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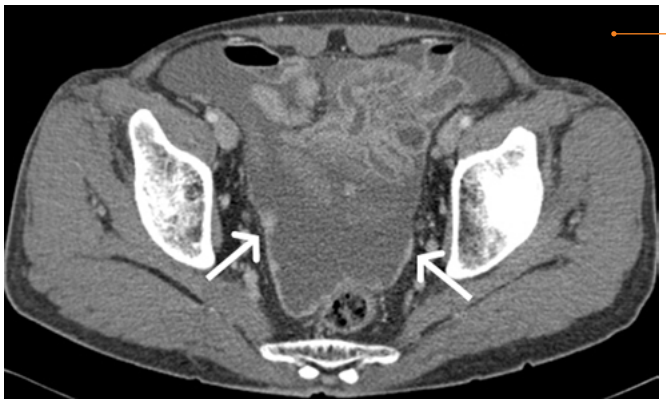

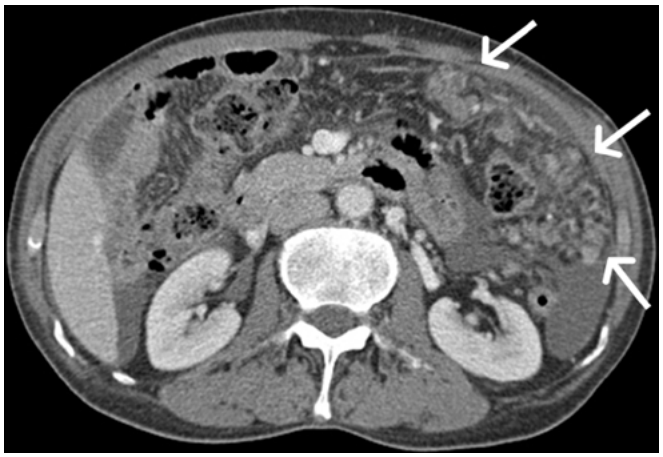

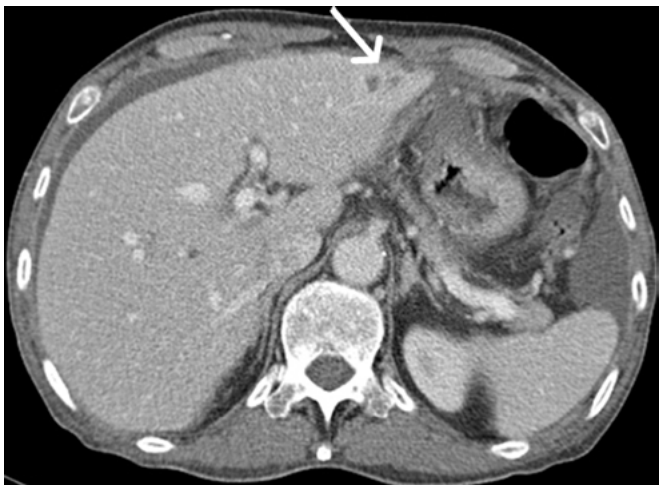

ARTICLES

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SECTIONS

ARTICLES

EDITORIAL

Opiophobia and opiophilia: the war continues

José Oswaldo de Oliveira Júnior[1]

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When there is a discussion around the topic of opioids (natural, semisynthetic, or synthetic), it is difficult to reach a consensus. The people contrary to its use are supporters of opiophobia and defend that substances that cause psychological changes along with drowsiness, lethargy, coma, discomfort reduction, pleasure, excitement, vigor, vitality, mental confusion, increased aggression, reduction of fatigue, delusion, and altered behavior due to physical dependence and/or psychic dependence, among others, can represent a risk for the individuals taking it as well as for the society of which they're part. Thus, the restrictions on the use of opioid analgesics are exaggerated, impairing the possibilities of pain control and promoting unnecessary suffering.

