia patients—even though we were unable to compare numeric values from 2008 to 2017 because of variations in the exchange rate of the Brazilian real (currency) in relation to the euro and the dollar. The high effective cost for patients, families, or health care systems is, however, clear.

Clearly, a long and winding road that must be traveled until we reach more efficient therapeutic strategies. Bernard-Arnoux and colleagues[28] developed a model for calculating the cost-benefit of adding some therapies to the standard treatment for GBs. As a result, they observed that the increase in life expectancy barely surpassed 4 months with a total cost per patient greater than €180,000 until decease. Our study showed that death rates and mean hospitalization time did not vary during the decade under analysis in Brazil, as also observed in literature.

Nevertheless, the literature shows that new therapies are being used *in vitro, in vivo* and even in clinical trials for EMN with the objective of improving the effectiveness of treatments, enhancing patients' lifespan and reducing the death rate. A recent emerging and low-cost approach is drug repositioning—i.e. revisiting old drugs in order to find new therapeutic targets and reformulating their clinical indications, including cancer treatment. This strategy is appropriate for EMN and GB, being one of the most promising approaches nowadays due to its low cost and the wide variety of targets when a combination of drugs are used.[15,27] As an example, we can cite the use of sulfasalazine, a well-known anti-inflammatory drug used since the 1940s to treat chronic bowel inflammatory diseases and arthritis, and its discovered action in blocking the xC- transport system, the essential mechanism in GB for generating glutathione and recovering from oxidative stress.[11,29,30] Higher cost options can be considered as well for improving the overall survival rate of EMN patients, such as the use of adjuvant monoclonal antibodies—especially bevacizumab, a vascular endothelial growth factor-receptor (VEGF-R) targeted antibody.[31,32] Specifically, many clinical trials concerning GB treatments highlight that, following the pioneering work of Stupp and colleagues,[33] the use of a treatment combining alkylating agent temozolomide and radiotherapy increases the overall survival rate of patients—which can be increased even further if GB cells exhibit tumoral O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[26,33-36]

Since EMNs are a genetically broad and heterogeneous group of tumors, it is clear to us that investment in basic and clinical studies that can unravel their biology, progression and pathogenesis is essential. With regard to genetic specificities, another practical approach is appropriate for EMNs. Precision medicine in cancer mainly looks for the variability of individual patient genetics for prevention, care and therapy, instead of a one-drug/one-dose/one-treatment-fits-all model, thereby helping to reach a better outcome for each patient.[37] Since 2016 we have identified genetically different GB subtypes (such as IDH gene mutant or wild-type), indicating that molecular subclassification is a useful tool for improving cancer treatments. In fact, precision medicine has already been pointed out as an excellent approach to achieve better results for EMN patients.[38-40]

Moreover, we can observe that EMN treatment in Brazil and worldwide is a high cost and low efficiency process with regard to decreasing the death rate of patients. However, new therapeutic approaches are now on the horizon and must be considered as adjuvant therapies for standard protocols. This study concluded that, from 2008 to 2017, SUS expenses with EMN patients surpassed mean expenditures per patient overall and on neoplasia in general, despite the small number of EMN patients. Even using state-of-the-art therapies, neither mean hospitalization time nor the death rate of EMN patients fell during the 10 years under analysis. Thus, these treatments still involve high costs that are not converted into significant increases in life expectancy, in concordance with other worldwide studies. Especially in the case of GB patients, palliative

care alternatives unfortunately still remain the only plausible solution despite all therapeutic protocols. Still, patients and families can have the option of advanced care planning (ACP) for decision-making, especially in the end-of-life phase.[41]

Acknowledgements

We thank FUNADESP for research funding through the Programa de Iniciação Científica-PIC/Anhanguera 2018/2019 (project number: 20180001).

References

1. McKinney PA. Brain tumours: incidence, survival, and aetiology. J Neurol Neurosurg & Psychiatry [Internet]. 2004 Jun 1;75(suppl 2):ii12 LP-ii17. Available from: https://doi.org/10.1136/jnnp.2004.040741
2. Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. JAMA [Internet]. 2013;310:1842–50. Available from: https://doi.org/10.1001/jama.2013.280319
3. Ostrom QT, Patil N, Cioffi G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013–2017. Neuro Oncol [Internet]. 2020 Oct 30 [cited 2021 April 14]; 22(1):iv1–iv96. Available from: https://doi.org/10.1093/neuonc/noaa200
4. Undabeitia J, Torres-Bayona S, Samprón N, et al. Indirect costs associated with glioblastoma: Experience at one hospital. Neurol (English Ed.) [Internet]. 2018 July 20 [cited 2021 April 14];33(2):85–91. Available from: https://doi.org/10.1016/j.nrl.2016.05.003
5. Chen DY, Chen CC, Crawford Jr WSG. Tumor-related epilepsy: epidemiology, pathogenesis and management. J Neurooncol [Internet]. 2018 May 24 [cited 2021 April 14];139(1)13-21. Available from: https://doi.org/10.1007/s11060-018-2862-0
6. Schreck KC, Grossman S. Role of Temozolomide in the Treatment of Cancers Involving the Central Nervous System. Oncol (willist Park) [Internet]. 2018 November 15 [cited 2021 April 15];32(11):555–60. Available from: Available from: https://doi.org/10.1007/s11060-018-2862-0
7. Kaibara T, Tyson RL, Sutherland G. Human cerebral neoplasms studied using MR spectroscopy: a review. Biochem Cell Biol [Internet]. 1998 May 30 [cited 2021 April 13];76(2–3):477–86. Available from: https://doi.org//10.1139/o98-048
8. Davis ME. Epidemiology and Overview of Gliomas. Semin Oncol Nurs [Internet]. 2018 Dec 1 [cited 2021 April 17];34(5):420–9. Available from: https://doi.org/10.1016/j.soncn.2018.10.001
9. Werneck de Carvalho LE, Sarraf JS, Semblano AAP, et al. Central nervous system tumours profile at a referral center in the Brazilian Amazon region, 1997–2014. PLoS One [Internet]. 2017 Apr 3 [cited 2021 Apr 6];12(4):e0174439. Available from: https://doi.org/10.1371/journal.pone.0174439
10. Stoyanov GS, Sarraf JS, Matev BK, et al. A Comparative Review of Demographics, Incidence, and Epidemiology of Histologically Confirmed Intracranial Tumors in Brazil and Bulgaria. Cureus [Internet]. 2018 Feb 19 [cited 2021 April 21];10(2):e2203–e2203. Available from: https://doi.org/10.7759/cureus.2203
11. Garcia CG, Kahn SA, Geraldo LHM, et al. Combination Therapy with Sulfasalazine and Valproic Acid Promotes Human Glioblastoma Cell Death Through Imbalance of the Intracellular Oxidative Response. Mol Neurobiol [Internet]. 2018 Jan 19 [cited 2021 April 24]; 55: 6816-6833. Available from: https://doi.org/10.1007/s12035-018-0895-1
12. Lukas RV, Wainwright DA, Ladomersky E, et al. Newly Diagnosed Glioblastoma: A Review on Clinical Management. Oncology (Williston Park) [Internet]. 2019 Mar 13 [cited 2021 April 23];33(3):91–100. Available from: https://doi.org/10.1080/10463356.2018.1462031
13. Balça-Silva J, Matias D, Carmo A, et al. Cellular and molecular mechanisms of glioblastoma malignancy: Implications in resistance and therapeutic strategies. Semin Cancer Biol [Internet]. 2019 Sep 25 [cited 2021 April 29];58:130–41. Available from: https://doi.org/10.1016/j.semcancer.2018.09.007
14. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol [Internet]. 2020 Aug 17 [cited 2022 March 20]; 22(8): 1073-1113. Available from: https://doi.org/10.1093/neuonc/noaa106
15. Zanders ED, Svensson F, Bailey DS. Therapy for glioblastoma: is it working? Drug Discov Today [Internet]. 2019 Marcj 13 [cited 2021 May 4];24(5):1193–201. Available from: https://doi.org/10.1016/j.drudis.2019.03.008
15. Cagney DN, Alexander BM. The cost and value of glioblastoma therapy. Expert Rev Anticancer Ther [Internet]. 2017 Aug 3 [cited 2021 May 7];17(8):657–9. Available from: https://doi.org/10.1080/14737140.2017.1351355
16. Zuccarini M, Giuliani P, Ziberi S, et al. The Role of Wnt Signal in Glioblastoma Development and Progression: A Possible New Pharmacological Target for the Therapy of This Tumor. Genes (Basel) [Internet]. 2018 Feb 17 [cited 2022 March 20]; 9(2):105. Available from: https://doi.org/10.3390/genes9020105
17. Becker J, Wilting J. WNT signalling in neuroblastoma. Cancers (Basel) [Internet]. 2019 Jul 19 [cited 2022 March 20]; 11(7): 1013. Available from: https://doi.org/10.3390/cancers11071013
18. Zafar A, Wang W, Liu G, et al. Molecular targeting therapies for neuroblastoma: Progress and challenges. Med Res Rev [Internet]. 2021 March [cited 2022 March 20]; 41(2):961-1021. Available from: https://doi.org/10.1002/med.21750
19. Ney GM, McKay L, Koschmann C, et al. The emerging role of Ras pathway signaling in pediatric cancer. Cancer Res [Internet]. 2020 Dec 1 [cited 2020 March 20]; 80(23):5155-5163. Available from: https://doi.org/10.1158/0008-5472.CAN-20-0916
20. Mariotto AB, Yabroff KR, Shao Y, et al. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst [Internet]. 2011 December 1 [cited 2021 May 9]19;103(2):117–28. Available from: https://doi.org/ 10.1093/jnci/djq495
21. Monteiro GTR, Koifman S. Mortalidade por tumores de cérebro no Brasil, 1980-1998 . Cadernos de Saúde Pública [Internet]. 2003 Sept 5 [cited 2021 May 4]; 19(4): 1139–51. Available from: https://doi.org/10.1590/S0102-311X2003000400035
22. Blomqvist P, Lycke J, Strang P, et al. Brain tumours in Sweden 1996: care and costs. J Neurol Neurosurg Psychiatry [Internet]. 2000 Jun 20 [cited 2021 May 13];69(6):792–8. Available from: https://doi.org/10.1136/jnnp.69.6.792

23. Raizer JJ, Fitzner KA, Jacobs DI, et al. Economics of Malignant Gliomas: A Critical Review. J Oncol Pract [Internet]. 2014 Dec 2 [cited 2021 May 21];11(1):59–65. Available from: https://doi.org/10.1200/JOP.2012.000560
24. Tykocki T, Eltayeb M. Ten-year survival in glioblastoma. A systematic review. J Clin Neurosci [Internet]. 2018 Aug 1 [cited 2021 May 12];54:7–13. Available from: https://doi.org/10.1016/j.jocn.2018.05.002
25. Silverstein MD, Cascino TL, Harmsen WS. High-Grade Astrocytomas: Resource Use, Clinical Outcomes, and Cost of Care. Mayo Clin Proc [Internet]. 1996 Oct 1 [cited 2021 May 11];71(10):936–44. Available from: https://doi.org/10.4065/71.10.936
26. Wasserfallen J-B, Ostermann S, Leyvraz S, et al. Cost of temozolomide therapy and global care for recurrent malignant gliomas followed until death. Neuro Oncol [Internet]. 2005 Apr 1 [cited 2021 May 11];7(2):189–95. Available from: https://doi.org/10.1215/S1152851704000687
27. Abbruzzese C, Matteoni S, Signore M, et al. Drug repurposing for the treatment of glioblastoma multiforme. J Exp Clin Cancer Res [Internet]. 2017 Nov 28 [cited 2021 May 13];36(1):169. Available from: https://doi.org/10.1186/s13046-017-0642-x
28. Bernard-Arnoux F , Lamure M, Ducray F, et al. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro-Oncology [Internet]. 2016 Aug 1 [cited 2021 May 12];18(8):1129–36. Available from: https://doi.org/10.1093/neuonc/now102
29. Chung WJ, Lyons SA, Nelson GM, et al. Inhibition of cystine uptake disrupts the growth of primary brain tumors. J Neurosci [Internet]. 2005 Aug 3 [cited 2022 March 20]; 25(31):7101-10. Available from: https://doi.org/10.1523/jneurosci.5258-04.2005
30. Lewerenz J, Hewett SJ, Huang Y, et al. The cystine/glutamate antiporter system xC- in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal [Internet]. 2013 Feb 10 [cited 2022 March 20]; 18(5):522-55. Available from: https://doi.org/10.1089/ars.2011.4391
31. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev [Internet]. 2020 June 01 [cited 2022 March 20]; 86: 1-18. Available from: https://doi.org/10.1016/j.ctrv.2020.102017
32. Sousa F, Moura RP, Moreira E, et al. Therapeutic monoclonal antibodies delivery for the glioblastoma treatment. Adv Protein Cher Struct Biol [Internet]. 2018 March 30 [cited 2022 March 20]; 112:61-80. Available from: https://doi.org/10.1016/bs.apcsb.2018.03.001
33. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. JAMA [Internet]. 2005 March 10 [cited 2022 March 20]; 352:987-96. Available from: https://doi.org/10.1056/NEJMoa043330
34. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Onc [Internet]. 2012 May 10 [cited 2022 March 20]; 13:707-15. Available from: https://doi.org/10.1016/S1470-2045(12)70164-X
35. Braun K, Ahluwalia MS. Treatment of glioblastoma in older adults. Curr Oncol Rep [Internet]. 2017 Oct 26 [cited 2022 March 20]; 19:81. Available from: https://doi.org/10.1007/s11912-017-0644-z
36. Di Nunno V, Franceschi E, Tosoni A, et al. Treatment of recurrent glioblastoma: state-of-the-art and future perspectives. Exp Rev Antican Ther [Internet]. 2020 Sep 03 [cited 2020 March 20]; 20(9): 785-95. Available from: https://doi.org/10.1080/14737140.2020.1807949
37. Collins H, Calvo S, Greenberg K, et al. Information needs in the precision medicine era: how genetics home reference can help. Interact J Med Res [Internet]. 2016 Apr 27 [cited 2022 March 20]; 5(2):e13. Available from: https://doi.org/10.2196/ijmr.5199
38. Zhou Y, Wu W, Bi H, et al. Glioblastoma precision therapy: from the bench to the clinic. Cancer Lett [Internet]. 2020 Apr 10 [cited 2022 March 20]; 475: 79-91. Available from: https://doi.org/10.1016/j.canlet.2020.01.027
39. White K, Connor K, Clerkin J, et al. New hints towards a precision medicine strategy for IDH wild-type glioblastoma. Ann Oncol [Internet]. 2020 December [cited 2022 March 20]; 31(12):1679-92. Available from: https://doi.org./ 10.1016/j.annonc.2020.08.2336
40 Liu D, Yang T, Ma W, et al. Clinical strategies to manage adult glioblastoma patients without MGMT hypermethylation. J Cancer [Internet]. 2022 Jan 1 [cited 2022 March 20]; 13(1):354-363. Available from: https//doi.org/10.7150/jca.63595
41 Fritz L, Dirven L, Reijneveld JC, et al. Advance care planning in glioblastoma patients. Cancers (Basel) [Internet]. 2016 Nov 8 [cited 2022 March 20]; 8(11):102. Available from: https://doi.org/10.3390/cancers8110102

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Original article

Covid-19 pandemic in the state of Piauí (Brazil): Reported cases, deaths and bed occupancy

Antonio A. I. Costa Filho,[1] Naila A. de Oliveira,[2] Deyna F. A. Próspero,[3] Mayla R. Guimarães,[4] Aline R. S. Ibiapina,[5] José A. Rabi[6*]

Abstract

Introduction: This work describes the evolution over time of the Covid-19 pandemic in terms of reported cases, deaths and bed occupancy in the state of Piauí (Brazil) from 6 April 2020 to 4 January 2021. Objectives: The aim is to provide quantitative information on decision-making related to preventive measures and their effectiveness. Methodology and resources: Data were surveyed from the "Covid-19 in Piauí – Panel" to support a cross-sectional study that includes gender, age group, reported deaths, and bed occupancy as variables for built-in descriptive statistics and mobile mean estimates. Results and discussion: The data pointed to a slightly higher incidence (54.63%) in women, the highest (22.64%) being among patients in the range from 30-39 years. Recovery comprised 140,420 patients (97.48%) while confirmed deaths included 2,862 patients (1.99%), along with 774 (0.53%) sub-notifications. With respect to the latter, lethality was higher (58.56%) in men, reaching 77.67% in the case of those older than 60 years. In 2020, demands for either clinical or intensive care unit beds increased quickly during the first months of the pandemic, whereas demand for stabilization beds fluctuated intensely. Conclusion: Since a high prevalence (71.55%) was observed in economically active age groups and the highest lethality occurred among the elderly, preventive measures are still required and should be continuously adopted to mitigate the spread of Covid-19 in the state of Piauí (Brazil).

Keywords: Public health; Epidemiological monitoring; 2019-nCoV pandemic.

1. Mestrado Profissional em Matemática, Estatística & Computação Aplicadas à Indústria (MECAI), Universidade de São Paulo (USP), São Carlos, SP, Brazil.
2. Escola Paulista de Enfermagem (EPE), Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.
3. Programa de Pós-Graduação em Farmacologia, Universidade Federal do Piauí (UFPI), Teresina, PI, Brazil.
4. Programa de Pós-Graduação em Enfermagem, Universidade Federal do Piauí (UFPI), Teresina, PI, Brazil.
5. Departamento de Enfermagem, Universidade Federal do Piauí (UFPI), Picos, PI, Brazil.
6. Faculdade de Zootecnia & Engenharia de Alimentos (FZEA), Universidade de São Paulo (USP), Pirassununga, SP, Brazil.

***Correspondence address:**
Av. Duque de Caxias Norte, 225
Pirassununga, SP, Brazil.
CEP: 13635-900.
E-mail: jrabi@usp.br
ORCID: http://orcid.org/0000-0001-5041-4680

BJHBS, Rio de Janeiro, 2022;21(1):47-53
DOI: 10.12957/bjhbs.2022.68181
Received on 03/02/2022. Approved on 16/05/2022.

Introduction

Belonging to the *Coronaviridae* family – *Nidovirales* order, coronaviruses are positive non-segmented enveloped RNA viruses that are widespread among humans (as well as other mammals), in whom they usually cause mild infections. Even so, high mortality rates were reported worldwide in the case of previous epidemics caused by two beta-coronaviruses, namely, severe acute respiratory syndrome coronavirus (SARS-CoV).[1,2,3] and Middle-East respiratory syndrome coronavirus (MERS-CoV).[4,5]

Previously identified coronaviruses can be starting points for epidemiological science to broadly assess and study potential newer as well as serious zoonotic events due to the increasing consumption of exotic animals as human food.[6] With clinical manifestations similar to viral pneumonia, in December 2019 a series of unknown-cause pneumonia cases emerged in Wuhan (China), which were subsequently identified as Covid-19.[7] SARS-CoV-2 transmission occurs from person to person in close contact, mainly via respiratory droplets produced when an infected person either coughs or sneezes. Fomites can be a major source of transmission, since SARS-CoV-2 has been found to persist on surfaces for up to 96 hours while other coronaviruses can persist for up to 9 days.[8,9]

Covid-19 ranges from a simple cold to severe pneumonia, clinically presenting a flu-like syndrome at the onset of disease but is capable of leading to death in more severe stages. Its physical symptoms customarily involve coughing, fever, anosmia, ageusia, fatigue and

breathing difficulties.[10] People with Covid-19 present signs and symptoms on average 5-6 days after contact with the virus and infectious condition development.[11]

Insofar as Covid-19 is a highly contagious disease, its early detection, isolation, hospitalization and diagnosis are vital for control purposes and can effectively mitigate disease transmission risks.[12-14] With respect to infectious disease (Covid-19) control, delays in hospitalization or isolation may lead to prolonged infection periods while increasing the rate of recovery of patients.

Previous studies have described characteristics of Covid-19 patients, including the time interval between major events.[15-17] Also, a reduction in the time interval from symptom onset to hospitalization-isolation is an evident result of the adoption of public health measures.[18,19] At the individual level though, little is known about the influencing factors associated with delayed hospital admission and length of stay. Identifying those factors may be helpful in making inferences about the workload of the medical and multidisciplinary team, while allocating medical resources rationally and assisting response efforts, as well as about their effectiveness at a global level.[20]

Located in Northeast region of Brazil, the state of Piauí confirmed its first Covid-19 case on March 19, 2020. In this Brazilian state, more than 146,000 cases and 2,895 related deaths due to Covid-19 were confirmed up to 9 January 2021 (those numbers may be even higher due to untested positive cases and delays in notification). In order to prevent the spread of Covid-19, the government of Piauí applied contingency measures and created crisis management committees, while social isolation measures were intensified and a health emergency declared.[11]

In Piauí, the monitoring of the dynamic evolution of Covid-19 cases, deaths and demand for hospital beds became necessary, since this evolution directly influences social and governmental decision-making. Accordingly, the present work describes the dynamic evolution of Covid-19 pandemic and the occupation of hospital beds in Piauí from 6 April 2020 to 4 January 2021. The survey data can provide quantitative information to support the planning of preventive measures while providing measures of their corresponding effectiveness.