The people favorable to the use of such medication are supporters of what is called opiophilia. They are not very restrictive regarding its use and defend that the alternative to it, feeling pain, and the suffering that stems from it can be higher than the possible deleterious effects caused by opioids. They exaggerate the analgesic properties of opioid medication and minimize its adverse effects, inadvertently exposing its users to risks. Opioids, far from being a panacea, constitute a class of the most effective and often used medication for pain relief. However, that does not apply to all types of pain. The best analgesic responses are obtained when the pain is classified as acute, with nociceptive predominance and/or in cancer patients. The worst analgesic responses from opioids come from its use in the treatment of chronic, neuropathic and/or dysfunctional pain. The analgesic responses are related to the several types of pain already described, but also to the variations arising from the genetic polymorphism of opioid receptors.

The prejudice from several social spheres, such as the commercial, religious, political, police, medical, paramedical, and lay, have progressively permeated the scientific and technical precepts. The outcome was a radicalization of opiophilic and opiophobic positionings, which culminated with the progressive abandonment of rationality.

There have been, in some communities, times

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when the predominance of opiophobia gave way to opiophilia, and vice-versa.[1]

THE HISTORY OF OPIUM: A BRIEF REVIEW

In the Middle East, over six millennia ago, the Sumerians already used opium as an analgesic and sleep inducing medication.

There are also records from ancient Greece, from about 4 thousand years ago, of its recreational use in addition to the medicinal use. In Homer's work, The Odyssey, Helen offers Telemachus a juice or filtered solution that would be capable of relieving his pain and making him forget unpleasant memories.

During the Middle Ages, the medicinal use of poppy juice became particularly popular in the Arab world and the East. India soon became the biggest producer and exporter of poppy latex. During the 17th and 18th centuries, the source of profit of the East Indian Companies, especially for its English branch, migrated from the previously successful commerce of tea and silk, to opium. China was molded by the British and their representatives to become, in the early 1800s, the primary consumer market.[2]

Opium dens proliferated across China and housed a tremendous and growing number of users. This dependent users were easy prey for merchants and were happy to buy the then valuable English product, opium.

It did not take long for the Tau Kuan emperor to become aware of the massive loss of Chinese riches due to the commerce of Indian opium by the Englishman. A Chinese imperial decree forbidding the import of opium due to its harmful effects, mainly because its users would sell all of their belongings just to buy the drug, which back then was even more valuable than gold.

The British Empire retaliated by declaring war against China. After an initial defeat at the Canton Port, England triumphed. In addition to receiving around 6 million Patacas, the British gained ruling over the Honk Kong Island. The territory was officially occupied on November 26, 1842 and remained under British ruling almost until the end of the second millennium A.D.

After being defeated, the Chinese Empire also had to, shortly after signing the treaty, declare new regulations that encouraged an increase in poppy plantations. Little over six years, the poppy production in China surpassed the Indian.

Opium dens slowly replaced opium for tobacco. In 1850, in China, despite the slow reduction of new users, over 15 million inhabitants were chronic opium users.

The Asian migration to the U.S. Pacific Coast brought Chinese cultural elements that included the habit of smoking opium. The Chinese became to the U.S. What the English had been to the Chinese Empire half a century before. The first reaction by the U.S. was to pass an act on the taxation of opium and morphine use in 1890.[2]

At the end of the 19th century and beginning of the 20th, opium use was linked to Chinese immigrants and the American government initiated a deprecatory campaign against the Chinese that was highly segregationist and suggested that American should keep their distance from the lying mischievous Asians. Several texts and lyrics described the Chinese as people with reproachable habits who could stain the pure soul of the American people.

The same imperial acumen that led China to defy the forces of the British Crown in the mid-19th century later inspired several nations to, by means of public and private bodies, draft programs aiming to inhibit production, sale, and consumption of the substances, making them licit or illicit, forbidden or available under stricter regulations. Measures were progressively implemented worldwide, restraining the use and commerce of opium and, later on, morphine, its substitute.