Methodology and resources

The present work focused on the state of Piauí, which is located in the Northeast region of Brazil. Its population comprises almost 3.3 million people (~5.75% of the population of the Northeast), distributed among 224 municipalities. The capital city of Piauí is Teresina, whose population is about 870,000 inhabitants.[21] Being of a descriptive cross-sectional quantitative nature, the present work was carried out by evaluating secondary data available online from the "Covid-19 in Piauí – Panel".[22]

The evaluated sample consisted of all confirmed Covid-19 cases in Piauí from 6 April 2020 to 4 January 2021. The variables investigated included gender, age group, confirmed deaths caused by Covid-19, and the evolution of beds occupied by Covid-19 patients (i.e. general, ICU and stabilization beds). The criteria for inclusion were all the reported Covid-19 cases in Piauí available in the State Department of Health database. Exclusion criteria were incomplete reports, registration outside the survey sample and variables not analyzed in this study. Data were organized, tabulated and processed via Microsoft Excel® software, with the help of built-in descriptive statistical analysis and moving average estimate numerical tools.

Since the present work used secondary data of public free access available from "Covid-19 in Piauí – Panel", no procedure in the Research Ethics Committee was required (in accordance with Brazilian National Health Council Resolution No. 466/2012 and current ethical norms). At this point, the commitment of the authors to data veracity and result content suitability is acknowledged.

Results and discussion

Until 4 January 2021, the "Covid-19 in Piauí – Panel" reported 144,056 cases in all 224 municipalities in the state,[22] with 140,420 cases of recovery (97.48%) and 2,862 confirmed deaths (1.99%), as well as 774 sub-notifications (0,53%). The percentage of confirmed deaths shows that the Covid-19 lethality rate in Piauí is slightly lower than either worldwide or Brazilian figures, which are respectively 2.14%[23] and 2.4%.[24]

As far as gender distribution is concerned, 65,360 reports (45.37%) referred to men whereas 78,696 notifications (54.63%) referred to women.[22] The above-mentioned incidence contrasts with existing data,[25] which point to SARS-CoV-2 infection as being more frequent in adult men.

In terms of lethality, 1,676 deaths (58.56%) referred to men while 1,186 deaths (41.44%) referred to women.[22] These differences in reporting deaths may refer to the cultural fact in Brazil that women are

more concerned with health issues while men only seek medical care in more extreme circumstances.[26] Moreover, these values may refer to lifestyle and/or epigenetic and hormonal differences that possibly affect innate immunity in males.[27]

With regard to distribution among age groups, Table 1 shows confirmed Covid-19 cases and subsequent deaths in Piauí. Economically active people (i.e. those 20-59 years old) comprise 103,076 reported cases (71.55%), mostly within the 30-39 years age group with 32,614 cases (22.64%). These findings are consistent with data from the State of Tocantins (also in Brazil) and the average age of 34 years found in surveys of Chinese hospitals.[28] As claimed in the latter work, this population segment forms the basis of economic activities and is more exposed to several risk factors that underlie the transmission chain.

The above-mentioned findings are reasonably close to data[29] for the State of Espírito Santo (also in Brazil). This latter cross-sectional study showed factors linked to higher mortality risks due to Covid-19, including age above 60 years, low education, either yellow or black skin color, and the presence of morbidity and multimorbidity.

SARS-CoV-2 is prone to infect people with chronic comorbidities, such as diabetes, cardiovascular and cerebrovascular diseases.[25] Serious cases are concentrated among adults older than 60 years and in those with the

Table 1. Covid-19 in Piauí (Brazil)[22]: Age group distribution of confirmed cases and deaths until 4 January 2021

Age group (years)	Confirmed cases	Confirmed deaths
0 – 9	7163	6
10 – 19	11752	10
20 – 29	27919	35
30 – 39	32614	83
40 – 49	24449	184
50 – 59	18094	321
60 – 69	11400	539
70 – 79	6597	752
Above 80	4068	932

Source: The authors (2022).

above-mentioned conditions.[30,31] Serious manifestations can equally be associated with co-infections of bacteria and fungi.[25]

Higher death risks after Covid-19 infection have indeed been noted in patients with comorbidities.[32] The presence of either chronic obstructive pulmonary disease (COPD) or chronic kidney diseases (CKD) may increase the risk of serious events by up to 6.6 or 5.3 times, respectively. The risks of serious events associated with cardiovascular diseases are about 4.5 times greater, while diabetes mellitus leads to a statistically significant 3.07-fold increase in the probability of severe Covid-19.

Figure 1 shows the evolution of the occupancy of clinical beds and the associated weekly moving average in Piauí until 4 January 2021. Bed demand increased rapidly during the initial months in 2020, with peaks in June and July, e.g. the highest peak reached 580 Covid-19 patients on 7 July 2020, followed by a fluctuating drop in occupation in subsequent months. Based on the moving average, Figure 1 suggests a downward trend of 14.03% in the final 14 days in the observed period.

With respect to the occupancy of beds due to Covid-19 in Piauí, recent official data[33] point to 738 beds in nursing wards, 180 beds in Intensive Care Units (ICUs), and 34 stabilization beds. While data show that the number of beds occupied was basically the same throughout 2020, mortality rates were indeed reduced due to vaccine campaigns, so that the occupation of beds in wards overlapped their counterparts in ICUs. However, the elderly remain a critical challenge in terms of immunization against Covid-19, since they still rep-

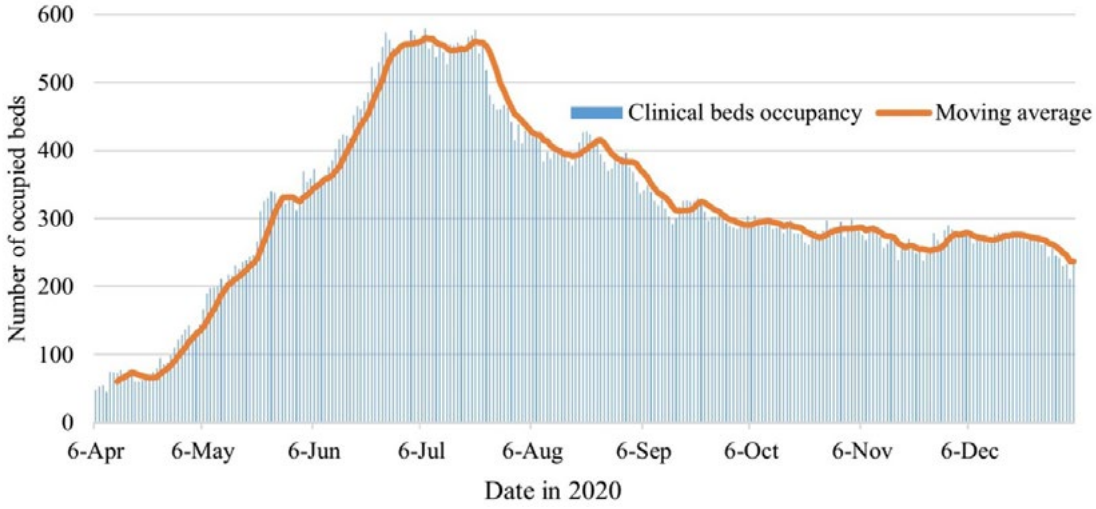

Figure 1. Covid-19 in Piauí (Brazil)[22]: Evolution of the occupancy of clinical beds and associated moving average until 1 January 2021

Source: The authors (2022).

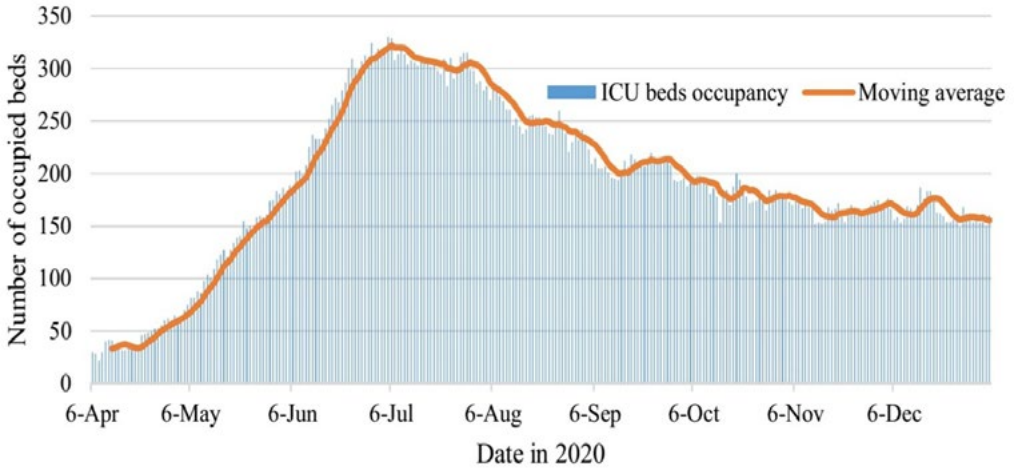

Figure 2. Covid-19 in Piauí (Brazil)[22]: Evolution of the occupancy of ICU beds and associated moving average until 1 January 2021

Source: The authors (2022).

resent about 50% of both bed occupancy and mortality rates. Even in scenarios with 3 or more vaccine doses, the elderly no longer have efficient immunity and, hence, vaccine effects tend to be weaker in this age group.[34]

Figure 2 shows the evolution in the occupancy of ICU beds and associated weekly moving average in Piauí up to 1 January 2021. Impressive growth occurred in the initial months, with a peak on 5 July referring to occupation by 330 patients requiring intensive care. Analysis of the variation of the moving average pointed to a downward trend of 9.33% in the last 14 days of the period under observation.

In addition to asymptomatic cases, Covid-19 symptoms can be either mild or severe. In the latter case, patients may also suffer from severe dyspnea and tachypnea (>30 rpm), thus requiring hospitalization, which explains the increase of ICU bed occupancy in July when compared to previous months.[35]

Data from Figures 1 and 2 may be the result of the adoption of social distancing measures by the population of Piauí, which practice has been pointed out as the most important prevention measure against the spread of coronavirus.[36] The evolution of bed occupancy in June-July may suggest a weakening of steps

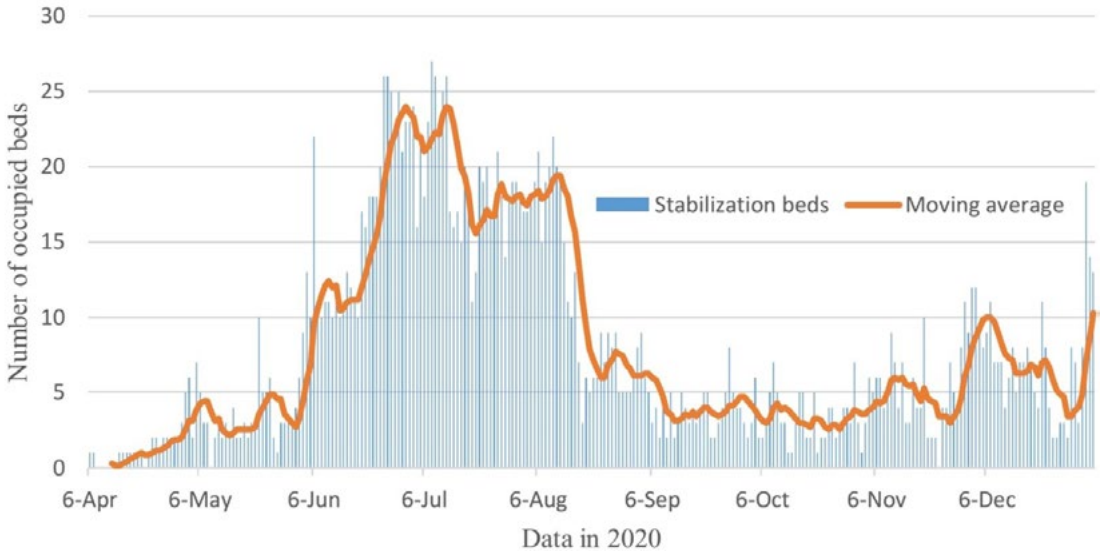

Figure 3. Covid-19 in Piauí (Brazil)[22]: Evolution of the occupancy of stabilization beds and associated moving average until 1 January 2021

Source: The authors (2022).

to prevent the spread of Covid-19, leading government authorities to adopt measures such as the opening of new field hospitals and the implementation of more stringent lockdowns.[37]

The available evidence[38-40] asserts that non-pharmacological interventions (e.g. hand hygiene, social distancing, mask use, and room ventilation) mitigate the spread of the virus, thus reducing bed occupancy and the saturation of the health care system. While social distancing remains a somewhat controversial non-pharmacological measure, the data in Figures 1 and 2 are prone to support its impact on Covid-19 cases and subsequent deaths in Brazil.[41]

Figure 3 shows the evolution in the occupancy of stabilization beds and the associated moving average in Piauí until 1 January 2021. Demand for stabilization beds experienced more intense fluctuations (when compared to their clinical and ICU counterparts), especially from June to August, with relatively high occupations reaching 27 beds on 8 July and 26 beds on 25-26 June. An upward trend is evidenced in the moving average, with a 46.94% increase over the last 14 days in the period under observation.

As far as the Covid-19 assistance framework is concerned, the occupancy data in Figures 1 to 3 are important factors in decision-making because beds (especially ICU ones) are extremely important in saving lives.[31] Such data might support not only the formation as well as the implementation of public policies against Covid-19, such as increasing the number of health service units and adopting social distancing (or instead flexibilizing it).[42]

While bed occupancy rates may possibly suggest some inefficiency with respect to Covid-19 mitigation in Piauí, Figure 3 supports the need to maintain measures to slow down SARS-CoV-2 propagation in this state of Brazil. Accordingly, prevention actions should always be adopted to reduce the number of Covid-19 cases and, hence, the occupancy of beds (clinical, ICU, stabilization) as a means to relieve and reorganize the health care system.[43]

Conclusion

As shown by the increasing number of confirmed cases in Piauí, Covid-19 shows a higher prevalence among economically active age groups (i.e. 20-59 years old) and higher lethality among the elderly (i.e. people older than 60 years). Accordingly, preventive measures are necessary and should be continuously adopted in order to mitigate the spread of the disease. While confirmed cases have increased, demands for general and ICU beds have decreased, declining respectively by 14.03% and 9.33% (on weekly moving average basis) in last 14 days of the period under study.

The limitations of the present work include the use of secondary data (which refer exclusively to registered notifications) and possible existence of un-

derreporting (which may affect the epidemiological profile, thus possibly introducing bias). Nevertheless, the present work contributes to the monitoring of the evolution of the Covid-19 infection-death binomial and its influence on bed occupancy in the state of Piauí as a means to assist decision-makers in planning as well as managing actions geared towards the prevention and mitigation of Covid-19.

References

1. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003 May 15;348:1967-76. doi: 10.1056/NEJMoa030747
2. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003 May 15;348:1953-66. doi: 10.1056/NEJMoa030781
3. Kuiken T, Fouchier RAM, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003 Jul 26;362(9380):263-70. doi: 10.1016/S0140-6736(03)13967-0
4. De Groot RJ, Baker SC, Baric RS, et al. Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the coronavirus study group. J Virol 2013 Jun 27;87:7790-2. doi: 10.1128/JVI.01244-13
5. Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012 Nov 08;367(19):1814-20. doi: 10.1056/NEJMoa1211721
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15-21;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5
7. World Health Organization – WHO. Report of the WHO-China joint mission on coronavirus [Internet]. Geneva: WHO; 2020 February 16-24 [cited 2021 Jan 09]. 40 p. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-Covid-19-final-report.pdf
8. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect 2020 Feb 06;104(3):246-51. doi: 10.1016/j.jhin.2020.01.022
9. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006 Aug 16;6:130. doi: 10.1186/1471-2334-6-130
10. Carvalho PMM, Moreira MM, de Oliveira MNA, et al. The psychiatric impact of the novel coronavirus outbreak. Psychiatry Res 2020 Feb 28;286:112902. doi: 10.1016/j.psychres.2020.112902
11. Araújo Filho ACA, Arrais KR, Silva MSG, et al. Analysis of confirmed cases and deaths by the new Coronavirus in Piauí. J Nurs Health 2020 Nov 24;10(4):e20104036 [in Portuguese]. https://periodicos.ufpel.edu.br/ojs2/index.php/enfermagem/article/view/19940
12. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of Covid-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 2020 Apr 27;20(8):911-9. doi: 10.1016/S1473-3099(20)30287-5
13. Rong XM, Yang L, Chu HD, et al. Effect of delay in diagnosis on transmission of Covid-19. Math Biosci Eng 2020 Mar 11;17(3):2725-40. doi: 10.3934/mbe.2020149
14. Thompson RN. Novel coronavirus outbreak in Wuhan, China, 2020: Intense surveillance is vital for preventing sustained transmission in new locations. J Clin Med 2020 Feb 11;9(2):498. doi: 10.3390/jcm9020498
15. Liang WH, Guan WJ, Li CC, et al. Clinical characteristics and outcomes of hospitalised patients with Covid-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China. Eur Respir J 2020 Mar 29;55(6):2000562. doi: 10.1183/13993003.00562-2020
16. Tian S, Hu N, Lou J. et al. Characteristics of Covid-19 infection in Beijing. J Infect 2020 Apr;80(4):401-6. doi: 10.1016/j.jinf.2020.02.018
17. Yu X, Sun X, Cui P, et al. Epidemiological and clinical characteristics of 333 confirmed cases with coronavirus disease 2019 in Shanghai. China. Transbound Emerg Dis 2020 Apr 29;67(4):1697-1707. doi: 10.1111/tbed.13604
18. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Eng J Med 2020 Mar 26;382(13):1199-1207. doi: 10.1056/NEJMoa2001316
19. Zhang J, Litvinova M, Wang W, et al. Evolving epidemiology of novel coronavirus diseases 2019 and possible interruption of local transmission outside Hubei Province in China: a descriptive and modeling study. medRxiv 2020 Feb 23 [preprint];20026328. doi: 10.1101/2020.02.21.20026328
20. Zhou F, You C, Zhang X, et al. Epidemiological characteristics and factors associated with critical time intervals of Covid-19 in eighteen provinces, China: A retrospective study. Int J Infect Dis 2021 Jan;102:123-31. doi: 10.1016/j.ijid.2020.09.1487
21. Cidades e Estados: Piauí [Internet]. Brasília: Instituto Brasileiro de Geografia e Estatística. 2021 [cited on 2021 Jan 07]. Available from https://www.ibge.gov.br/ estatisticas/sociais/populacao/9103-estimativas-de-populacao.html
22. Painel Epidemiológico Covid-19 [Internet]. Teresina: Governo do Estado do Piauí. 2021 [cited on 2021 Jan 06]. Available from https://datastudio.google.com/u/0/ reporting/a6dc07e9-4161-4b5a-9f2a-6f9be486e8f9/page/2itOB
23. Coronavirus disease (Covid-19) Weekly Epidemiological Update and Weekly Operational Update [Internet]. Geneva: World Health Organization. 2021 [cited on 2021 Jan 02]. Available from https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
24. Secretaria de Vigilância à Saúde (SVS): Guia de Vigilância Epidemiológica [Internet]. Brasília: Ministério da Saúde. 2021 [cited on 2021 Jan 02]. Available from https://bvsms.saude.gov.br/bvs/publicacoes/guia_vigilancia_epidemiologica_ 7ed.pdf
25. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020 Jan 30;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7
26. Levorato CD, Mello LM, Silva AS, et al. Factors associated with the demand for health services from a gender-relational perspective. Cienc Saude Colet 2014 Apr;19(4):1263-74 [in Portuguese]. doi: 10.1590/1413-81232014194.01242013