The world consumption of illicit drugs is continuously increasing, despite the regulations. In the United States, there is also a rise in the use of licit opioids. Such problem is linked to the excessive prescription of these drugs. Over the past years, elective surgeries have been postponed due to an insufficient number of hospital beds in intensive care units, usually occupied by patients undergoing treatment for complications from opioid abuse. In addition to the overcrowding of intensive care units by the ones who survive, a high number of deaths caused by opioid abuse has been detected and, consequently, reported by the country's centers for disease control and prevention. The legal and illegal opioids have been and still are the cause for an average of 150 death per day in the U.S., according to data presented by the White House. In 2016, its combined economic impact between healthcare, work, and legal costs was estimated to be around US$ 92 billion in the U.S.

Measures to curb the excessive increase of opioid

prescriptions have been implemented in the country since the first decade of this millennium. A recent call for action to reduce abuse and overdoses on prescribed opioids was jointly made by the White House Office of National Drug Control Policy, the Drug Enforcement Administration, and the U.S. Food and Drug Administration.

In Brazil, we have seen a significant increase only in the use of illicit drugs, not licit ones. There is still undertreatment of pain here, and opioids are underused (with restricted prescription). [6,7]

The low consumption of licit analgesics in Brazil has a multi-factor origin, which includes lay and medical culture filled with opiophobic prejudice, bureaucratic barriers to its prescription, low per capita income, and the relatively high costs of such medications, aggravated by average taxes of over 30%.

In the past years, also in Brazil, elective surgeries have been postponed due to a lack of hospital beds in intensive care, occupied by patients with multiple trauma. Most of them are car accident victims, many other victims of motorcycle and domestic accidents.

PROPOSED SOLUTIONS

In the United States, measures and solutions were adopted to prevent the abuse of prescription drugs, especially opioids. A strategy of the U.S. Administration for the control of opioids was deployed, including actions in four fronts for reducing prescription: education,[8,9] sale and prescription monitoring, and judicial, legal, and police support.

The purpose of the educational pillar is to raise awareness among lay people and health professionals to the risks of prescription drug abuse. The monitoring will be perfected with programs for monitoring prescription, which will identify prescribers and of potential duplicates of prescriptions. Other programs will be created to improve sale control. Tools for law enforcement will be developed, production of medication reduced, abusive, duplicate, and triplicate prescriptions retained, and prescription drug traffic contained.

The American measures already implemented have already shown early results, many of which are worthy of celebration, such as the reduction in deaths in some states. On the other hand, some are worthy of reprimand and disapproval, such as the joint defense by several institutions in the area of suppressing the use of pain as a fifth vital sign.[10]

The strategy of recognizing pain, known to be a symptom, as a vital sign represents the active search of those who needlessly suffer in silence. There has been a new awakening in the medical community in favor of opioid-free anesthetics in American educational centers on Anesthesiology but, despite the efforts, with few adepts.

The November 2017 White House decision to sponsor scientific works on opioids aiming at mitigating overprescription will influence doctors worldwide and may cause a bias in countries where this is not a public health issue, especially those where there is an insufficient treatment of pain.

The recognition of pain as a fifth vital sign should be maintained and more widely adopted by health institutions. Opioid-free anesthesia techniques deserve to be developed but are still indicated for exception cases.

The Brazilian Society for the Study of Pain (Sbed), chapter of the International Association for the Study of Pain (Iasp) in a project entitled "Brazil with no pain", proposed: the creation and compulsory deployment of a Commission for the Control and Treatment of Pain in all private and public hospitals, clinics, and Immediate Care Units (UPAs); creation and compulsory deployment of a Unit for Treatment of Acute Pain in all hospitals with up to 100 beds, within three years from the approval of the new regulation; creation and compulsory deployment of a Unit for Treatment of Chronic Pain in all hospitals with up to 100 beds, within three years from the approval of the new regulation; creation of the National Pain Combat Day (August 29).

Sbed also defends the government support to the scientific investigation and teaching of pain, by means of clinical, experimental, psychosocial, social-cultural, and behavioral studies and postgraduate programs (lato sensu) in all University Hospitals in the country.

After the new regulation comes into effect, Sbed and the "Brazil with no pain" campaign will promote training on the treatment and control of acute and chronic pain to the staff of public and private hospitals, UPAs, and other services of primary and secondary care.