27. Kadel S, Kovats S. Sex hormones regulate innate immune cells and promote sex differences in respiratory virus infection. Front Immunol 2018 Jul 20;9(1653):1-15. doi: 10.3389/fimmu.2018.01653
28. Chang D, Lin M, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA 2020 Feb 07;323(11):1092-3. doi: 10.1001/jama.2020.1623
29. Mascarello KC, Vieira ACBC, Souza ASS, et al. Covid-19 hospitalization and death and relationship with social determinants of health and morbidities in Espírito Santo State, Brazil: a cross-sectional study. Epidemiol Serv Saúde 2021 Jul 09;30(3):e2020919. doi: 10.1590/S1679-49742021000300004
30. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 Feb 07;323(11):1061-9. doi: 10.1001/jama.2020.1585
31. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of Covid-19. JAMA 2020 Feb 21;323(14):1406-7. doi: 10.1001/jama.2020.2565
32. Nandy K, Salunke A, Pathak SK, et al. Coronavirus disease (Covid-19): a systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabetes Metab Syndr Clin Res Rev 2020 Sep-Oct;14(5):1017-25. doi: 10.1016/j.dsx.2020.06.064
33. Coronavírus - Governo do Piauí [Internet]. Teresina: Governo do Estado do Piauí. 2022 [cited on 2022 May 09]. Available from https://coronavirus.pi.gov.br/
34. Jansen, R. Covid: Número de mortes entre idosos volta a crescer no país [Internet]. 2022 [cited on 2022 May 09]. Available from https://www.terra.com.br/ noticias/coronavirus/covid-numero-de-mortes-entre-idosos-volta-a-crescer-no-pais,b-5d86d8678b5d4768c4bfcf2d695e8b46we0qm8l.html
35. Kluge S, Janssens U, Welte T, et al. German recommendations for treatment of critically ill patients with Covid-19 - version 3 [in German]. Pneumologe 2020;17:406-25. doi: 10.1007/s00101-020-00879-3
36. Prem K, Liu Y, Russell TW, et al. The effect of control strategies to reduce social mixing on outcomes of the Covid-19 epidemic in Wuhan, China: a modelling study. Lancet Public Health 2020 May 01;5(5):e261-e270. doi: 10.1016/S2468-2667(20)30073-6
37. Decreto No. 19.890 de 6 de julho de 2020. Dispõe sobre a intensificação das medidas de isolamento social no município de Teresina [Internet]. Teresina: Governo do Estado do Piauí. 2020 [cited on 2021 Jan 02]. Available from https://pmt.pi.gov.br/wp-content/uploads/sites/34/2020/07/New-Scan-2020-07-06-1842. pdf
38. Garcia LP, Duarte E. Nonpharmaceutical interventions for tackling the Covid-19 epidemic in Brazil. Epidemiol. Serv. Saúde 2020 Apr 09;29(2):1-4. doi: 10.5123/S1679-49742020000200009
39. Smolski FMS, Battisti IDE, Soder RM, et al. Disponibilidade de leitos hospitalares e ventilação mecânica no Rio Grande do Sul: desafios no enfrentamento da Covid-19 [Internet]. 2020 [cited on 2022 May 09]. Available from https://www. researchgate.net/publication/341651488_Disponibilidade_de_leitos_hospitalares_e_ventilacao_mecanica_no_Rio_Grande_do_Sul_desafios_no_enfrentamento_da_Covid-19
40. Volpe RAG. Possíveis cenários do Covid-19 no RN e levantamento de leitos necessários [Internet]. 2020 [cited on 2022 May 09]. Available from http://covidrn. lais.ufrn.br/wp-content/uploads/2020/05/09_04-Cen%C3%A1rio-Covid-19-RN-e-Planejamento-de-Leitos-Ricardo-Volpe.pdf
41. Oliveira CA. Ficar em casa salva vidas? uma estimação dos impactos do isolamento social nos casos e nos óbitos por Covid-19 registrados no Brasil [Internet]. 2020 [cited on 2022 May 09]. https://www.researchgate.net/profile/ Cristiano_Oliveira10/publication/341135386_Does_staying_at_home_saves_lives_An_estimation_of_the_impacts_of_social_isolation_in_the_registered_cases_and_deaths_by_Covid19_in_Brazil/links/5eb09cf645851592d6b94434/Does-staying-at-home-saves-lives-An-estimation-of-the-impacts-of-social-isolation-in-the-registered-cases-and-deaths-by-Covid-19-in-Brazil.pdf
42. Aquino EML, Silveira IH, Pescarini JM, et al. Social distancing measures to control the Covid-19 pandemic: potential impacts and challenges in Brazil. Cienc Saude Colet 2020 Apr 22;2(1):2423-46. doi: 10.1590/1413-81232020256.1.10502020
43. Noronha KVMS, Guedes GR, Turra CM, et al. The Covid-19 pandemic in Brazil: analysis of supply and demand of hospital and ICU beds and mechanical ventilators under different scenarios. Reports Publ Health 2020 May 12;36(6):e00115320. doi: 10.1590/0102-311X00115320

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

How stem cell therapy can act in the treatment of patients with Covid-19

Mateus A. Rainho,[1] Aline de A. Azevedo,[1] Gustavo C. Paris,[1] Adriana L. Ferreira,[1] Yanca M. de A. Azevedo,[1] Júlia L. T. Sodré,[1] Giovanna F. de L. Mynssen,[1] Genilza P. de Oliveira,[1] Karina R. Silva,[1] Erika A. C. Cortez,[1] Ana C. Stumbo,[1] Simone N. Carvalho,[1] Lais de Carvalho,[1] Alessandra A. Thole[1,*]

Abstract

Introduction: The emergence of a new coronavirus has changed the world and caused one of the biggest global health crises of the past 100 years. The protagonist of the pandemic, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is responsible for the coronavirus disease 2019 (Covid-19), which leads to dysfunctions in a plethora of systems, especially in severe cases. Therefore, researchers and healthcare professionals are making great efforts to develop a therapy that helps the many organs affected by the disease, for which mesenchymal stem cells (MSCs) arise as promising candidates. MSCs can offer benefits at different phases of Covid-19, since they have important anti-inflammatory and tissue repair properties. Objective: This review aims to elucidate how MSCs can contribute in the Covid-19 scenario by considering their properties and mechanisms of action. Methods: A review of the scientific literature was conducted on electronic databases, such as PubMed, Scielo and Web of Science, in the period of 2020-2021. Results: Therapeutic effects of MSCs in preclinical models of respiratory, nervous, renal, and cardiovascular systems were observed. Conclusion: MSCs can be a therapeutic resource for patients with severe Covid-19.

Keywords: SARS-CoV-2; Covid-19; Mesenchymal stem cells; Immunomodulation; Cell therapy.

1. Laboratório de Pesquisa em Células-Tronco (LPCT), Departamento de Histologia e Embriologia, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
LPCT, Instituto de Biologia, UERJ
Avenida Prof. Manoel de Abreu 444, 3° andar
Rio de Janeiro, RJ, Brazil.
CEP: 20550-170.
E-mail: alethole@gmail.com
ORCID: https://orcid.org/0000-0002-0623-9587

BJHBS, Rio de Janeiro, 2022;21(1):54-60
DOI: 10.12957/bjhbs.2022.68182
Received on 28/06/2021. Approved on 16/11/2021.

Introduction

In 2019, the emergence of a distinct coronavirus revolutionized daily life all over the world. Everything began at the Huanan Seafood Wholesale Market, in Wuhan, China, where many of the staff showed clinical symptoms related to a viral airway disease.[1] This illness has not been restricted to China and has spread to many other countries, including Brazil, in which the first confirmed case occurred in São Paulo on February 26, 2020.[2] The virus was named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) by the International Committee on Taxonomy of Viruses and the disease baptized as Covid-19 (coronavirus disease 2019) by the World Health Organization on January 30, 2020 and assessed as a pandemic on March 11, 2020.[1,3] To this date, more than 180 million cases and over 3.9 million deaths due to Covid-19 have been reported all over the world.[1]

SARS-CoV-2 is classified as a coronavirus belonging to the β-coronavirus genus.[3] Among all the members of the *Coronaviridae* family, it is the seventh virus that is known to be able to infect humans. Its capacity to promote acute respiratory distress syndrome (ARDS) causes the virus to be an important concern, since two other coronaviruses with this syndrome (SARS-CoV and MERS-CoV) have been responsible for epidemics during the last two decades.[4]

SARS-CoV-2

SARS-CoV-2 is a spherical-enveloped virus, with a diameter of 80-120 nm, and a genome composed of a positive-sense single-stranded RNA. The latter is covered by one of the four major structural proteins: the nucleocapsid protein (N). The other three are the

spike glycoprotein (S), the envelope protein (E) and the membrane protein (M), which are contained within the viral envelope.[5] The S is a trimeric glycoprotein that gives the aspect of a crown to the virus surface. It is formed by two subunits: S1, or bulb, and S2, or stalk, and plays an important role in infection.

The gateway for the cell entry of SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), a protein related to the renin-angiotensin system (RAS). This transmembrane receptor can be found in many different sites, including the respiratory, cardiovascular, urinary and digestive organs.[6] The S protein mediates viral entry, and the protein is processed by a serine protease named TMPRSS2, another enzyme that has been shown to be crucial to the infection process. The cleavage of the S protein exposes the S1 subunit, which contains the receptor-binding domain (RBD) that is responsible for interacting with ACE2. Meanwhile, the S2 subunit allows the fusion of the viral and host cell membranes. Replication and translation steps start as soon as the viral RNA reaches cytosol, producing new virions that are able to infect other cells.[5]

The human airway is the main entry point for SARS-CoV-2. Once inside the lungs, the virus primarily infects type-II pneumocytes and alveolar macrophages, while reaching other organs through the bloodstream after some viral cycles.[7] The respiratory tract is not only the entry point but also the major exit point of the virus. Droplets and aerosol exhaled by infected patients are the most important means of transmission, followed by direct contact with contaminated fomites.[8]

Covid-19

Since its outbreak, researchers and healthcare professionals have been thoroughly studying Covid-19, which appears to be a complex disease as new data arise over time. Five different clinical conditions of Covid-19 have been observed: asymptomatic, mild, moderate, severe and critical cases. Most patients manifest mild to moderate symptoms, which include fever, dry cough, sore throat, loss of smell and taste, fatigue and shortness of breath. In severe and critical cases, these symptoms rapidly evolve to pneumonia and hypoxemia (low oxygen saturation), and can develop into ARDS and multiple organ dysfunction as a result of an impaired immune response, which can be fatal.[9] Comorbidities, such as cardiovascular diseases and diabetes, enhance the risk of the worst outcomes.[10]

Cell-based therapies

Currently, vaccines are considered as one of the few promises for better days. Since February of 2021, some of them have already been approved and applied worldwide, while others are undergoing clinical trials and approval.[11] However, vaccination campaigns are slow and mortality rates remain high, either due to the risk factor associated with age or the appearance of new variants of the virus in many different countries. Therefore, new therapies, such as cell-based therapies, are essential to provide an adjuvant treatment for Covid-19. Over the years, stem cells have been widely used as a form of therapy for several acute and chronic diseases in experimental models and clinical trials. These cells show promise due to their ability to promote tissue parenchyma regeneration and repair, whether they are embryonic stem cells (ESCs), induced pluripotency stem cells (iPSCs), bone marrow mononuclear cells (BMMC) or mesenchymal stem cells (MSCs).[12] ESCs and iPSCs have therapeutic potential because of their capacity to differentiate into various cell lines, giving hope to patients suffering from diabetes, Parkinson's disease, cardiovascular disease and liver disease. Currently, iPSCs have been used to generate organoids of the liver, stomach, kidney, nervous system, thyroid glands and lungs, whose potential for expansion at an industrial level for translational use is helpful. Organoid applications aim to modulate responses from patient-specific drugs in tumorigenesis or infectious diseases.[13] Nevertheless, taking into account ethical, legal and biological limitations, the use of adult stem cells, such as MSCs, is more favorable in clinical practice.[14]

Mesenchymal stem cells

MSCs are a promising tool in cell therapy for treating many incurable diseases, due to their multipotent differentiation, self-renewal, immunoregulation, tissue regeneration effects and capacity for inflammation reduction. In addition, MSCs have the ability to differentiate into three types of cells: osteoblasts, chondroblasts and adipocytes.[15] Easily obtainable, MSCs can be found in most vascularized tissues, such as bone marrow, adipose tissues, umbilical cords, fetal livers, fetal lungs, mobilized peripheral blood, dental pulp, placentas and even menstrual blood, but can also be generated from embryonic stem cells.[16] These cells are considered safe, even in an allogeneic

environment, and avoid immune responses due to their low expression of MHC-I and MHC-II.

MSCs can act in many different ways within the body, using their immunomodulatory, paracrine properties, differentiation and antimicrobial potential.[16] They can provide an ideal environment for hematopoietic stem cells in the bone marrow by releasing some extracellular matrix proteins, such as laminin and fibronectin.[15]

The therapeutic effects of MSCs are mainly expressed through growth and survival factors by paracrine signaling, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and insulin-like growth factor-1 (IGF-1). These promote angiogenesis, cell survival and cell proliferation, thereby reducing inflammation, apoptosis and fibrosis of injured tissues. Furthermore, MSCs can directly inhibit the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), by immunosuppressive responses in innate and adaptive immune systems. For example, MSCs can interact with Th2 lymphocytes and attenuate NK cell responses by inducing the transition of M1 macrophages to M2 anti-inflammatory phenotypes, thereby increasing the secretion of anti-inflammatory cytokines, including IL-10, IL-12p40.[15]

Recently, it has been discovered that the immunomodulatory action of MSCs is activated only if exposed to a sufficiently high level of pro-inflammatory cytokines and nitric oxide, such as the cytokine storm in Covid-19 infection. Therefore, MSCs have great antimicrobial potential, whether acting through immunomodulation or directly through the expression of antimicrobial peptides (AMPs).[16] MSCs can also transfer healthy mitochondria to other cells through tunneling nanotubes, thereby improving the anti-inflammatory response.[15]

Extracellular vesicles (EVs) are another mechanism of action of MSCs, by acting as mediators for intercellular communication, which involves carrying biological messengers into injured sites.[17] EVs comprise microvesicles and exosomes, which contain transcription factors, growth factors, cytokines, mRNAs, and microRNAs (miRNAs), and are responsible for homeostasis, coagulation, angiogenesis, inflammation and antiapoptotic effects. EVs are nanovesicles measuring 30–150 nm that originate from the direct budding of the cell membrane or via endosomal secretion. They are composed of cytosolic contents and a lipid bilayer similar to their mother cell and, therefore, can mimic cell interactions between the source and the target.[18]

Moreover, MSCs and MSC-EVs are considered potential instruments in therapy due to acting simultaneously in crucial mechanisms of tissue damage, mainly through tissue remodeling, by modulating inflammatory cells and signals, thus enhancing tissue survival, and favoring angiogenesis, while presenting a low risk of immunogenicity and tumorigenicity.[18] Thus, MSCs are suitable candidates for cell therapy in Covid-19.

Pathophisiology of Covid-19

The main site of SARS-CoV-2 infection is the lungs, more specifically the alveoli, through the invasion of type 2 pneumocytes, macrophages and ACE2-receptor positive cells.[7] The lungs of Covid-19 patients develop diffuse alveolar damage, intra-alveolar fibrosis, bronchopneumonia, and even necrotizing bronchiolitis in severe cases.[19] The interplay between SARS-CoV-2 infected cells and resident immune cells, such as macrophages and dendritic cells, triggers a cascade of inflammatory events, producing cytokines and chemokines while stimulating the recruitment of inflammatory cells.[20] As the epithelial lining is damaged and inflammatory infiltration takes place, exudate builds up and occupies the air space within the lungs. This process also contributes to the thickening of the alveolar wall and interstitial fibrosis, culminating in the formation of a hyaline membrane that hinders air exchange.

Covid-19 pathogenesis also affects the circulatory component of the lungs. SARS-CoV-2 can directly infect endothelial cells, since these cells express ACE2 receptors.[10] Covid-19 causes more thrombotic disorders and endothelial damage than other respiratory viruses, such as SARS-CoV, MERS-CoV, and influenza.[21] These thrombotic microvascular lesions are mediated by an intense activation and deposition of complement system proteins, such as C5b-9, C4d, and MASP2, within the pulmonary septum microvasculature.[20] Therefore, disturbances in circulation and air exchange result in lower O2 distribution throughout the body.

Notably, SARS-CoV-2 triggers the release of pro-inflammatory cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6). GM-CSF stimulates inflammatory monocytes and macrophages to produce more IL-6 and TNF-α. With the progression of Covid-19 pathogenesis, infected cells and nearby cells are exposed to

intracellular components not usually found outside the cell, which causes pyroptosis.[22] This type of cell death leads to inflammasome signaling, starting a cascade of IL-1 and the release of other inflammatory factors. This further increases the process of inflammation, forming a vicious cycle of continuous inflammatory damage.

If the body is unable to limit the damage and subsequent inflammation, the condition evolves into a cytokine storm, characterized by increased levels of circulating inflammatory cytokines (IL-6, IL-8, TNF-α, monocyte chemoattractant protein-1 (MCP1), and RANTES) and ultimately damages other organs.[23]

Since Covid-19 treatment is still deficient, novel therapies that might help bed-ridden patients are in great need. In this regard, the capacity of MSCs to regulate the immune response or improve tissue regeneration may be used to control the principal components of Covid-19 pathology in severe cases: exacerbated inflammation with cytokine storm and severe lung damage.

Possible therapeutic targets and mechanisms of mesenchymal stem cells in Covid-19

Therapies using MSC are a potentially promising alternative strategy for the treatment of Covid-19, since when it comes to lung diseases, MSCs can modulate the activation and effector function of immune cells by suppressing infiltrated cells and reducing edemas.[24] Repair is provided by the property that MSCs have to incorporate into traumatized tissue and secrete growth factors, RNAs, microRNAs by paracrine/endocrine mechanisms, forming a beneficial microenvironment that aids in tissue repair.[25] However, the available records on MSC therapy for Covid-19 are still limited.

The therapeutic potential of MSCs has been demonstrated in other viral respiratory diseases. In H9N2 avian influenza-infected mice, MSC therapy reduced acute lung injury and inflammation. MSCs were capable of increasing the survival rate, decreasing lung edemas and histological injury and improving gas exchange, as well as reducing alveolar pro-inflammatory chemokines and cytokines. In a swine model of H1N1, the extracellular vesicles of MSCs reduced lung injury by reducing the production of pro-inflammatory cytokines, viral shedding and replication while also decreasing virus-induced apoptosis of alveoli epithelial cells.[26]

However, H1N1-infected mice administered with MSCs, although showing a modest reduction of viral load and lower thrombocytosis, did not display any improvements in survival, histopathology, inflammatory profile resolution or prevention.[27] Since the virus-induced ARDS model is not yet fully established, the therapeutic effect of MSCs is still under question in certain viral scenarios.

Nonetheless, MSCs have demonstrated many possible mechanisms for improving the resolution of ARDS through their anti-inflammatory and antiapoptotic effects on host cells. They reduce the permeability of the lung alveolar epithelium, increase the clearance of alveolar fluid and enhance host mononuclear cell phagocytic activity.[28] MSCs have demonstrated an ability to restore alveolar fluid clearance in *ex vivo* perfused human lungs. They have also improved epithelial integrity and regulation by transferring healthy mitochondria to epithelial cells, reducing oxidative damage and apoptosis, thus increasing survival in mice.[29]

Direct mitochondrial transfer can also modulate immune response by favoring Treg cell phenotype, which restricts inflammatory responses or the production of macrophages, thereby increasing phagocytosis.[30]

MSCs can modulate inflammation and protect the endothelial tissue of the lung.[31] MSCs secrete VEGF, which promotes angiogenesis, and HGF, which stabilizes the endothelial barrier function by restoring pulmonary capillary permeability. This proangiogenic signaling inhibits pulmonary vascular endothelial cell apoptosis.[32] In *ex vivo* human lungs, MSCs reduced endothelial permeability and protected against inflammatory disruption of barrier function, thereby restoring alveolar fluid clearance in the LPS-ARDS model.[31]

Thus, we can speculate that MSC therapy could modulate inflammation, by regulating the permeability of both endothelial and epithelial barriers during Covid-19 and preventing dysfunction.

Covid-19 multi-organ damage and potential mesenchymal stem cells therapy

Besides the classical and expected symptoms in virus-induced pneumonia, such as hypoxemia and ARDS, Covid-19 has proven to be more than a respiratory disease, causing symptoms in a variety of organs. If the cytokine storm persists, it may progress to mul-

tiple organ dysfunction syndrome,[9] affecting renal, cardiovascular, nervous, and gastrointestinal systems, which have high expression of ACE2 receptors.[6]

Severe Covid-19 seems to trigger myocarditis-like disorders, causing chest pressure and displaying increased protein levels of cardiac troponin, myoglobin, creatine kinase and NT-proBNP. Myocardial injury occurs in ~25% of Covid-19 hospitalized patients and is associated with a greater need for mechanical ventilator support and higher hospital mortality.[33] Therapeutic effects of MSCs in cardiac tissue have been reported.[31] In a model of mouse myocarditis by Coxsackievirus B3, MSCs exhibited a cardioprotective role in the recovery of myocardial contractility and fibrosis by the activation of resident cardiac stem cells.[34]

Covid-19 can also promote acute renal injury.[4] SARS-CoV-2 can infect renal cells, since viral particles are found near ACE-2 expressing cells, such as renal tubular epithelium and glomerular capillaries.[4,35] MSCs have been shown to improve renal injury by reducing tubulointerstitial fibrosis and TGF-β, which plays a key role in fibrogenesis.[36] In addition, MSCs also have the ability to promote anti-inflammatory effects at long distances. Even though intravenously infused MSCs are retained in the lungs, evidence has shown that a combination of exosomes with soluble factors secreted by MSCs contributes to anti-inflammatory response and the regeneration of renal tissues.

Moreover, MSCs can be beneficial even in indirect Covid-19 injuries. In a ventilator-induced lung injury, MSCs or even MSC-conditioned media decreased bronchoalveolar liquid concentrations of cytokines and inflammatory cells.[37]

Therefore, Covid-19 can generate an immune system overreaction causing a cytokine storm followed by edemas, inefficient gas exchange, ARDS, cardiac and renal impairments and possibly allowing secondary infections. Since the resolution of Covid-19 is mainly dependent on the function of patients' immune systems, avoiding cytokine overproduction is decisive in the recovery of patients with Covid-19. MSCs can play a crucial role, by minimizing the symptoms of Covid-19 and giving a chance for the patient's immune system to react against the virus and promote pulmonary regeneration.

Future challenges and perspectives

Since the outbreak of Covid-19 in early 2020, numerous studies have been made with the aim of developing new therapeutic interventions to control the disease and its possible impacts on the population. MSCs are a major cornerstone in the advancement of cell therapy, presenting positive results in multiple disease clinical trials, such as virus-induced ARDS.[34] The applicability of MSCs is not restricted to utilizing only the cells themselves, but also extends to MSC-derived products, such as the secretome and EVs, opening one more possibility in the future.[17,18] Their therapeutic action is probably attributable to their broad range of anti-inflammatory and regenerative effects, which help to heal damaged tissue.[38] Most importantly, MSCs do not express ACE2 and TMPRSS2 since they are not conducive to SARS-CoV-2 infection, which supports the safety of MSCs as a plausible therapy.[39]

It is also relevant to consider aspects that will reflect on the effectiveness of MSC therapy for Covid-19. For example, the donor tissue source of MSCs, which constitutes the MSCs' microenvironment and modulates their behavior and capacity, can greatly affect their therapeutic potential. Metabolic diseases, such as obesity and *diabetes mellitus*, also have an influence on the behavior of MSCs and compromise their therapeutic efficacy.[40] Therefore, exploratory studies that seek to maintain the phenotype and potential of MSCs are necessary for clinical practice, to understand better how the clinical conditions of MSC donors influence the viability and therapeutic capacity of this treatment.

Moreover, the timing and dosage of MSCs for Covid-19 are still in question, since defining the optimal stage of Covid-19 at which the cells present the most benefit to the patient must still be clarified. Also, with the emergence of long Covid patients who suffer from Covid-related symptoms over an extended period of time even after the resolution of the acute infection, interest in the antifibrotic and regenerative potential of MSCs will increase. Standardized protocols are needed to further investigate and validate this therapeutic approach in order to enhance the applicability of MSCs in the treatment of Covid-19 disease.

Acknowledgments

This study was supported in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

References

1. WHO. Coronavirus Disease (Covid-19) Situation Reports. Situat Reports WHO Accessed June 30, 2021; 2021
2. Candido DDS, Watts A, Abade L, et al. Routes for Covid-19 importation in Brazil. J Travel Med. 2020 May;27(3). doi: 10.1093/jtm/taaa042
3. Gorbalenya AE, Baker SC, Baric RS, et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5(4):536–44. doi: 10.1038/s41564-020-0695-z
4. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265–9. doi: 10.1038/s41586-020-2008-3
5. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of Covid-19. Viruses. 2020;12(4):1–17. doi: 10.3390/v12040372
6. Li M-YY, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020 Apr;9(1):45. doi: 10.1186/s40249-020-00662-x
7. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in Covid-19. Vol. 75, Allergy: European Journal of Allergy and Clinical Immunology. Blackwell Publishing Ltd; 2020. p. 1564–81. doi: 10.1111/all.14364
8. Meyerowitz EA, Richterman A, Gandhi RT, et al. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med. 2021;174(1):69–79. doi: 10.7326/M20-5008
9. Robba C, Battaglini D, Pelosi P, et al. Multiple organ dysfunction in SARS-CoV-2: MODS-CoV-2. Expert Rev Respir Med. 2020 Sep;14(9):865–8. doi: 10.1080/17476348.2020.1778470
10. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5. doi: 10.1016/j.ijid.2020.03.017
11. Li Y, Tenchov R, Smoot J, et al. A Comprehensive Review of the Global Efforts on Covid-19 Vaccine Development. ACS Cent Sci. 2021 Apr;7(4):512–33. doi: 10.1021/acscentsci.1c00120
12. Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: past, present, and future. Stem Cell Res Ther. 2019;10(1):68. doi: 10.1186/s13287-019-1165-5
13. Eguizabal C, Aran B, Chuva de Sousa Lopes SM, et al. Two decades of embryonic stem cells: a historical overview. Hum Reprod Open. 2019 Jan;2019(1). doi: 10.1093/hropen/hoy024
14. Esquivel D, Mishra R, Soni P, et al. Stem Cells Therapy as a Possible Therapeutic Option in Treating Covid-19 Patients. Stem Cell Rev Reports. 2021;17(1):144–52. doi: 10.1007/s12015-020-10017-6
15. Dabrowska S, Andrzejewska A, Janowski M, et al. Immunomodulatory and Regenerative Effects of Mesenchymal Stem Cells and Extracellular Vesicles: Therapeutic Outlook for Inflammatory and Degenerative Diseases. Front Immunol. 2021;11:3809. doi: 10.3389/fimmu.2020.591065
16. Verma YK, Verma R, Tyagi N, et al. Covid-19 and its Therapeutics: Special Emphasis on Mesenchymal Stem Cells Based Therapy. Stem cell Rev reports. 2021 Feb;17(1):113–31. doi: 10.1007/s12015-020-10037-2
17. Rezakhani L, Kelishadrokhi AF, Soleimanizadeh A, et al. Mesenchymal stem cell (MSC)-derived exosomes as a cell-free therapy for patients Infected with Covid-19: Real opportunities and range of promises. Chem Phys Lipids. 2021 Jan;234:105009. doi: 10.1016/j.chemphyslip.2020.105009
18. Keshtkar S, Azarpira N, Ghahremani MH. Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. Stem Cell Res Ther. 2018;9(1):63. doi: 10.1186/s13287-018-0791-7
19. Vasquez-Bonilla WO, Orozco R, Argueta V, et al. A review of the main histopathological findings in coronavirus disease 2019. Hum Pathol. 2020;105:74-83. doi: 10.1016/j.humpath.2020.07.023
20. Schaefer I-M, Padera RF, Solomon IH, et al. In situ detection of SARS-CoV-2 in lungs and airways of patients with Covid-19. Mod Pathol. 2020;33(11):2104-14. doi: 10.1038/s41379-020-0595-z
21. Bikdeli B, Madhavan M V., Jimenez D, et al. Covid-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. Vol. 75, Journal of the American College of Cardiology. Elsevier USA; 2020. p. 2950-73. doi: 10.1016/j.jacc.2020.04.031
22. Ferreira AC, Soares VC, de Azevedo-Quintanilha IG, et al. SARS-CoV-2 engages inflammasome and pyroptosis in human primary monocytes. Cell Death Discov. 2021;7(1). doi: 10.1038/s41420-021-00477-1
23. Hu B, Huang S, Yin L. The cytokine storm and Covid-19. J Med Virol. 2021 Jan;93(1):250–6. doi: 10.1002/jmv.26232
24. Liu S, Peng D, Qiu H, et al. Mesenchymal stem cells as a potential therapy for Covid-19. Stem Cell Res Ther. 2020;11(1):169. doi: 10.1186/s13287-020-01678-8
25. Lindoso RS, Collino F, Bruno S, et al. Extracellular Vesicles Released from Mesenchymal Stromal Cells Modulate miRNA in Renal Tubular Cells and Inhibit ATP Depletion Injury. Stem Cells Dev. 2014 Mar;23(15):1809–19. doi: 10.1089/scd.2013.0618
26. Khatri M, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. Stem Cell Res Ther. 2018;9(1):17. doi: 10.1186/s13287-018-0774-8
27. Laffey JG, Matthay MA. Cell-based therapy for acute respiratory distress syndrome: Biology and potential therapeutic value. Vol. 196, American Journal of Respiratory and Critical Care Medicine. American Thoracic Society; 2017. p. 266–73. doi: 10.1164/rccm.201701-0107CP
28. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe Covid-19 infection: A report of five cases. Transl Res. 2020;220:1–13. doi: 10.1016/j.trsl.2020.04.007
29. Islam MN, Das SR, Emin MT, et al. Mitochondrial transfer from bone-marrow–derived stromal cells to pulmonary alveoli protects against acute lung injury. Nat Med. 2012;18(5):759–65. doi: 10.1038/nm.2736
30. Court AC, Le-Gatt A, Luz-Crawford P, et al. Mitochondrial transfer from MSCs to T cells induces Treg differentiation and restricts inflammatory response. EMBO Rep. 2020 Feb;21(2). doi: 10.15252/embr.201948052
31. Németh K, Leelahavanichkul A, Yuen PST, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E2–dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med. 2009;15(1):42–9. doi: 10.1038/nm.1905
32. Wang J, Jiang M, Chen X, et al. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 Covid-19 patients in China and emerging pathogenesis

and therapy concepts. J Leukoc Biol. 2020 Jul;108(1):17–41. doi: 10.1002/JLB.3COVR0520-272R

33. Giustino G, Pinney SP, Lala A, et al. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(17):2011–23. doi: 10.1016/j.jacc.2020.08.059
34. Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: Mechanisms of potential therapeutic benefit in ARDS and sepsis. Vol. 2, The Lancet Respiratory Medicine. Lancet Publishing Group; 2014. p. 1016–26. doi: 10.1016/S2213-2600(14)70217-6
35. Allison SJ. SARS-CoV-2 infection of kidney organoids prevented with soluble human ACE2. Nat Rev Nephrol. 2020;16(6):316. doi: 10.1038/s41581-020-0291-8
36. Lira R, Oliveira M, Martins M, et al. Transplantation of bone marrow-derived MSCs improves renal function and Na++K+-ATPase activity in rats with renovascular hypertension. Cell Tissue Res. 2017 Aug;369(2):287–301. doi: 10.1007/s00441-017-2602-3
37. Curley GF, Ansari B, Hayes M, et al. Effects of Intratracheal Mesenchymal Stromal Cell Therapy during Recovery and Resolution after Ventilator-induced Lung Injury. Anesthesiology. 2013 Apr;118(4):924–32. doi: 10.1097/ALN.0b013e318287ba08
38. Pittenger MF, Discher DE, Péault BM, et al. Mesenchymal stem cell perspective: cell biology to clinical progress. npj Regen Med. 2019;4(1):22. doi: 10.1038/s41536-019-0083-6
39. Avanzini MA, Mura M, Percivalle E, et al. Human mesenchymal stromal cells do not express ACE2 and TMPRSS2 and are not permissive to SARS-CoV-2 infection. Stem Cells Transl Med. 2021 Apr;10(4):636-42. doi: 10.1002/sctm.20-0385
40. de Oliveira GP, Cortez E, Araujo GJ, et al. Impaired mitochondrial function and reduced viability in bone marrow cells of obese mice. Cell Tissue Res. 2014 Jul;357(1):185–94. doi: 10.1007/s00441-014-1857-1

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Changes in the nutritional status of elderly patients with HIV diagnosis undergoing antiretroviral treatment

Glauciane L. Miranda,[1*] Aline Ignácio,[1] Ana Carla D. O. Lopes,[2] Camila F. Lima[2]

Abstract

Introduction: Acquired immunodeficiency syndrome (AIDS) is an infectious contagious disease produced by the human immunodeficiency virus (HIV) that causes progressive immunosuppression, making individuals susceptible to infections and opportunistic diseases. Despite its benefits, antiretroviral therapy has side effects, such as insulin resistance, dyslipidemia, high blood pressure and increased risk of cardiovascular disease. Objective: The aim of this study was to identify metabolic alterations in elderly patients with AIDS who use antiretroviral therapy (ART). Methods: The study consisted of a retrospective bibliographic review, including indexed articles published over the last 10 years, written in Portuguese and English, which evaluated changes in nutritional status and metabolic changes in HIV-positive patients who used ART. Results: According to the Brazilian Ministry of Health, the number of people over 65 with HIV grew by 103% in the last decade. The HIV virus has a long incubation period before the onset of the first symptoms of the disease, which results in AIDS. Dyslipidemia affects approximately 70% of HIV-infected patients who use ART, and occurs due to an increase in serum cholesterol, triglycerides and/or a reduction in HDL-cholesterol. Conclusion: The WHO recommends that nutritional interventions form part of HIV/AIDS control and treatment programs since they improve treatment adherence and ART effectiveness. In this context, a healthy diet that is adequate for the needs of the individual contributes to increased levels of CD4 T lymphocytes and reduces the harm caused by opportunistic infections, while improving intestinal absorption, as well as decreasing muscle loss and lipodystrophy syndrome, whose symptoms can significantly reduce the survival rates of patients.

Keywords: HIV; AIDS; ART; Lipodystrophy syndrome (LS); Dyslipidemia; Insulin resistance.

1. Instituto de Nutrição Josué de Castro, Universidade Federal do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.

2. Instituto de Nutrição, Universidade do Estado do Rio de Janeiro. Rio de Janeiro, RJ, Brazil.

***Correspondence address:**
Avenida Cláudio Besserman Viana, 3, bloco 4, ap. 812
Rio de Janeiro, RJ, Brazil.
CEP: 22775-036.
E-mail: glaucianelacerda@gmail.com
ORCID: https://orcid.org/0000-0003-4086-1406

BJHBS, Rio de Janeiro, 2022;21(1):61-67
DOI: 10.12957/bjhbs.2022.68186
Received on 30/06/2021. Approved on 29/11/2021.

Introduction

Acquired immunodeficiency syndrome (AIDS) is an infectious contagious disease caused by the human immunodeficiency virus (HIV) that causes progressive immunosuppression, which makes individuals vulnerable to infections and opportunistic diseases. Clinical treatment is usually based on drugs, which can cause numerous side effects. Clinically, the disease manifests itself in a sequence of stages: acute infection, asymptomatic or clinical latency phase, then the early or early symptomatic phase and, finally, AIDS, which is the final stage of infection by the HIV virus.[1]

Malnutrition, due to metabolic changes caused by the virus, is one of the main side effects evident in these patients. In addition, antiretroviral treatment (ART) leads individuals with the human immunodeficiency virus (HIV) to develop metabolic changes resulting from the use of this treatment to fight the HIV virus.[2]

In 2005, HIV infection affected 42 million people all over the world. Latin America accounted for about 1.8 million of these, and Brazil was the most affected country, with about 1.2 million infected inhabitants, of which 257,780 had AIDS. The latest data presented by the Joint United Nations Program on HIV (UNAIDS), in 2008, showed an increase in the number of people infected in Latin America and Brazil.[3] More recent data from the Brazilian Ministry of Health (2017) found that the number of people over 65 of age with HIV rose by 103% in the last 10 years.

During the last decade, the introduction of ART in the treatment of HIV has been found to improve the condition of terminally ill patients, restore the immune system and reduce the number of deaths, while increasing the survival and quality of life of

patients infected by the virus. However, this therapy has also caused metabolic events characterized by dyslipidemia, lipodystrophy syndrome (LS), insulin resistance/glucose intolerance, and systemic arterial hypertension.[4,5]

As a result of the increased survival rate of patients using the treatment, the most current phenomenon of HIV is the emergence of a new vulnerable population: senior citizens. According to law n°10.741 of 1 October, 2003, this group is constituted by individuals aged over 60 years.[6] However, ART can cause metabolic alterations, which constitute risk factors for cardiovascular disease (CVD), with a probable association caused by HIV infection, and also due to the impact of the treatment on glucose and lipid metabolisms.[7]

Studies report that some patients presented LS with the use of ART, which is a worrisome problem resulting from treatments to combat the HIV virus. SL is a side effect, characterized by the redistribution of body fat. The typical manifestations of LS are represented by lipoatrophy (reduction of fat in peripheral regions); lipohypertrophy (accumulation of fat in the abdominal region, breasts and dorsocervical region); or a mixture of both.[2,8]

These nutritional and metabolic changes in patients with HIV should be minimized through adequate drug therapy and dietary intervention in order to control eventual changes caused in these patients.[9]

In this context, this study aims to assess nutritional and metabolic changes in elderly patients who use ART and how dietary intervention in these individuals can directly interfere in the improvement of the altered biochemical picture, especially in cases exhibiting mixed dyslipidemia and insulin resistance.[7]

Materials and methods

This study consists of a retrospective bibliographic review, covering indexed articles written in Portuguese and English, published over the last 10 years, which evaluated changes in nutritional status and metabolic changes in HIV-positive patients who use ART.

A systematic literature review technique was used for data collection, in which articles indexed in the Scielo and *Pubmed* databases, published between 2007 and 2017, were searched, listing the scientific production by year and subsequently choosing the most relevant publications on the subject. To find articles of interest, the following descriptors were used: AIDS, HIV, AIDS, nutritional assessment, malnutrition, lipodystrophy, dyslipidemia and metabolic alterations.

Literatura review

HIV epidemiology

The incidence of HIV in the Brazilian population over 50 years old increased from 3.6 to 7.1 per 100,000 inhabitants between 1996 and 2006, representing a 50% increase of new cases. The disease in this specific group has particular epidemiological relevance due to its high incidence, prevalence and lethality rates.

Of the HIV cases reported since the beginning of the epidemic in people over 50 years old, 29,393 (62%) were registered from 2001 to June 2008, suggesting underreporting before the year 2000. In this group, 37% were women and 63% were men. The HIV rate among seniors in Brazil is now higher than that of adolescents aged between 15 and 19 years.[10]

Epidemiologists estimate that persons newly diagnosed with HIV infection who are involved with and maintained using ART have a life expectancy of 20 years, thus allowing them to lead a normal or almost normal life, which permits those infected to reach an older age.[11]

The literature emphasizes knowledge about HIV in young individuals and health professionals; however, information related to HIV among seniors is lacking.[12]

The increase in the number of HIV cases among seniors has been associated with the aging of the Brazilian population, the increased survival of people living with HIV and access to medication for erectile disorders, a factor that has prolonged sexual activity among seniors, in combination with the demystification of sex in old age. The experience of sexuality has made the elderly more vulnerable to sexually transmitted diseases (STD), contributing to a higher incidence of these diseases in individuals over 50 years old.[10]

Due to lack of information, studies in this area must be developed, since knowledge is important both to promote the reduction of prejudice against HIV carriers and to introduce prevention measures.[12]

Social and economic factors

The relationship between both economic and social impacts on HIV patients is closely linked to costs and the issue of education, which is the main means

for the assimilation of information and adherence to information campaigns.[13]

According to Okuno *et al.* (2014), low income exerts a negative influence on the quality of life of elderly people with HIV who received a minimum wage or less. Quality of life is a multifaceted issue, as mentioned above, and is related to economic issues, lifestyle, health condition, housing, among others. In addition, a high level of education has been associated with higher quality of life and longevity scores.[14]

Another important factor is the mental state of patients with HIV, which can interfere with their nutritional issues.[15] It is necessary to understand the clinical, economic and psychosocial history in which patients are inserted in order to design a therapeutic plan compatible with their lifestyle, which respects their food preferences, aversions and the relationship between food and the ART used.

Physiological changes related to aging

Although aging is a normal process inherent to human beings, this process promotes physiological changes. These modifications can progress differently in each individual and depend on factors such as genetics, diseases, socioeconomic status and lifestyle. In the aging process, changes in the body composition of these individuals are common. These modifications are characterized by an increase in fat mass and visceral fat and a reduction in lean mass. In many cases, malnutrition is prevalent.[16] In addition, sarcopenia can be found, which is characterized by a reduction in muscle mass, strength and function, thus contributing to a worsening in the quality of life of the elderly and possibly increasing the risk of falls.[15]

Another very important change is related to taste and smell. Sensory losses are closely related to a declining appetite and reduced nutrient intake. The changes can be due to aging itself, but in some cases are the consequence of the use of medications and pathologies. Because of this, many seniors can overdo spices, especially those with added salt, causing a negative effect on health.[15]

Hearing loss affects 25 to 40% of elderly Americans, mainly due to presbycusis, although it can also be caused by the cumulative effect of sounds throughout life, such as construction work, exposure to music and noises, among others. Vision changes, such as age-related macular degeneration, glaucoma and cataracts, promote poor vision that interferes with shopping, cooking and eating.[15]

Very frequent changes that can compromise the nutritional status of elderly patients occur due to the absence of teeth, the presence of dentures and the occurrence of dry mouth, which can can impair the chewing and swallowing of certain foods, such as fruits, vegetables and vegetables and, as a consequence, worsen digestion.[16] This exacerbates the condition of hypochlorhydria (insufficient acid production) that is already expected in these patients. In addition to these changes in the gastrointestinal tract, one should also mention constipation, which is quite frequent in the elderly population as a result of reduced fluid intake, medication, low fiber intake and physical inactivity.[15]

Assessment methods and nutritional screening of elderly patients

Several simple and easy-to-apply tools for nutritional screening are available in the literature, incldng NRS (Nutritional Risk Screening) 2002, MNA SF (Mini Nutritional Assessment Short Form),[17] MUST (Universal Malnutrition Screening Tool) and NRS (Nutritional Risk Score). These are sensitive to nutritional risk and the nutritional profile of the patient.

On the other hand, the nutritional screening of elderly patients can lose sensitivity to the physical and metabolic changes that occur in the aging process. These include height, in which the individual may have problems with the spine, inability to stand upright and being bedridden, as well as the replacement of muscle by fatty fat.[15]

Therefore, it is important to choose the best screening method for the profile of the elderly person who will be evaluated, taking into account the limitations and the method with the best sensitivity for that patient. For example, the MNA-SF includes the alternative of using the circumference of the calf, which is a sensitive measure of muscle mass in the elderly.[17]

Malnutrition in elderly patients with HIV

The HIV virus is characterized by a long period of incubation before the onset of the first symptoms of the disease, which results in AIDS.[18]

HIV-infected individuals also present other complications, such as cardiorespiratory, anthropometric (wasting syndrome), muscle (muscle wasting- sarcopenia) and psychiatric (depression) diseases, which may be associated with the worsening of their clinical condition and cause a decrease in their functional independence.

It must be borne in mind that sarcopenia is a predictor of morbidity and mortality, since it promotes a decrease in muscle strength, making individuals physically debilitated and thus contributing to the progression of HIV infection.[19]

Although ART is associated with an improvement in the quality of life of HIV patients, it is also linked to cardiovascular events, since there has been a frequent increase in the number of cases of coronary events related to increased survival of these patients and to the toxicity of therapy. The use of ART and protease inhibitors has been connected with dyslipidemia, insulin resistance and *diabetes mellitus*, which are risk factors for the development of cardiovascular diseases.[7]

The gastrointestinal tract (GIT) is one of the areas most susceptible to damage in these patients, especially in the part that integrates the immune tissue. The nutritional status of HIV/AIDS patients becomes a concern, due to reduced appetite and insufficient energy intake associated with increased energy expenditure at rest. Weight loss typically occurs in 95 to 100% of AIDS patients. In addition, most have nausea, bloating and vomiting, which further impair their nutritional status.[20]

A significant minority also reports diarrhea and oral moniliasis, in which the appearance of gastrointestinal symptoms, mainly due to opportunistic diseases, is cause for frequent hospitalization. This makes the immediate nutritional assessment of hospitalized patients essential to diagnose the risks of malnutrition and the presence of gastrointestinal symptoms that directly interfere with their nutritional status.[20]

The literature has indicated that food supplementation in HIV-positive individuals, especially males, whether or not they use use a protease inhibitor (PI), preferentially promotes the gain of fat mass at the expense of lean mass, probably as a result of a marginal testosterone deficiency observed in such patients.[21]

Nutritional interventions are important to control the progression of metabolic syndromes that affect patients with HIV/AIDS. Since nutritional risk is a predominant factor in these patients, continuous nutritional assessment and periodic biochemical tests become relevant to identify and set goals for the avoidance of possible nutritional deficiencies. This helps nutritionists to define the exact moment to start providing supplements to the HIV-positive patient and thereby minimizes and reverses possible nutritional damage caused by the side effects of ART.[22]

Most common micronutrient deficiencies in elderly HIV patients

Nutritional deficiencies are common in these patients, many of which are closely related to the immune function. Many of these deficiencies are caused by gastrointestinal changes, such as malabsorption, drug-nutrient interactions and changes in the intestinal barrier. Some nutrients that may occur in lower concentration in the body are vitamin A, zinc, selenium and vitamin D. Reduced levels of these nutrients are associated with faster progression of the disease. While data on these deficiencies exist, uncertainty still prevails as to whether this is in fact a deficiency or an acute response to the virus. Therefore, attention must be paid to the supplementation of multivitamins.[23]

Diet therapy for the elderly and/or adult patients with HIV

The WHO recommends that nutritional interventions be included in all HIV control and treatment programs since, in addition to improving adherence to treatment, they make ART therapy more effective, as well as contribute to the improvement of metabolic abnormalities. According to the Brazilian Ministry of Health, healthy and adequate food for the needs of each individual contributes to increased levels of CD4 T lymphocytes and reduces harm caused by opportunistic infections, as well as improving intestinal absorption, muscle loss, and SL.[24]

According to a study on the importance of nutrition in adults with HIV, the association of drug therapies with nutrition favors their health status and reduces the mortality rate. However, despite the use of (medicament-nutrition) treatment to bring benefits to people with HIV, the patient's body continually develops viral resistance, which impairs the action of the medication.[24]

Furthermore, studies have shown a close link between adequate nutrition and the strengthening of the immune system, which improve the nutritional status of the patientas well as achieve more favorable results in the treatment.[25]

In this context, diet therapy works mainly with the objective of: protecting muscle mass, which reduces the chances of developing malnutrition; recovering or maintaining nutritional status; providing adequate amounts of nutrients; and reducing the complications, opportunistic infections

and side effects of ART that may interfere with nutrient intake and absorption.[24]

In other words, the role of nutrition education should be to lead patients to adopt healthy eating habits, related to quality, quantity, harmony and nutritional adequacy, and to improve the quality of life of these individuals, who should be made aware of the importance of nutrition in the context of the disease.[24]

Furthermore, recent studies demonstrate that the adoption of a Mediterranean dietary pattern (characterized mainly by the intake of plant foods, such as whole grains, fruits, vegetables, legumes and olive oil; a moderate intake of fish and dairy products; and a low intake of red meat, saturated fats and sweets) has been associated with decreased mortality, as well as with improved health conditions and cardiovascular risk factors associated with aging. Increased blood triglyceride levels have been observed especially among individuals with HIV treated with ART containing a protease inhibitor (PI). Such increases can be observed a few weeks after the start of treatment. And supplementation with omega-3 fatty acids has been shown to be effective in reducing drug-induced elevated triglyceride levels.[26]

In the case of interventions aimed at dyslipidemia, the presence of symptoms, the clinical picture, the type and duration of use of nutritional therapy, in addition to the presence of cardiovascular risk factors, are fundamental conditions for monitoring and nutritional treatment aimed at this guy.[24]

The Brazilian Ministry of Health states that a healthy diet, adequate for the individual needs of each patient, contributes to an increase in the levels of CD4 T lymphocytes, improves intestinal absorption, reduces the problems caused by diarrhea, improves muscle wasting, SL, and all other symptoms that, in one way or another, can be minimized or reversed through a balanced diet. In this context, proper nutritional guidance is extremely important as an integral part of the treatment of HIV-positive patients who use ART.[26]

Insulin resistance in elderly patients with AIDS

Insulin resistance (IR) can be caused by weight gain, changes in the distribution of body fat and the use of retroviral protease inhibitors.[5]

In this context, IR, glucose intolerance and type 2 *diabetes mellitus* (DM2) show significant increases in seropositive patients after the introduction of ART. Furthermore, the clinical picture of DM2 and IR has been reported in 3% to 17% of those who receive the treatment, as a function of alterations in glucose homeostasis.[7]

The clarification of the factors involved in the process of alterations in glucose homeostasis, especially insulin resistance, still remains a major challenge for improving the quality of life of patients. Among users of protease inhibitors, an increased occurrence of insulin resistance has been observed without the development of diabetes mellitus.[7]

Hyperglycemia in patients using ART has a prevalence of 46% to 54%, and is caused by selective inhibition of the GLUT-4 receptor. This leads to loss of sensitivity to insulin from the major glucose transporter present in skeletal muscle, liver and adipocytes, and causes IR. When not treated correctly and quickly, this can lead to the development of *diabetes mellitus*. Thus, it is essential to identify those who have this metabolic change, and start treatment immediately.[27]

Dyslipidemia in elderly patients with AIDS

Dyslipidemia associated with ART is characterized by an increase in the levels of VLDL (greater triglyceride transporter), LDL, lipoprotein (a) and a reduction in HDL. In individuals without HIV, the accumulation of these substances in the plasma is associated with the development of atherosclerosis and its complications, such as myocardial infarction and peripheral vascular disease.

It has not yet been established whether dyslipidemia is a direct effect of ART or a result of the interaction of several elements, such as antiretroviral treatment, genetic predisposition, environmental factors (such as diet and exercise), or other factors, such as the host's response to infection by HIV.[7]

Insulin resistance increases the release of free fatty acids, while in the liver it determines a lower suppression of VLDL synthesis. This results in an excess of large, triglyceride-rich VLDL particles which, in turn, generate a cascade of switch events that result in a reduction in HDL cholesterol levels.[7]

The mechanisms that lead to these changes are not yet fully understood, but some hypotheses have been raised. One of these is that lipid complications arise or are aggravated as a result of ART, which leads to an increase of lipids in the bloodstream and a reduction in the peripheral storage of these molecules. When accumulated in the plasma and associated with the arterial inflammation itself resulting from the infection by the HIV, these lipids may clog arteries and facilitate

the formation of fatty plaques, which can lead to the development of CVD.[28]

Two main hypotheses have been raised about the mechanisms of interference in the lipid metabolism. The first would be the similarity between the viral active site where the binding of protease inhibitors (PI) occurs, leading to an increase in triglycerides and the freeing of fatty acids , combined with a reduction in plasma hydrolysis and uptake of triglycerides by the liver. The second hypothesis would be a proposed mechanism that would lead to dyslipidemia, due to the competition between PI and remnant chylomicrons (QR) by liver receptors, which prevent the removal of QR from the plasma and result in an increase in circulating triglycerides.[28]

Conclusion

The present review study shows that, despite the high importance of the use of antiretroviral treatment by HIV-positive patients, which lead to increased survival rates and higher quality of life for these patients, antiretroviral therapy has a significant pathophysiological impact on patients undergoing treatment. The relationship between the type and duration of therapy used, more common in elderly patients, can lead to metabolic syndrome resulting from the use of these drugs, and cause the development of DM2 and CVD.

This treatment highlights the importance of the intervention of nutritionists, who should direct patients towards an adequate food intake, significantly intervening in the metabolic changes caused by the use of therapy. Nutritional therapy plays a fundamental role in the recovery of these patients by conserving muscle mass and reducing the risk of malnutrition and opportunistic diseases. Nutritional guidance and consequent healthy eating habits alleviate the organic changes caused by the use of ART and improve the quality of life of patients with HIV.

References

1. Araújo ApSd, Bertoline SMMG, Martins Junior J. Influence of physical exercise on practice standards morphofunctional, immune function and quality of elderly with aids: case study. Man. Ther., Posturology Rehabil. J.. 2014:112-120. doi: 10.17784/mtprehabjournal.2014.12.176
2. Tsuda LC, da Silva MM, Machado AA. Body changes: antiretroviral therapy and lipodystrophy syndrome in people living with HIV/AIDS. Latin American Journal of Nursing. 2012 Oct;20(5). doi: 10.1590/S0104-11692012000500005
3. Domingos H, da Cunha RV, Paniago AMM, et al. Rosuvastatin and ciprofibrate in the treatment of dyslipidemia in HIV patients. Arq. Bras. Cardiol. 2012 Nov;99(5). doi: 10.1590/S0066-782X2012005000096
4. Wink CC, Pozzobon A, Morelo Dal Bosco S. Nutritional status and lipid profile assessment in seropositive patients treated at a specialized assistance service in Vale do Taquari - RS. ConScientiae Saúde. 2012 April-June:312-319. doi: 10.5585/ConsSaude.v11n2.2938
5. Falco M, Castro AdCdO, Silveira EA. Nutritional therapy for metabolic changes in people living with HIV/AIDS. Public Health Magazine. 2012;46(4):737-746. doi: 10.1590/s0034-89102012005000050
6. Brazil Ln17D1DOD2. Presidency of the Republic Civil House Sub-Chief Legal Affairs. [Online].; 2003 [cited 2021 November 18. Available from: http://www.planalto.gov.br/ccivil_03/leis/2003/l10.741.htm
7. Kramer AS, Lazzarotto AR, Sprinz E, et al. Metabolic alterations, antiretroviral therapy and cardiovascular disease in elderly people with HIV. Arch. Bras. Cardiol. 2009 November;93(5). doi: 10.1590/S0066-782X2009001100019
8. Da Silva IRP, Dias RM, Dutra CDT, et al. Dyslipidemia and nutritional status in HIV-positive patients with lipodystrophy syndrome. Journal of Epidemiology and Infection Control. 2014;4(3):200-207.
9. Silva MCA, Burgos MGP, Silva RA. Nutritional and metabolic changes in AIDS patients using antiretroviral therapy. J Bras Sex Transm. 2010;22(3):118:122.
10. Santos AFdM, Assis M. Vulnerability of older women to HIV/AIDS: policy awakening. Rev. Bras. Geriatr. Gerontol. 2011;14(1):147-157. doi: 10.1590/S1809-98232011000100015
11. Brooks JT, Buchacz K, Gebo KA. HIV infection and older Americans: The Public Health Perspective. Am J Public Health. 2012 August;102(8):1516-1526. doi: 10.2105/AJPH.2012.300844
12. Lazzarotto AR, Kramer AS, Hadrich M. Knowledge of HIV/AIDS in old age: an epidemiological study in Vale do Sinos, Rio Grande do Sul, Brazil. Science & Public Health. 2008;13(6):1833-1840. doi: 10.1590/S1413-81232008000600018
13. Irffi G, Soares RB, DeSouza SA. Socioeconomic, Demographic, Regional and Behavioral Factors Influencing Knowledge about HIV/AIDS. Economia Magazine. 2010 May/August;11(2):333-356.
14. Okuno M, Gomes A, Meazzini L, et al. Quality of life of elderly patients living with HIV/AIDS. Public Health Cad. 2014 July;30(7):1551-1559. doi: 10.1590/0102-311X00095613
15. Mahan LK, Raymond JL. Krause: Food, Nutrition and Diet Therapy. 14th ed. Rio de Janeiro: Elsevier; 2018. p. 367-375
16. Martins and Silva SC, Aires C, Figueira YLV, et al. Physiological changes in the elderly and their impact on food intake: A literature review. Electronic Journal Collection Health. 2017 January;6(6):288-295. doi: 10.25248/REAS-S19_2017

17. Arruda NR, Oliveira ACdCC, Garcia LJC. Nutritional risk in the elderly: comparison of nutritional screening methods in a public hospital. RASBRAN - Journal of the Brazilian Nutrition Association. 2019 Jan-Jun;10(1):59-65.
18. Brazil. MS. Department of Diseases of Chronic Conditions and Sexually Transmitted Infections. [Online].; 2014 [cited 2015 September 16. Available from: http://www.aids.gov.br/sites/default/%20files/anexos/publicacao/2014/56677/%20boletim_2014_final_pdf_15565.pdf
19. Lazzarotto AR, Deresz LF, Sprinz E. HIV/AIDS and Competitive Training. Rev Bras Med Sport. 2010 Mar/Apr;16(2). doi: 10.1590/S1517-86922010000200015
20. Pinto AF, Kauffman LKdO, Penha HPdS, et al. Nutritional status and gastrointestinal disorders of patients hospitalized with HIV/AIDS at the João de Barros Barreto University Hospital in Belém, State of Pará, Brazil. Pan Amazonian Health Magazine. 2016 December;7(4):47-52.
21. Marques MRdO, Kondo K, Bonilha de Moraes HA. Effects of food supplementation on the nutritional status of men. Universidad del Centro Educativo Latinoamericano. 2005 November;8(15):143-154.
22. Leones JR, Mauricio DdB, Caporossi C. The influence of glutamine as an immunopharmaceutical nutrient for the control of metabolic alterations in patients with HIV/AIDS. Scientific Journal of Hospital Santa Rosa. 2013;3:40-44.
23. Liguori MMdBC, Lisbon RC, Coutinho VF. Nutritional profile of HIV-positive patients using antiretroviral drugs. Rev de Nutr. 2017;16(5):344-350.
24. Braga IS, Guimarães NS, De Figueiredo SM. Nutritional and metabolic disorders caused by the use of antiretroviral therapy and nutritional approach: a narrative review. Nutri. Clin. Diet. Hospital. 2015;1(35):71-75.
25. Neres PEP, Santini S, E. Reis Filho AD. Nutritional Considerations for Adults with HIV/AIDS. Matogrossense Nursing Magazine. 2010 November/December;1(2):148-165.
26. Licks P, Horvath JDC. Nutritional therapy in HIV-positive patients using ART in the face of the development of medication-induced metabolic disorders. Clinical & Biomedical Research. 2016 August;36(2).
27. Júnior MGt, Issa A, Soares VE. Dyslipidemia associated with antiretroviral therapy in patients with AIDS. SOCERJ Magazine. 2005 November/December;18(6):542-546.
28. Bonifácio FPS, Godoy FSdP, Francisco DKdF, et al. Metabolic alterations associated with antiretroviral therapy in HIV-positive patients. Notebooks of the School of Health. 2014;1(9):138-149.

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND
BIOMEDICAL SCIENCES

Review article

Eating disorders and their impact during the gestational period

Fernanda B. Silva,[1] Luciana Pietro[2*]

Abstract

Introduction: Eating disorders can cause numerous problems for the physiology of the female body and consequences, such as infertility and difficulties during pregnancy and childbirth, can occur if they are present during a woman's reproductive age. Objective: The objective of this research was to analyze the impacts for mother and child that may be somehow related to the nutritional deficiency, whether active or not, of these women. Methodology: The methodology used was a bibliographic survey in the platforms PubMed, BIREME, SCIELO, using combinations of the following keywords in English: Eating Disorder AND Pregnancy, Anorexia, Bulimia. Result: According to the studies analyzed, the existence of some type of eating disorder, whether active or not, had a negative impact on the pregnancies of these women. Miscarriages, stillborn babies, premature birth, premature placental displacement, small newborn gestational age, umbilical cord knots and even neurological deficits could occur. Discussion: Low body mass index (BMI) was one of the main subjects of discussion in the studies, since it can increase the risk of pregnancy because the mother's nutrients are crucial for a healthy gestation. Conclusion: it was concluded that medical, nutritional and psychological follow-up are essential for women with eating disorders, regardless of type, to be able to have a safe pregnancy for themselves and their babies..

Keywords: Eating disorders; Mother-child impacts; Nervous bulimia; Anorexia nervosa; Gestational complications.

1. Curso de Biomedicina, Universidade Paulista Unip. Campinas, SP, Brazil.

2. Departamento de Biomedicina, Universidade Paulista Unip. Campinas, SP, Brazil.

***Correspondence address:**
Rua Moacir Pinto, 229
Leme, SP, Brazil.
CEP: 13613-180.
E-mail: lucianapietro1@gmail.com
ORCID: https://orcid.org/0000-0002-8511-2196

BJHBS, Rio de Janeiro, 2022;21(1):68-74
DOI: 10.12957/bjhbs.2022.68187
Received on 17/02/2022. Approved on 23/03/2022.

Introduction

The standard of beauty is something that has been imposed by society, and this pressure has increased more and more over the years. It is mainly a result of social networks, in which many exalt a body and an appearance that, in most cases, are not even real. This can result in high demands and low self-esteem on the part of those involved.[1-3]

This combination of psychological, genetic, social and behavioral factors, both among females and males, results in eating disorders (EDs). Due to an overestimation of thinness and an extreme fear of gaining weight, the result is drastic forms of compensations, such as restrictive diets, excessive exercise, purgative means and even eating compulsions.[1,3-4]

Among the most common EDs, Anorexia Nervosa (AN) has the highest mortality rates when compared to other disorders, with a prevalence ranging from 0.5% to 3.7%, according to data compiled by Pizon & Nogueira.[5]

Characterized by a distortion of the perception of body image and an obsession with control over the amount and type of food that will be ingested, as well as, in many cases, meals that are not even eaten, AN can easily lead individuals to severe malnutrition, hormonal dysregulation, loss of lean body mass, anemia and the growth of fine protective hairs throughout the body, called lanugo. According to data from the Ambulatory of Bulimia and Eating Disorders (AMBULIM), between 0.5% and 4% of women are likely to have anorexia nervosa at some point in their lives.[1]

Another type of eating disorder is Bulimia Nervosa (BN), which is characterized by episodes of binge eating, followed by remorse, and efforts to get rid of ingested calories by inducing vomiting, using laxatives, engaging in extreme physical exercise and following highly restrictive diets. Like AN, BN can also be associated with mortality, with prevalence rates ranging from 1.1% to 4.2%, according to Pizon & Nogueira.[5] Among its most common consequences are the appearance of sensitivity in the teeth, inflammation in

the throat, esophagus and gastrointestinal problems, mainly caused by the stimulation of vomiting.[1,6-7]

In addition, eating disorders can also be classified as unspecified eating disorders, characterized by cases of chronic EDs, which can easily vary between the subtypes mentioned above. They are characterized by numerous functional disorders in women's bodies, such as weight gain or loss, feelings of inadequacy, sexual dysfunction, menstrual dysregulation and/or nullification, low bone mineral density, and even infertility.[8-10]

Moreover, when pregnancy eventually occurs, a low body mass index (BMI) can trigger obstetric complications in both the mother and the baby, because women who have some type of eating disorder must gain weight during pregnancy, which is a big challenge. Data show that pregnant women with EDs have increased intrapartum and postpartum risks, since these conditions favor bleeding, congenital malformation, intrauterine growth restriction (IUGR), miscarriage, premature birth, small newborn gestational age (SGA) and microcephaly, increased likelihood of infections, hypoglycemia, hypothermia, adverse neurological effects and even the death of both mother and child.[1,11-15]

According to studies, pregnant women with AN had a 60% increased risk of preterm birth when compared with pregnant women who had never been exposed to the disorder. Pregnant women with BN faced a greater probability of induced abortion, and pregnant women with eating disorders not otherwise specified (EDNOS) had a 70% increased risk of preterm birth.[6,3,10]

Research on the future consequences for children of mothers who had some contact with an eating disorder showed that the social and psychological factors affecting these children included difficulties in emotional functioning, such that these mothers perceived that their children to have a difficult temperament when compared to the offspring of healthy women. According to these studies, the EDs of these women caused impairment of the development of children's speech, cognitive and motor capacity, as well as impacts even on the eating behaviors of the children.[16-21]

Based on the studies examined, we highlight the importance of recognizing eating disorders before a possible pregnancy, in order to avoid the resulting complications from the beginning of pregnancy through to the development of these children.

The objective of this study is to analyze the impacts of Eating Disorders (EDs) on women in the gestational period.

Objectives

To analyze the impacts generated, both on mothers and their children, by Eating Disorders (EDs) on women during the gestational period.

Methodology

This study is a narrative/critical review of the literature evaluating bibliographies about the consequences for the mother and the fetus, in the case of women with past or active eating disorders. The articles for the research were duly selected on the platforms National Library of Medicine (PubMed) and the Latin American and Caribbean Center for Information on Health Sciences (BIREME), published between 2004 and 2020, using the following combinations of keywords to generate results: Eating Disorder AND Pregnancy; Anorexia Nervosa; Nervous bulimia; Types of Eating Disorder.

The articles selected (Table 1) were those that presented data from a resulting problem, in which comparisons of these impacts were highlighted between women who had eating disorders and those who never had any type of EDs.

Results

As a result, we obtained 618 articles on the BIREME platform and 1,554 on the PubMed platform, which, after filtering by year of publication and text format, resulted in 574 articles. The authors read titles and abstracts in order to exclude articles that did not match the objective of this study, resulting in the selection of a total of 30 articles.

We observed that the study by Lai and colleagues.[22] in the prenatal period (T1), showed that the majority (58%) of the women studied were primiparous. Participants were pregnant from 6 weeks to 40 weeks: 10% in the first trimester, 18% in the second trimester, and 72% in the third trimester. In terms of their history of pregnancy, 20% had a history of miscarriage, 18% had a miscarriage, 1% had a stillbirth, while 62% reported none of the aforementioned experiences. For the babies' conditions at birth, 6% were premature and 2% were born with low birth weight. Approximately 81% of the participants had their births assisted by both midwives and relatives.

The study by Sollid and colleagues[15] analyzed 302 women with a total of 504 children who were hospitalized with disorders before pregnancy and later followed up. The control group consisted of 900 women who had

Table 1. Authors, year of publication, study design and objectives found in the articles used as a review for the study

Reference	Place	Study Design	Objetives
Lai *et al.*,[22]	Hong Kong	Population-based study	Exploring the prevalence and social factors of eating disorders among Chinese new mothers in Hong Kong.
Sollid *et al.*,[15]	Denmark	Population-based study	To determine the association of an eating disorder that was diagnosed before pregnancy and preterm delivery and/or delivery of a low birth weight or small-for-gestational-age baby.
Aaron *et al.*,[23]	Missouri, USA	Missouri maternity cohort study (years 1989-1997)	Determine whether there is a relationship between pre-pregnancy and BMI with placental abruption.
Linna *et al.*,[14]	Helsinki, Finland	Population-based study	To evaluate how eating disorders are related to reproductive health outcomes.
Micali *et al.*,[24]	Denmark	Population-based longitudinal cohort study	Investigate whether eating disorders are associated with smaller birth size, symmetrical growth restriction, and preterm birth.
Watson *et al.*,[25]	Norway	Study MoBa, by the Norwegian Institute for Public Health	Determining whether maternal nutrition increases risk after analyzing the contribution of family transmission of perinatal diseases and events.
Barona *et al.*,[20]	United Kingdom	Longitudinal prospective study	To investigate neurobehavioral regulation and cognitive development in newborns and babies of mothers with EDs.
Eik-Nes *et al.*,[26]	Norway	Population-based study	Identify associations between lifetime EDs and obstetric outcomes.
Chan *et al.*,[27]	China	Prospective longitudinal study with a quantitative approach	To determine the prevalence and levels of eating disorders in the perinatal period, and to identify risk factors and adverse outcomes of eating disorders during pregnancy.
Mantel *et al.*,3	**Sweden**	**Population-based cohort study**	**To investigate the relative risk of adverse pregnancy and neonatal outcomes for women with eating disorders.**

Source: The authors (2022).

never had any type of eating disorder and who had 1552 children altogether. The study found that children of pregnant women with disorders were twice as likely to be born underweight compared to the control group. In addition, pregnant women with disorders also ran a higher risk of having premature births, and the prob-

ability of their babies being born small for gestational age increased from 70% to 80%.

The study by Aaron and colleagues[23] analyzed 439,235 women, of which 58,222 (13.3%) were underweight and 381,013 (86.7%) had normal weight. This work showed that underweight mothers had a 40% higher probability of placental abruption. The perinatal risks analyzed included low birth weight, morbidities related to preterm birth, neurological deficits and fetal death. However, there was a trend towards a decreased risk of placental abruption in those women who gained weight during pregnancy.

In Finland, Linna and colleagues[14] evaluated possible relations between eating disorders and reproductive health. They therefore studied a population base of women with Anorexia Nervosa (N=5,502), Atypical Anorexia Nervosa (N=5,365), Bulimia Nervosa (N=5,786), Atypical Bulimia Nervosa (N=5,445) and Binge Eating Disorder (N=5,149). In the prenatal period, the researchers noted an increased number of spontaneous and induced abortions in cases of Anorexia Nervosa (AN) and Bulimia Nervosa (BN). In relation to women with Binge Eating Disorder (BED), which was often accompanied by obesity, the study observed an association with an increased risk of miscarriage and an increased risk of stillbirth or neonatal death, such that miscarriages occurred in 46.7% of pregnancies. They found a similar trend in women with atypical BN, in which miscarriages were associated with 21.4% of pregnancies.

In cases of active Anorexia Nervosa, the study conducted by Micali and colleagues[24] found an association with lower weight, length, head and abdominal circumference, and ponderal index (PI) at birth. These babies were more likely to be small for gestational age and to be born prematurely. The study included women with Anorexia Nervosa (n=1,609), Bulimia Nervosa (n=1,693) and both (Anorexia + Bulimia nervosa, n=634), who were compared with women not exposed to Eating Disorders (n=76,724).

In Norway, a study by Watson and colleagues,[25] examined 70,881 pregnant women grouped in grandmother-mother-child triads for analysis of exposure to eating disorders during pregnancy and 52,348 for analysis of lifetime exposure to maternal eating disorders. Diabetes (gestational), preeclampsia, umbilical cord knot and bleeding during pregnancy were included in the study, and neonatal outcomes included (standardized) birth weight, birth length for age and sex <10th percentile, birth length for age and sex >90th percentile, preterm birth (<37 weeks), postmature birth (≥42 weeks), small for gestational age (SGA), and large for gestational age (LGA) for pregnant women with diabetes.

Barona and colleagues,[20] in a prospective longitudinal study, included women with active Eating Disorders (EDs), n=15; past EDs, n=20; and healthy women, n=28. The results showed that newborns of mothers with active EDs were more likely to achieve lower scores on autonomic stability. Exploratory analysis showed that babies of mothers with a diagnosis of Lifetime AN and BN were more likely to have lower overall cognitive development, poorer receptive language, general language, and gross motor development compared to babies of healthy mothers.

The study conducted by de Eik-nes and colleagues,[26] they[26] included women admitted between January 2003 and March 2015 and with at least one birth registered in the Norwegian Medical Birth Registry (MBRN) in the period from 1967 to 2015. In the reference cohort, 21,510 women and their 49,735 births were identified. Women with unspecified Eating Disorders and below-threshold EDs were more likely to have children with an Apgar score below 5 compared to women in the reference group. After adjusting for parity, maternity, marital status and year of delivery, women with a history of AN were more likely to have children who were SGA, and women with a history of BN were more likely to have a cesarean section. In the reference cohort, 508 (1.2%) perinatal deaths were recorded, 0.8% were stillborn or died within 7 days after birth (all of which children of women with a lifetime history of AN).

Another study carried out in China by Chan and colleagues[27] aimed to determine the prevalence and levels of eating disorders in the perinatal period, and to identify risk factors and adverse outcomes of eating disorders during pregnancy. A consecutive sample of 1,470 Chinese pregnant women from hospitals in Hong Kong was assessed using standardized instruments at five points in time, from the first trimester to 6 months postpartum. Compared with the normal birth weight groups, babies who were large for gestational age (LGA) were more likely to have mothers with higher levels of eating disorders in the second trimester ($p<0.05$) and third trimester ($p<0.05$). Small-for-gestational-age (SGA) babies were more likely to have mothers with higher levels of EDs at T2 ($p<0.01$), in addition, the study found that prenatal anxiety and depressive symptoms were independently associated with BED and BN throughout the three trimesters of pregnancy. These factors can have a long-term impact on child growth and development.

Another study, conducted by Mantel et al.[3] in Sweden, included 2,769 women with AN; 1,378 with BN; and 3,395 with BED. They were compared with 1,225,321 women without EDs. This study found that the risk of hyperemesis was approximately doubled for women with EDs. Maternal AN was associated with a 60% increased risk of bleeding, and women with BN or EDNOS received a diagnosis of anemia more often than healthy women, but this risk was doubled for women with active AN. Preeclampsia did not differ between exposed women with any of the ED subtypes and unexposed women. Women with all ED subtypes were at increased risk of preterm delivery, SGA and neonatal delivery with microcephaly, and those with AN and EDNOS had a reduced risk of instrument-assisted vaginal deliveries.

Discussion

According to the Hospital Santa Mônica,[1] using data from the Eating Disorders Treatment Program (Ambulim) of the Brazilian National Health Service, 0.5 to 4% of women will have EDs throughout their lives. However, when these women become pregnant, problems related to mother-child health can arise, increasing the chances of risky pregnancies.

The study by Lai and colleagues[22] sought to examine the prevalence of eating disorders among Chinese women during pregnancy (T1) and 6 months postpartum (T2). Participants completed questionnaire reports about themselves, attachment and concerns about the fetus. Finally, the overall prevalence of EDs during the study was 8.4% during pregnancy (T1) and 19.08% in the postnatal period (T2). Only a small percentage (3%) of mothers with EDs at T1 attained complete relief from their symptoms after delivery. In addition, from 25 to 50% of women reported a deterioration or resurgence of EDs after birth.

Sollid and colleagues[15] describe previous studies and case reports, which indicated that women with EDs are at greater risk of bearing a low birth weight child. Possible contributors to the causes of impaired fetal growth are weight control behaviors (such as restricted dieting, vomiting, and excessive exercise leading to malnutrition) and compromised flow of essential nutrients to the fetus in the maternal blood. Subnutrition can also cause compromised immune systems, which can lead to an increased risk of maternal infectious diseases, also contributing to preterm birth.

The risk of placental abruption due to the low BMI of these women was also confirmed in the study by Aaron and colleagues.[23] Weight gain during the gestational period contributed to a reduction in the chances of displacement. However, risk factors normally associated with obesity (e.g. hypertension, preeclampsia, ruptured membranes, and preterm delivery) were also strongly associated with placental abruption. One of the reported findings is that the nutrition of these women may have a protective effect in relation to placental displacement during pregnancy.

According to the study by Lina and colleagues,[14] induced abortions were more common in women with lifetime BN, while spontaneous abortions were the most common in women with lifetime BED. This study also prominently observed that women with AN had fewer children throughout their lives compared to reference women.

According to the study by Micali and colleagues,[24] the children of mothers who had AN showed the lowest birth weight, being 50-60% more likely to be small for gestational age (SGA). On average, these children were 297g lighter, 1.1cm smaller, and had a smaller head and abdominal circumference in comparison to women in the control sample.

Major complications in childbirth, such as prolonged labor, cesarean section and induced labor, were observed in all eating disorders in the study by Watson and colleagues.[25] The question of whether maternal EDs negatively influence perinatal outcomes or whether this is a result of generational factors that increase risk for both eating disorders and perinatal complications was also addressed. Preeclampsia and gestational diabetes were addressed as negative effects in BN and BED, which are also impairments and are associated with BMI and maternal death as well as a consequent increase in risks during the gestational period . However, this study has several limitations that also need to be taken into account.

No previous study known to Watson and colleagues,[25] with the exception of that of Bulik and colleagues,[28] reported on perinatal risks with lifetime assessments of EDs in the same individuals. Bulik and colleagues[28] compared women with AN and women who had recovered from AN with women from healthy controls and descriptively reported that lower birth weight and risk of cesarean section were similar and more common in the AN groups. Most studies on the associations between eating disorders and perinatal risks have used lifetime assessments.[14,24,29,30]

The initial hypothesis and previous research by Barona and colleagues[20] found that the newborns of women

with active EDs during pregnancy had worse autonomic and motor stability than other newborns, and also found it more difficult to stabilize their breathing and temperatures compared to babies borne by healthy mothers. As these children developed during their childhood, it was noticeable that their language skills were less developed and motor stability also continued to be impaired, but no previous study has actually investigated the neurological responses of these children.

The study by Eik-nes and colleagues,[26] showed that women with anorexia nervosa were more likely to have SGA children, but, this finding was not closely associated with AN during their research. The reason is that, although the population studied may overlap to some degree in the study, women with eating disorders may be less likely to participate in population studies overall. For example, only 28 women (8.5%) with EDs from the local patient registry agreed to participate in the MoBa. The inconsistency in the conclusions among the studies may be due to methodological differences, such as low statistics or a different classification of EDs. Since there was a lack of information, such as the duration of the disease of these women, it was impossible to assess the differences between the women, mothers in remission, compared with those with active EDs, which would result in different interpretations.

The aim of the study by Chan and colleagues[27] was to examine the course, risk factors and adverse outcomes of EDs at different stages of pregnancy, and their results showed an alleviation of eating disorders from pre-pregnancy to pregnancy. However, a worsening of these EDs was reported until the postpartum period, even though these variations may not be indicative of clinically significant changes. As expected, the results show that EDs vary across the trimesters, and that these are independently associated with depressive symptoms and prenatal anxiety, which were linked to BE and BN. In addition, the risk factors for babies born with abnormal weight and small or large for gestational age could, in the long term, lead to impaired child development.

Mantel and colleagues[3] reported that eating disorders were associated with an increased relative risk of multiple pregnancies and neonatal complications (which varied between subtypes and differed in strength depending on active or prior disease) compared with the control group. The pathophysiological mechanisms behind these observations are unknown, but several hypotheses were raised, such as maternal-fetal stress, which is considered a potential mechanism for preterm birth.

The basis of this hypothesis is findings that the stress hormone is increased in women with AN and BN, and that high cortisol levels have been associated with microcephaly among women with AN. An inadequate diet during pregnancy with nutritional deficiency would undoubtedly be associated with fetal growth restrictions, and certain nutritional deficiencies were also associated with an increased risk of preterm birth. This issue is also addressed by Aaron and colleagues[23] and Watson and colleagues.[25] Therefore, although they are not solutions, adequate nutrition and adequate psychological support are believed to be capable of preventing or reducing the impacts generated for these women during the gestational period, thus avoiding greater negative consequences for the mother-child binomial.

Conclusion

According to the studies analyzed, EDs can have negative impacts, both for the mother and for their offspring. These impacts can also be harmful in the long term, in addition to being associated with both prepartum and postpartum risks. When present, they can affect the development of these children, since maternal EDs result in nutritional impairment.

Low BMI was one of the main findings of the studies; it can increase the risks associated with pregnancy, since the nutrients of these mothers are a crucial factor for a healthy gestation. Therefore, the article concluded that medical, nutritional and psychological follow-up is essential for women with EDs, regardless of the type, in order to have a safe pregnancy for themselves and for their babies.

References

1. Hospital Santa Mônica. Transtorno alimentar: conheça os diferentes tipos de distúrbios [Internet]. São Paulo; [citado 2018 Jun 01]. Disponível em: https://hospitalsantamonica.com.br/transtorno-alimentar-conheca-os-diferentes-tipos-de-disturbios/
2. Gonçalves J, Moreira E, Trindade E, et al. Eating disorders in childhood and adolescence. Rev Paul Pediatr. 2013;31(1):96-103. doi: 10.1590/s0103-05822013000100016
3. Mantel Ã, Lindén Hirschberg A, Stephansson O. Association of Maternal Eating Disorders With Pregnancy and Neonatal Outcomes. Jama. Psychiatry. 2020;77(3): 285-293. doi: 10.1001/jamapsychiatry.2019.3664
4. Schaumberg K, Welch E, Breithaupt L, et al. The Science

Behind the Academy for Eating Disorders' Nine Truths About Eating Disorders. Eur. Eat. Disord Rev. 2017;25(6):432-450. doi: 10.1002/erv.2553
5. Pinzon V, Nogueira FC, et al. Epidemiologia, curso e evolução dos transtornos alimentares. Rev. psiquiatr. clín. [Internet]. 2004 [cited 2021 May 18];31(4):158-160. Disponível em: https://doi.org/10.1590/S0101-60832004000400004
6. Hay PJ, Claudino AM. Bulimia Nervosa. BMJ. Clin. Evid. 2010:1009. PMCID: PMC2907970
7. Gravina G, Milano W, Nebbiai G, et al. Medical Complications in Anorexia and Bulimia Nervosa. Endocr. Metab. Immune. Disord. Drug. Targets. 2018;18(5):477-488. doi: 10.2174/1871530318666180531094508
8. Jagielska G, Kacperska I. Outcome, comorbidity and prognosis in anorexia nervosa. Psychiatr. Pol. 2017;51(2):205-218. doi: 10.12740/PP/64580
9. Andersen AE, Ginny RL. Eating Disorders in the Obstetric and Gynecologic Patient Population. Obstet. Gynecol. 2009;114(6):1353-1367. doi: 10.1097/AOG.0b013e3181c070f9
10. Kimmel MC, Ferguson EH, Zerwas S, et al. Obstetric and gynecologic problems associated with eating disorders. Int. J. Eat. Disord. 2016;49(3):75-260. doi: 10.1002/eat.22483
11. Aliyu MH, Alio AP, Lynch O, et al. Maternal pre-gravid body weight and risk for placental abruption among twin pregnancies. J. Matern. Fetal Neonatal Med. 2009;22(9):745-750. doi: 10.3109/14767050902994523
12. Deutsch AB, Lynch O, Alio AP, et al. Increased risk of placental abruption in underweight women. Am. J. Perinatol. 2010;27(3):235-240. doi: 10.1055/s-0029-1239490
13. Arnold C, Johnson H, Mahon C, et al. The effects of eating disorders in pregnancy on mother and baby: a review. Psychiatr. Danub. 2019;31(3):615-618. PMID: 31488801
14. Linna MS, Raevuori A, Haukka J, et al. Reproductive health outcomes in eating disorders. Int. J. Eat. Disord. 2013 Dec;46(8):33-826. doi: 10.1002/eat.22179
15. Sollid CP, Wisborg K, Hjort J, et al. Eating disorder that was diagnosed before pregnancy and pregnancy outcome. Am. J. Obstet. Gynecol. 2004;190(1):206-210. doi: 10.1016/s0002-9378(03)00900-1
16. Charbonneau KD, Seabrook JA. Adverse Birth Outcomes Associated with Types of Eating Disorders: A Review. Can. J. Diet. Pract. Res. 2019;80(3):131-136. doi: 10.3148/cjdpr-2018-044
17. Watson HJ, O'Brien A, Sadeh-Sharvit S. Children of Parents with Eating Disorders. Curr. Psychiatry. Rep. 2018 Sep 17;20(11):101. doi: 10.1007/s11920-018-0970-3
18. Torgersen L, Ystrom E, Siega-Riz AM, et al. Maternal eating disorder and infant diet. A latent class analysis based on the Norwegian Mother and Child Cohort Study (MoBa). Appetite. 2015;84:291-298. doi: 10.1016/j.appet.2014.10.009
19. Cimino S, Cerniglia L, Porreca A, et al. Mothers and Fathers with Binge Eating Disorder and Their 18–36 Months Old Children: A Longitudinal Study on Parent–Infant Interactions and Offspring's Emotional–Behavioral Profiles. Front. Psychol. 2016;7:580. doi: 10.3389/fpsyg.2016.00580
20. Barona M, Taborelli E, Corfield F, et al. Neurobehavioural and cognitive development in infants born to mothers with eating disorders. J. Child. Psychol. Psychiatry. 2017 Aug;58(8):931-938. doi: 10.1111/jcpp.12736
21. Kothari R, Barona M, Treasure J, et al. Social cognition in children at familial high-risk of developing an eating disorder. Front Behav Neurosci. 2015 Aug 7;9:208. doi: 10.3389/fnbeh.2015.00208
22. Lai BP, Tang CS, Tse WK. A longitudinal study investigating disordered eating during the transition to motherhood among Chinese women in Hong Kong. Int J Eat Disord. 2006 May;39(4):303-11. doi: 10.1002/eat.20266
23. Deutsch AB, Lynch O, Alio AP, et al. Increased risk of placental abruption in underweight women. Am J Perinatol. 2010 Mar;27(3):235-40. doi: 10.1055/s-0029-1239490
24. Micali N, Stemann Larsen P, Strandberg-Larsen K, et al. Size at birth and preterm birth in women with lifetime eating disorders: a prospective population-based study. BJOG. Julho de 2016;123(8):1301-10. doi: 10.1111/1471-0528.13825
25. Watson HJ, Zerwas S, Torgersen L, et al. Maternal eating disorders and perinatal outcomes: A three-generation study in the Norwegian Mother and Child Cohort Study. J Abnorm Psychol. 2017 Jul;126(5):552-564. doi: 10.1037/abn0000241
26. Eik-Nes TT, Horn J, Strohmaier S, et al. Impact of eating disorders on obstetric outcomes in a large clinical sample: A comparison with the HUNT study. Int J Eat Disord. Out 2018;51(10):1134-1143. doi: 10.1002/eat.22916
27. Chan CY, Lee AM, Koh YW, et al. Course, risk factors, and adverse outcomes of disordered eating in pregnancy. Int J Eat Disord. 2019 Jun;52(6):652-658. doi: 10.1002/eat.23065
28. Bulik CM, Sullivan PF, Fear JL, et al. Fertility and reproduction in women with anorexia nervosa: a controlled study. J Clin Psychiatry. 1999 Feb;60(2):130-5; quiz 135-7. doi: 10.4088/jcp.v60n0212
29. Eagles JM, Lee AJ, Raja EA, et al. Pregnancy outcomes of women with and without a history of anorexia nervosa. Psychol Med. 2012 Dec;42(12):2651-60. doi: 10.1017/S0033291712000414
30. Koubaa S, Hällström T, Lindholm C, et al. Pregnancy and neonatal outcomes in women with eating disorders. Obstet Gynecol. 2005 Feb;105(2):255. doi: 10.1097/01.AOG.0000148265.90984.c3

BRAZILIAN JOURNAL
BJHBS
OF HEALTH AND BIOMEDICAL SCIENCES

Review article

Communication tools among professionals in intensive care: An integrative review

Cinthia P. Siqueira,[1] Héllian S. da Silva,[1] Larissa B. Cypriano,[1] Lilia N. Figueredo,[1] Luana F. de Almeida,[2*] Ana Lúcia C. Marins[2]

Abstract

Introduction: Communication is important to ensure safety in demands regarding patients, processes and staff in intensive care units (ICUs), a complex area that requires good communication and dynamism in order to achieve positive results for patients. Hence, the identification of tools that may provide improvements in communication among professionals working in the ICU in the scientific literature is essential. Objective: To map in the literature the types of tools for improving communication among professionals in intensive care. Method: Rand integrative vision performed between April and May 2021, with searches in the medline, LILACS and BDENF databases. We used the descriptors: "Patient Safety"; "Intensive Care Units"; "Applications of Medical Informatics", with Boolean operator "AND". The search covered articles published between 2016 and 2021, full texts, in the Portuguese, English and Spanish languages. Duplicates, case reports, annals, editorials, letters to the editor, dissertations and theses were excluded. Results: We identified two categories: tools for changes of shift and tools for transfers of care. Conclusions: Communication tools are effective because they reduce the incidence risk of errors in direct patient care.

Keywords: Patient safety; Health communication; Intensive Care Units; Applications of medical informatics.

1. Pós-Graduação, Enfermagem Intensivista. Universidade do Estado do Rio de Janeiro. Rio de Janeiro, Rio de Janeiro, Brazil.
2. Departamento de Enfermagem Médico-Cirúrgica. Faculdade de Enfermagem. Universidade do Estado do Rio de Janeiro. Rio de Janeiro, Rio de Janeiro, Brazil.

***Correspondence address:**
Rua Ituverava, 314/401
Rio de Janeiro, RJ, Brazil
CEP: 22.750-006.
E-mail: luana.almeida3011@gmail.com
ORCID: https://orcid.org/0000-0001-8433-4160

BJHBS, Rio de Janeiro, 2022;21(1):75-82
10.12957/bjhbs.2022.68188
Received on 25/12/2021. Approved on 29/04/2022.

Introduction

Patient safety has been a subject of permanent interest in different scenarios of the hospital environment, especially in intensive care units (ICUs). The ICU is a highly complex care area, intended for the hospitalization and treatment of patients with serious clinical, medical and/or surgical conditions. The demands of these patients involve great risk to life and therefore require specialized professional attention.[1]

The theme of this study focuses on the goal of patient safety,[2] recommended by the World Health Organization for improving communication between medical professionals. Studies indicate that inadequate communication represents one of the major causes in more than 70% of adverse events (AEs) in patient care, such as medication errors, incorrect identification of patients, and inadequate prescription.[2]

The theme is justified by the great importance that effective communication has on the routine of a complex unit such as an ICU. The standardization of language within the multiprofessional team is an effective instrument for ensuring security in the performance of the routine of demands regarding patients, processes and the team.

Since the ICU is a sector with complex activities and patient profiles, it is an environment with an intense pace of work and requires professionals to pay great attention to the performance of daily tasks, where any misstep can lead to irreversible damage. Therefore, communication must be accurate and understandable to all those involved, and no information should be lost at any time during the care of patients or the changeover of professionals.[3]

In addition, communication problems that occur in a hospital environment, especially in the ICU, can

cause disturbances in the routine activities of the multidisciplinary team, leading to disagreements among the staff and causing them to blame themselves for errors. This scenario generates emotional fatigue among those involved; delays or omission in providing care to the patient, with consequent risks of damage; and increases in hospital expenses and length of stay.[3]

The occurrence of these AEs is caused mainly by failures in the passage of information, long and exhausting working hours, noise pollution in the ICU environment, stress and inadequate hospital management.[4]

With the objective of guaranteeing effectiveness, improvements and safety of health care, some information standardization strategies have been developed to ensure clear, objective, concise, efficient, timely and comprehensive communication among teams. Nevertheless, these strategies must be implanted concomitantly with changes in both the behavioral and cultural aspects of institutions in order to produce norms that promote patient safety.[5]

Since ineffective communication between teams that provide care can generate failures in the continuous therapeutic plan and thus result in direct damage to critically ill patients, actions must be implemented to improve processes in order to minimize the risks inherent to the communication gaps among professionals. Thus, the establishment and implementation of care protocols are of fundamental importance in the prevention of errors and incidents in the daily routine of professional activities in health care.[6]

Highlighting this topic is important because effective communication leads to a reduction in human errors, improves the quality of care provided to the patient, strengthens ties within the team and reinforces the bond of trust in mutual work, in addition to providing safety in work processes. Hence, studying the recommended tools for improving communication among professionals can contribute to better quality of care, since it enables improvements in knowledge and techniques in the healthcare field, optimizes the daily work of teams, standardizes language among professionals and care and assistance units, with the objective of reducing unnecessary harm to the patient.

Effective communication occurs in a two-way model. The read-back technique ("read back") is used to validate information transmitted during changes in shifts or within work shifts: to confirm that the information has been understood correctly, so that communication can take place more securely. This technique is also used in aviation and other industries to prevent messaging errors and has become part of the international patient safety goals of the Joint Commission International manual.[7]

Given this context, the following guiding question emerged: "What are the tools used to improve communication among professionals in intensive care units that can be found in the current scientific literature?" To answer this question, this study aimed to map the types of tools to improve communication between professionals in intensive care units that can be found in the literature.

Method

This work is an integrative literature review, based on data collected between April and May 2021. This type of study uses a method to address a specific topic, through definitions of concepts, a review of theories and evidence, and analysis of problems. The integrative review was carried out in six stages, conducted in order to identify, analyze and integrate the results of independent studies on the same subject. These stages are: elaboration of the guiding question; search or sampling of the literature; data collection; critical analysis of the included studies; discussion of results; and presentation of the integrative review.[8]

The research question was defined based on the selection of the objective and identification of the desired study. In the case of this study, P/I/C were used, that is, P (patient); I (intervention); C (context). This strategy favors the direction in which the research should be based, contributing with the most important evidence without being too general and avoiding searches outside the previously determined axis.[9]

Thus, the question was based on the health team (P), communication tools (I), and intensive care (C). Hence, the question that guided the research was: "What are the tools used to improve communication among professionals in intensive care units that can be found in the current scientific literature?"

The survey of articles took place between April and May 2021, through a search of the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS) and Database in Nursing (BDENF).

The descriptors were chosen through a search in controlled vocabularies of the Descriptors in Health Science (DeHS) and the Medical Subject Heading (MeSH).

After consultation, the following terms were chosen: "Communication in Health"; "Patient safety"; "Intensive Care Units"; "Applications of Medical Informatics"; "Health Communication"; "Patient Safety"; "Intensive Care Units"; and "Medical Informatics Applications". The terms were associated by use of the Boolean operator "AND".

Articles published between 2016 and 2021 were included with full texts, in Portuguese, English and Spanish. The following types of works were excluded: duplicate articles, case reports, proceedings, editorials, letters from the editor, dissertations and theses.

The search in the databases generated an initial sample of 232 articles, of which 162 from Medline, 39 from LILACS and 31 from BDENF. A prior screening was conducted, based on the title, abstract and descriptors, to assess whether these articles fell within the inclusion and exclusion criteria of the study. Thus, 33 articles were excluded due to duplication, and another 177 articles for not meeting the theme of the study, leaving 22 manuscripts for reading in full. Subsequently, the full reading was carried out and 17 studies were excluded for not answering the guiding question. In the end, the study selected five articles, as shown in the flowchart (Figure 1).

Five articles were selected for analysis, organized by journal, authors, year of publication, title, type of study and communication tools used among the health team in intensive care.

Results

Of the five articles analyzed, three (60%) were published in 2018, one in 2017 (20%) and one (20%) in 2019. With regard to language, all five studies were published in English. With regard to the type of study, there were two (40%) literature reviews, one (20%) exploratory qualitative, one (20%) action research with content validation and one (20%) quantitative descriptive (Table 1). After reading the articles, two categories were identified: instruments for shift changes and instruments for transfer of care.

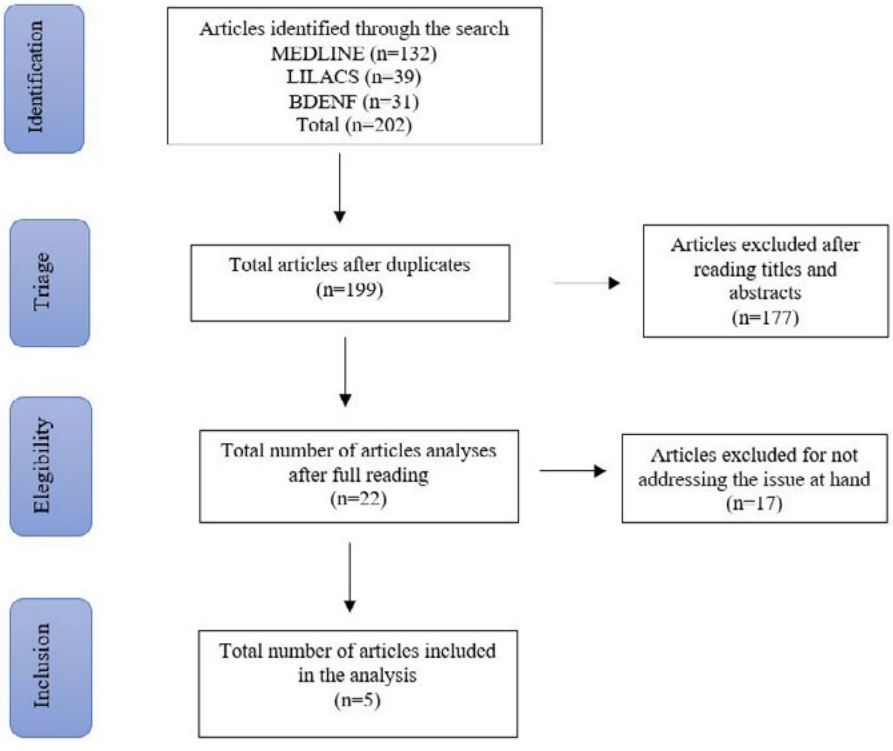

Figure 1. Flowchart of the process of search, selection and analysis of review articles

Source: Adapted from PRISMA (2015).

Table 1. Distribution of articles, according to journal, authors, year of publication, title, type of study and communication tools used among health teams in intensive care. Rio de Janeiro, RJ, 2021

Periodical/ Authors/ Year	Title	Type of study	Communication tools used among the health team in intensive care
Texto & Contexto Enfermagem/ Santos; Barros; Broca e Silva/ (2019)	Communication noise during the nursing team handover in the intensive care unit	Qualitative and exploratory	- Handover instrument
Medicina intensiva, Elsevier/ Rodríguez *et al.*/ (2018)	Handover in Intensive Care	Literature review	- Use of mnemonic tools
Escola Anna Nery/ Santos; Campos; Silva/ (2018)	Handoff communication in intensive care: links with patient safety	Integrative review	- Handoff instrument
Revista Brasileira de Enfermagem/ Corpolato *et al.*/ (2018)	Proposal for the standardization of the shift in an adult general intensive care unit	Action research, descriptive, content validation.	- Handover instrument in Checklist format - Shift change always at the bedside
Cuidarte Enfermagem/ Beccaria; Meneguesso; Barbosa; Pereira/ (2017)	Interferences in the nursing duty shift change in an intensive therapy unit	Descriptive, quantitative	- Handover instrument

Source: The authors (2022).

Discussion

Instruments for shift changes

The communication process is understood as the understanding and sharing of messages sent and received by verbal or non-verbal means, considering that the content and the way they are transmitted can influence the behavior of the people involved.[10]

Thus, we can affirm that communication among the professionals of the multidisciplinary team is essential for the safe care of patients. The risks of communication failures between these professionals can lead to errors, adverse events and a deficit in the quality of care.[11] The studies analyzed observed that communication failures among the professionals responsible for care is a weak point.[12-15]

The communication process in ICUs is complex, since this environment has its particularities, where the care of the critical patient, who is at imminent risk of death, requires close attention and continuous observation by the team, demanding immediate responses for both decision-making and adequate intervention. In this context, communication within teams needs to be effective and clear, in order to eliminate possible AEs caused by ineffective communication.[16]

Communication noise, side conversations, lack of focus on the part of the team and forgetfulness when passing on some information/intervention that was or should be provided to the patient generates vulnerability and negligent care, which can cause direct or indirect harm to the patient.[12-15]

The fast pace at which the teams conduct their tasks is considered the main reason for the difficulties in communication among professionals, leading to failures of communication within the ICU environment becoming predictable.[16]

An important element is the organization of the team during the process of change of shift. The implementation and standardization of an easy and objective instrument that presents the main items of information about the patient is essential to guide this process and remedy the flaws described above.[12-15]

To achieve this objective, professionals should be trained and guided to not abandon the narrative approach and to go through each case in detail, by presenting their assessment and the interventions that were necessary during the shift, thus carrying out a complete, clear and effective transfer of care.[12-15]

Noise in communication is directly related to incomplete or absent information about the patient, with communication focusing on intercurrences and clinical evolution during the previous 24 hours and with little appreciation of data on assessment, care plan and the patient's clinical status. Other noise in communication relates to late arrivals, low voices, side conversations and the use of cell phones. These events generate unnecessary, wrong or ineffective procedures.[12] Knowing that communication is a key instrument to ensure quality and safety in patient care, the team must receive training in order to build a cohesive and structured relationship with an adequate set of information necessary to minimize risks and improve health safety and quality, without causing harm to the patients under care.[6]

The existence of a structured process for the modalities of information transfer, emphasizing those that are considered most relevant, with adequate identification by the professional by means of mnemonic tools is useful, but must be accompanied by a narrative approach, which adds enriching nuances.[14]

In another study, the tools developed in order to optimize shift changes showed that the standardization of nursing activities and procedures contributes to the promotion of safe patient care and improvements in the quality in health services. A specific instrument is helpful in the transmission of information during shift changes in order to ensure patient safety through the standardization of this activity.[12,15]

It is important to develop a Standard Operating Procedure and an instrument for recording information, which must be validated in terms of appearance, clarity, suitability and content. If used correctly, these tools can improve shift changes in ICUs, minimizing the risk of failures in the communication process.[13]

An instrument for transfer of care helps to pass on information in full, thus reducing instances where important patient data is forgotten, while enhancing the continuity of necessary interventions, as well as improving communication within the multiprofessional team.[17]

In response to the increase in AE incidents, the Joint Commission International (JCI) points to tools for the transfer of care as means to resolve failures arising from deficient communication. Thus, communication strategies in the health organization facilitate the process of transfer of care .[18]

Other tools for effective communication, such as shift handover instruments that are standardized and in a checklist format, showed great relevance in the opinion of nurses regarding the optimization of their daily practice, when combined with the transmission of bedside information.[18]

A variety of mnemonic instruments used in practice is mentioned in the literature, of which the most recommended in hospital environments is the ISBAR (Introduction, Situation, Background, Assessment, Recommendation).[19] Mnemonic tools were described in the 1990s and include the goals, information, strategies and roles of members in a given activity.[20]

The SBAR (Situation, Background, Assessment, Recommendation) was structured in the United States of America, initially used in the US Navy and later improved for the healthcare area. It is a structured method of communication, designed to streamline communication within professional teams, by creating a standardized information structure that allows nurses to be more direct with important information and optimizes the transmission time of this information.[21] This methodology has shown evident gains in terms of the satisfaction of the teams that use the instrument. It speeds up the transmission of information, is clear and objective, and helps to define treatment goals in conjunction with the medical team, thus minimizing the incidence of errors in emerging situations.[21]

It is also the precursor of other methods, such as ISBAR and ISOBAR (I-Identification; S-Situation; O-Observation B-Background; A-Assessment and R-Recommendations), which share the same basis, differing only in that the part related to physical observation of the patient is present in the ISOBAR methodology and absent in ISBAR. These methods are used in other parts of the world, such as Australia.[21]

Ineffective communication is one of the main factors leading to the occurrence of AEs, as well as in care transitions, which is a critical situation where communication failures happen.[6]

Thus, studies consider that the effective performance of shift changes brings great benefits to health institutions, patients and all professionals, by guaranteeing the continuity of care. The quality of the information will depend on the person verbalizing it,

the time dedicated to this task, the transfer pattern used and the team's commitment to recording the necessary information.[22]

Instruments for the transfer of care

The use of an instrument for the transfer of care of a patient involves the transfer of responsibility to another team that will receive the patient, as well as the transfer of care itself.[23]

Handoff was configured as a gold protocol for the standardization of communication in patient transfers, bearing in mind the importance of communication among medical, nursing and pharmaceutical teams in the care of hospitalized patients, regarding processes involving the filling of drug prescriptions, test results, procedures, diet therapy, adverse drug reactions, comorbidities and any information relevant to the required care.[23]

The handover is an instrument used to transfer a case from one professional to another. Normally, this exchange of information about the patient occurs during shift changes, usually in exchanges between 12 or 24-hour service teams, thus characterizing a very important tool to ensure the continuity of quality care that is free from adverse events. It is a widely efficient, effective and simple protocol that has shown expressive results, guaranteeing safe care based on information about the patient's status, previous disease history, allergies, procedures performed, pending issues, among others.[24]

It is noteworthy that in intensive care, for example, there is no defined consensus on what information is essential for a flawless transfer of care, and the mention of information that is assumed to be vitally important is often forgotten. A study carried out in Rio de Janeiro showed that, despite the use of this instrument for transferring patients, professionals failed to describe significant information when transferring care between shifts. This finding corroborates the need for continuous training in communication skills to improve team engagement, as well as for follow-up action to standardize and update the instrument, as required.[25]

In another study, the data prioritized in the handover of patients were information regarding medication, water balance, patient history, invasive devices, skin lesion or integrity, therapeutic proposal, pending issues, allergy and nursing care. The authors state that subjective data, such as complaints, pain reports, family-patient interaction, coping with the disease, and fears related to diagnosis and treatment should also be taken into account in the transfer of care, in order to relate signs and symptoms and to optimize nursing care and planning.[26]

Effective communication is essential to the extent that failures in the transfer among units with no verbal passage, patient identification or omission of these, begin to become routine, since these are considered to be important enabling circumstances for potential damage. In addition, failures in relation to the assistance itself are highlighted, for example, the transmission of vital signs, which if erroneously passed, become an issue for the use of information.[23] Such information, about patients or their therapy, when cited wrongly, turns into communication noise, causing failures and damage to the effectiveness of the care provided. This disorganization can lead the client to be harmed, the quality of care provided to decrease, duplication or lack of interventions, whether therapeutic or not.[27]

Factors listed as interference in the transfer of care were described in a recent study. These included: ringing alarms that are not responded to, parallel conversations, low tone of voice, lack of clarity and objectivity, interruptions, assistance to patients during communication (especially in cases of emergency) and the ringing of cell phones. Since these are the most important enemies of communication that is free from noise and interference, those involved in this process should pay close attention in order to avoid losses generated by distractions in the information necessary for a flawless transfer.[27]

Healthcare professionals, especially nurses and nursing technicians, should recognize that standardized transfer of care improves and facilitates communication and ensures that no information is lost along the way.[28]

Knowing that communication is a key instrument to ensure quality and safety in patient care, the team must receive training in order to build a cohesive and structured relationship, with an adequate set of information necessary to minimize risks and improve health safety and quality, without generating losses and damages to the patients under care.[6]

In addition, it is important to note that the transfer of care is described as the continuity of the patient's treatment from one professional to another and includes the transfer of responsibility, and both complete and updated information about clinical status, therapeutic plan or necessary interventions.[1]

Conclusion

In view of the above, communication tools for professionals in the ICU, such as instruments for shift changes and transfer among units are effective, since they reduce the incidence of risks, damages and errors in direct patient care.

Studies on this theme are scarce, despite its great importance. Most of the articles addressed instruments for handover and transfer of care related to the patient, without showing other tools that could be used by health professionals in other situations, such as in relation to processes and the team.

Studies should be carried out to evaluate the use of tools or instruments at times other than shift change or transfer of care, and also to assess their effectiveness in common situations of communication between professionals in the ICU, such as sector organization, human resources, processes involving the prescription of drugs and other procedures.

References

1. Souza CS, Tomaschewski-Barlem JG, Rocha LP, et al. Cultura de segurança em unidades de terapia intensiva: perspectiva dos profissionais de saúde. Revista Gaúcha de Enfermagem. 2019;40(1). doi: https://doi.org/10.1590/1983-1447.2019.20180294
2. IBSP – Instituto Brasileiro para Segurança do paciente. Comunicação ineficaz está entre as causas-raízes de mais de 70% dos erros na atenção à saúde. 2017. Disponível em: https://segurancadopaciente.com.br/seguranca-e-gestao/comunicacao-ineficaz-esta-entre-as-causas-raizes-de-mais-de-70-dos-erros-na-atencao-a-saude/. Acesso: 21. Abri. 2021
3. Silva F da MV, Oliveira Júnior, JC de, Alves A dos S, et al. Estratégias utilizadas por enfermeiros para minimizar a assimetria na comunicação em Unidade de Terapia Intensiva. Rev. Aten. Saúde. 2018;16(57):111-117. doi: https://doi.org/10.13037/ras.vol16n57.5258
4. Oliveira JGAD, Almeida LF de, Hirabael LF de A, et al. Interrupções nas passagens de plantão de enfermagem na terapia intensiva: implicações na segurança do paciente. Rev enferm UERJ. 2018;26:e33877. doi: http://dx.doi.org/10.12957/reuerj.2018.33877
5. Mello JF, Barbosa SFF. Cultura de segurança do paciente em unidade de terapia intensiva: perspectiva da equipe de enfermagem. Revista Eletrônica de Enfermagem. 2017;19(7). doi: https://doi.org/10.5216/ree.v19.38760
6. Pena MM, Melleiro MM. Eventos adversos decorrentes de falhas de comunicação: reflexões sobre um modelo para transição do cuidado. Revista de Enfermagem da UFSM. 2018;8(3):616-625. doi: https://doi.org/10.5902/2179769225432
7. Sousa P. Segurança do paciente: criando organizações de saúde seguras. Revista e ampliada. Rio de Janeiro, 2.ed RJ: CDEAD, ENSP, Fiocruz, 2019. doi: https://doi.org/10.7476/9788575416426
8. Souza MT da, Silva MD da, Carvalho R de. Integrative review: what is it? How to do it?. Einstein (São Paulo). 2010;8(1):102-106. doi: https://doi.org/10.1590/S1679-45082010RW1134
9. Santos CM da C, Pimenta CA de M, Nobre MRC. A Estratégia pico para a construção da pergunta de pesquisa e busca de evidências. Rev Latino-am Enfermagem. 2007;15(3). doi: https://doi.org/10.1590/S0104-11692007000300023
10. Barbosa I de A, Silva KC da C da, Silva VA da, et al. O processo de comunicação na Telenfermagem: revisão integrativa. Rev Bras Enferm, 2016;69(4):765-72. doi: https://doi.org/10.1590/0034-7167.2016690421i
11. Nogueira JW da S, Rodrigues MCS. Comunicação efetiva no trabalho em equipe em saúde: desafio para a segurança do paciente. Cogitare Enfermagem. 2015;20(3):636-640. doi: http://dx.doi.org/10.5380/ce.v20i3.40016
12. Santos GRS, Barros F de M, Broca PV, et al. Ruídos na comunicação durante o handover da equipe de enfermagem da unidade de terapia intensiva. Texto Contexto Enferm. 2019;28:e20180014. doi: https://doi.org/10.1590/1980-265x-tce-2018-0014
13. Corpolato RC, Mantovani M de F, Willig MH, et al. Padronização da passagem de plantão em unidade de terapia intensiva geral adulto. Ver Bras Enferm. 2019;72(Suppl1):95-102. doi: http://dx.doi.org/10.1590/0034-7167-2017-0745
14. Rodríguez SG, Fernández CM, Vidal GF, et al. Handover in Intensive Care. Medicina Intensiva Elsevier. 2018;42:168-179. doi: http://dx.doi.org/10.1016/j.medin.2017.12.002
15. Beccaria LM, Menequesso B, Barbosa TP, et al. Interferências na passagem de plantão de enfermagem em unidade de terapia intensiva. Revista Cuidarte Enfermagem. 2017;11(1):86-92.
16. Quitério LM, Santos E de V, Gallotti RDM, et al. Eventos adversos por falhas de comunicação em unidades de terapia intensiva. Espacios, 2016;37(30).
17. Guest M. Patient transfer from the intensive care unit to a general ward. Nursing Standard. 2017;32(10):45-51. doi: http://dx.doi.org/10.7748/ns.2017.e10670
18. Alert SE. Inadequate hand-off communication. Sentinel Event Alert. 2017 Sep 12;(58):1-6. PMID: 28914519
19. Stewart KR. SBAR Communication, And Patient Safety: An Integrated Literature Review. UTC scholar. 2016;1:1-45.
20. Silva MF. Construção e Validação Do Instrumento Para Passagem De Caso Em Unidades Pediátrica. 189 f. Tese (Doutorado) - Curso de Enfermagem, Universidade Federal de Santa Catarina, Florianópolis, 2017.
21. Saias HAV. Transição Segura de Cuidados do Doente Crítico. 238 f. Dissertação (Mestrado) - Curso de Enfermagem, Instituto Politécnico de Setúbal, 2019.
22. Almeida FAV, Costa MLA de S. Passagem de Plantão na Equipe de Enfermagem: Um Estudo Bibliográfico. Arq Med Hosp Fac Cienc Med Santa Casa. 2017;62(2):85-91.
23. Santos, GR da S dos, Campos JF, Silva RC da. Comunicação No Handoff Na Terapia Intensiva: Nexos Com A Segurança Do Paciente. Esc. Anna Nery Rev. Enferm. 2018;22(2):e20170268.

doi: http://dx.doi.org/10.1590/2177-9465-EAN-2017-0268
24. Santos GRDSD, Barros FDM, Silva RCD. Comunicação no handover na terapia intensiva: sentidos e práticas da equipe de enfermagem. Revista Gaúcha de Enfermagem. 2020;41. doi: https://doi.org/10.1590/1983-1447.2020.20180436
25. Araujo R de M, Almeida LF de, Paula, VG de. Aplicabilidade do método ISBAR em uma unidade de terapia intensiva adulto. Cogitare enferm. 2020;25:e70858;1-12. doi: http://dx.doi.org/10.5380/ce.v25i0.70858
26. Oliveira JGAD, Almeida LF, Andrade KBS de, et al. Transferências de cuidados entre turnos de enfermagem em uma unidade intensiva. Saúde Coletiva. 2019;9(51):1-4. doi: https://doi.org/10.36489/saudecoletiva.2019v9i51p1973-1976
27. Oliveira JGAD de, Almeida, LF de, Hirabae, LF de A et al. Interrupções nas passagens de plantão de enfermagem na terapia intensiva: implicações na segurança do paciente. Ver enferm UERJ. 2018;26:e33877:1-4. doi: http://dx.doi.org/10.12957/reuerj.2018.33877
28. Alves M, Melo CL. Transferência de cuidado na perspectiva de profissionais de enfermagem de um pronto-socorro. REME – Rev Min Enferm. 2019;23:e-1194. doi: http://www.dx.doi.org/10.5935/1415-2762.20190042

Paper submission – Brazilian Journal of Health and Biomedical Sciences

Brazilian Journal of Health and Biomedical Sciences (BJHBS), formely titled **Revista HUPE**, publishes new articles about several themes all related to health and biomedical sciences, provided they're not in simultaneous analysis for publication in any other journal. It rejects promptly any plagiarism and selfplagiarism practices. It features dedicated sections to original research, literature reviews, case studies, and letters to the editor. Papers must be submitted in one of three languages: Portuguese, Spanish, and English. The submission process comprises the following steps:

Peer review: papers are reviewed by at lest two specialists. Accepted papers will be edited according to the publishing standards of **BJHBS**, to improve readability and minimize redundancy, without loss of original meaning. The final edited version will be sent to authors for approval.

Copyright/conflicts of interest agreement: after the final approval, authors must send the copyright transfer agreement signed by the first author representing each additional author. In this agreement must be stated any conflicts of interest.

Introduction letter: a letter that must come with the submitted paper and contains at least the following information:

- a statement that the paper has not been submitted for publication in another journal;
- recommendation of two specialists for consulting in the scientific field of the submitted paper. The Editorial Board may or may not choose any of these consultants;
- conflicts of interest statement: state if the authors have any conflicts of interest. Conflicts of interest are those with potential influence over the published content, compromising the objectivity, integrity, or perceived value of the paper;
- author information: to provide full name and institutional affiliations of every author and a mailing address of the main author (postal and e-mail). Authors will be required to objectively state that the submitted paper consists of original content, informing it has not been previously published nor is it being analysed with this intent elsewhere.

  If the authors had assistance from technical writers or language reviewers, it must be explicitly stated in the introduction letter, along with the assurance that the authors are fully responsible for the scientific content of the paper.

  Authorship information: scientific authorship must be limited to those who contributed with intellectual work, with actual collaboration in the research. Therefore, to be considered an author, each contributor must meet the following conditions: (a) significant contribution to the creation and design of the study or to the analysis and interpretation of its results; (b) substantial contribution to the production of the paper, or critical review of its intellectual content, and (c) approval of the final version for publication. Leading or supervising a research lab/group does not in itself qualify as authorship. Sole contributions to fund raising or to data gathering also do not qualify as authorship. To ensure transparency in this aspect authors are expected to include a statement of authorship detailing the role of each author in the study and in the production of the paper. In the absence of this authorship statement within the introduction letter, the paper will be disqualified for analysis.

The letter must be signed by the main author, who will represent all other authors in this document.

Title page: this page must contain title and author information as follows:

- title (in Portuguese, English, and Spanish) 100 characters maximum, counting spaces;
- short title (in Portuguese, English, and Spanish) 50 characters maximum, counting spaces;
- the name of each author with their affiliation in this particular order: first name, abbreviated middle names, last name. Department (or service). Course. University (or institution). City, state/province/territory, country.
- contact information for an author: first name, abbreviated middle names, last name, mailing address, e-mail.

Types of papers

1. **Original papers**:

Papers resulting of original research. Maximum of 5,000 words (excluding abstract and references) and five images or tables. Maximum of 40 listed references. They must be submitted in the following format:

- **abstract**: must be written in Portuguese, English, and Spanish, with a maximum of 250 words. Must follow the structured abstract model, with mandatory introduction, methodology and resources, results and discussion. It is well known that the abstract gets more visibility and distribution than the full text of the paper. Therefore, it must contain the essential information in the paper, but cannot be just a patchwork of sentences from it. It must be succinct and direct, highlighting what is most important in the full text in order to encourage a full reading. In the conclusion, all results must be related to the objectives of the study. The discussion must assert the contribution of the results to the body of knowledge about the subject of research.
- **keywords**: three to six terms related to the subject must be given, separated by semicolons, according to DeCS (Descritores em Ciências da Saúde) for Portuguese and Spanish, and also MeSh (Medical Subjects Headings) for English.

Full text

- **introduction**: it must be short and present the purpose (context and justification) of the study, including a short review of relevant studies about the subject, mentioning any recent progress, and referencing just what is appropriate.
- **methodology and resources**: this section must briefly present all the information needed for other researchers to replicate the study. Adopted procedures must be clearly described, as must the analysed variables and tested hypotheses. Definitions must be given whenever necessary. Population, sample, and measurement instruments must be described and information about data gathering and processing must be given. If possible, validity scores must be included. Methods an techniques used must be duly detailed, including statistic methods. New or substantially modified methods must be described, with a justification for its use and mention of its limitations. Research ethics must be observed. Authors must explicitly state that the research was done within ethical standards and with the approval of an ethics committee.
- **results**: this section must be a concise report of all new information found, with minimum personal bias and judgment. The data must be presented in a logical sequence, starting with the most important information. Data from tables and images must not be repeated, but briefly referred to. It must state the significance of the new data and the relevance of the new findings in relation to established theories and to scientific literature. In this section must also be mentioned the limitations of the present work, as well as its implications for future research. Finally, conclusions must be included in this section, always related to the initially stated objectives.
- **acknowledgments**: must be concise and limited to people and institutions that contributed to the research in some degree, but could not be included as authors.
- **in-text citations**: **BJHBS** follows the Vancouver style, according to the general rules of The NLM Style Guide for Authors, Editors, and Publishers, second edition (www.ncbi.nlm.nih.gov/books/NBK7256/). For in-text citations, use Arabic numerals superscript,[1] without spaces,

right after a word or punctuation: "Parkinson's Disease[1] description began in the 1950s,[2] when..." In some cases, the names of the authors may figure in the text: "Phillips[12] analysed several conditions of..."; and up to two authors can be named: "Handel and Matias[15] conducted a study about..." However, when the number of authors is three or more, the first author must be named along with the expression "et al": "Silveira et al[13] have proposed a new methodology..."

- **references**: all referenced cited in-text must be in the reference list. References are limited to published material, papers, and abstracts. Authors are responsible for providing precise and complete references. In references with more than one author, authors up to three must be named. From there on, an "et al" must follow the first three authors. There must be no more than 40 references.
- **tables and/or images**: up to a maximum of five.
- **tables**: must be created in dedicated software, such as Excel. The width must be proportional to one page in the current layout. The font must be Arial, size 9, single space. Tables must be imported to and submitted in a text file: .doc/.docx (Microsoft Word), .rtf (Rich Text Format), or .odt (Open Document Text). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text. The content of a table must not replicate that of an image nor vice versa. Their numbers must be assigned according to the order in which they are referenced in-text.
- **images**: can be photos, illustrations, graphics, drawings, etc. Images must be submitted as separate files (.tiff or .jpeg). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text

2. **Clinical cases:**

a. **Case report**: usually describes one to three patients or a family case. The text must be up to 2,000 words long, with up to three tables or images and up to 25 references. The abstract must be no more than 100 words long.

b. **Clinical case solution**: must contain a step by step description of the decision process of clinical cases. Patient information must be presented to one or more clinical experts in stages (text in bold) to simulate the way information is made available in clinical practice. The expert must answer (text in regular font) as new information is added, sharing their reasoning/arguments with the reader. The text must be up to 2.500 words long, and must have up to 15 references.

3. **Literature review**:

Must be about subjects relevant to medical practice. These will form a section about the common theme of each issue. These are limited to 5,000 words (excluding abstract and references) and a maximum of five images and/or tables. Maximum of 40 listed references. Literature reviews will be submitted for the editorial board analysis under invitation by the guest editor of this section, and must conform to the following standards:

Title page: this page must contain title and author information as follows:

- title (in Portuguese, English, and Spanish) 100 characters maximum, counting spaces;
- short title (in Portuguese, English, and Spanish) 50 characters maximum, counting spaces;
- the name of each author with their affiliation in this particular order: first name, abbreviated middle names, last name. Department (or service). Course. University (or institution). City, state/province/territory, country.
- contact information for an author: first name, abbreviated middle names, last name, mailing address, e-mail.

Full text:

- **abstract**: must be written in Portuguese, English, and Spanish, with a maximum of 250 words for each language. Must follow the structured abstract model, with mandatory introduction, methodology and resources, results and discussion. It is well known that the abstract gets more visibility and distribution than the full text of the paper. Therefore, it must contain the essential information in the paper, but cannot be just a patchwork of sentences from it. It must be succinct and direct, highlighting what is most important in the full text in order to encourage a full reading. In the conclusion, all results must be related to the objectives of the study. The discussion must assert the contribution of the results to the body of knowledge about the subject of research.
- **keywords**: three to six terms related to the subject must be given according to DeCS (Descritores em Ciências da Saúde) for Portuguese and Spanish, and also MeSh (Medical Subjects Headings) for English. Keywords must be separated by semicolons.

Literature reviews may fall into two types:

a. **Systematic review and meta-analysis** – Through a synthesis of original studies' results, the paper must answer specific relevant health sciences questions about the theme of its issue (see **BJHBS'** focus). It must detail the search process to find the original studies, selection criteria, and synthesis procedures for the results of the reviewed studies (which may or may not be meta-analysis procedures).

b. **Narrative/critic review –** Narrative or critic review has a descriptivediscoursive character, and aims to offer a broad presentation and to discuss themes of scientific interest within the health field. It must have a clear formulation of the scientific subject of interest, a theoretical-methological critic of the reviewed works, and a conclusive synthesis. It must be elaborated by experienced researchers in the field in question or by renowned experts of notorious knowledge.

- **Acknowledgments:** must be concise and limited to people and institutions that contributed to the research in some degree, but could not be included as authors.
- **In-text citations: BJHBS** follows the Vancouver style, according to the general rules of The NLM Style Guide for Authors, Editors, and Publishers, second edition (www.ncbi.nlm.nih.gov/books/NBK7256/). For in-text citations, use Arabic numerals superscript,[1] without spaces, right after a word or punctuation: "Parkinson's Disease[1] description began in the 1950s,[2] when..." In some cases, the names of the authors may figure in the text: "Phillips[12] analysed several conditions of..."; and up to two authors can be named: "Handel and Matias[15] conducted a study about..." However, when the number of authors is three or more, the first author must be named along with the expression "et al": "Silveira et al[13] have proposed a new methodology..."
- **References:** all referenced cited in-text must be in the reference list. References are limited to published material, papers, and abstracts. Authors are responsible for providing precise and complete references. In references with more than one author, authors up to three must be named. From there on, an "et al" must follow the first three authors. There must be no more than 40 references.
- **Tables and/or images:** up to a maximum of five.
- **Tables:** must be created in dedicated software, such as Excel. The width must be proportional to one page in the current layout. The font must be Arial, size 9, single space. Tables must be imported to and submitted in a text file: .doc/.docx (Microsoft Word), .rtf (Rich Text Format), or .odt (Open Document Text). They must be assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text. The content of a table must not replicate that of an image nor vice versa. Their numbers must be assigned according to the order in which they are referenced in-text.
- **Images:** can be photos, illustrations, graphics, drawings, etc. Images must be submitted as separate files (.tiff or .jpeg). They must be

assigned a number in ascending order and receive a title and/or subtitle explanation. They must also be referenced within the text

4. Other submissions:

Editorial: it's a commentary on or analysis of papers in a given issue. It may include an image or table and be no more than 750 words long, containing up to five references. It will be written by the editor in chief or by an invited contributor at their request.

Letters to the editor: space for reader's to talk about recently published papers. Each letter must have up to 200 words (excluding references), five references and one image or table. It must be submitted no later than six months after the publication of the relevant paper. Letters non-related to papers published by **BJHBS** are limited to 500 words (excluding references), five references, and one image or table. Authors of letters will be required to provide their details, as well as contact information and possible conflicts of interest. The decision about the publication of a letter is made by the editor in chief.

5. On-line submission:

Papers and other types of material must be sent to submission.bjhbs@gmail.com, along with the introduction letter. The subject of the e-mail must be: "Type of paper [original paper, case report, literature review]" or "Letter to the editor" -- title" + last name of its main author in UPPER CASE.

All subsequent communication must happen through responses to the original e-mail.

The editorial committee will analyse the material according to the editorial policies of **BJHBS** and will answer regarding acceptance for peer review as soon as possible. If it's considered fit for publication, it will be processed and proceed to editing, proofreading and layout.

After a paper's acceptance, the term of copyright transfer and the statement of conflicts of interest must be sent as soon as possible.

The final layout will be forwarded to the authors for final approval in .pdf format. This approval must be given according to a deadline defined by the editorial team.

Papers and other texts that do not conform to the specifications of these guidelines will be returned without any analysis by the editorial board of **BJHBS**. Such material must be re-submitted for new analysis once specifications are followed.

bjhbs.hupe.uerj.br