CONCLUSIONS

The strategy for the proper control of pain includes the deployment of programs of community education and training of health professionals, such as doctors,

nurses, pharmacists, administrators, among others. It also provides for the availability of medicaments, adequate prescription, distribution, and administration of drugs and the creation of health policies that emphasize the need for pain relief.

The inadequate pain treatment in Brazil and the crisis related to the abuse of opioid prescription in the United States are distinct public health problems, that require equally separate solutions.

The acknowledgment of these differences should not induce the risks of future abuse, probably even as a result of our incentive to the study and use of pain treatment, to be overlooked.

Hospital commissions for pain control can, based on hard scientific evidence, interfere and curb abuse cases, at the same time they reduce undertreatment and promote the improvement of pain control, thus reducing the suffering associated with it. The "Brazil with no pain" program, supported by Sbed can be the answer for us to reach proper pain treatment without the risk of drug abuse.

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Lumbar herniated disc - endoscopic discectomy treatment

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1. Brazilian Medical Association **2.** Brazilian Society of Neurosurgery

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

METHODOLOGY FOR EVIDENCE COLLECTION

This guideline followed the pattern of a systematic review with evidence collection based on the movement of Evidence-Based Medicine, in which clinical experience is integrated with the ability of critical analysis, rationally applying scientific information, thus improving the quality of medical assistance.

We used the structured version of the question synthesized by the P.I.C.O. acronym, in which **P** stands for patients with a **lumbar herniated disc with surgical indication**; **I** for **endoscopic lumbar discectomy** intervention; **C** for comparison between **microdiscectomy and open discectomy**; and **O** for the outcomes related to the **clinical effectiveness and safety**. From the structured question, we identified the keywords used as a basis for the evidence search in the sources of data: Medline-PubMed (886 papers) and, after we applied the eligibility criteria (inclusion and exclusion), 25 papers were selected to answer the clinical questions (**Appendix I**).

CLINICAL QUESTION

Is endoscopic lumbar discectomy effective and safe when compared with microdiscectomy and open discectomy for patients with lumbar herniated disc and nerve compression or severe persistent symptoms who did not respond to conservative treatment?

Grades for recommendation and levels of evidence:
A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies or animal models.

OBJECTIVE:

To identify the best evidence currently available related to the use of endoscopic lumbar discectomy as a treatment for lumbar herniated discs.

CONFLICT OF INTEREST:

No conflict of interest was declared by the participants in the preparation of this guideline.

INTRODUCTION

Lumbar herniated discs occur when the nucleus pulposus of an intervertebral disc protrudes through a rupture in the fibrous ring surrounding it. Its symptoms include lumbar or lower limb pain, accompanied by numbness and weakness. Permanent severe neurological damages, including foot drop, bladder dysfunc-

tion, and cauda equina syndrome may sometimes occur. Lumbar discectomy is considered when there is no serious nerve compression or persistent symptoms that did not respond to conventional treatment. The surgical techniques include open discectomy, microdiscectomy, or minimally-invasive alternatives, using percutaneous endoscopic approaches. The choice of surgical procedure can be influenced by several factors, including the symptoms and signs presented, in addition to the location and size of the prolapsed disc. The full-endoscopic discectomy (ED) is a new type of minimally invasive surgery developed to reduce surgical trauma, accelerate postoperative recovery and maintain the integrity of the normal anatomy of the spinal column[1,2]. The terminology varies quite a lot, with several names to indicate the same procedure, with minimal changes. ED includes two different approaches, basically, with distinct indications and techniques: the transforaminal and the interlaminar[3].

RESULTS OF THE SELECTED EVIDENCE

Patients with lumbar herniated disc confirmed by clinical symptoms and imaging exams (X-ray and MRI) were randomized into two groups: transforaminal percutaneous endoscopic lumbar discectomy (TPELD) and conventional fenestration discectomy (FD). The exclusion criteria were: (1) LHD associated to other diseases, including neuropathy, metabolic diseases, any heart, lung, liver, or kidney related diseases, or chronic/acute inflammation; (2) multilevel disc herniations; (3) spinal column infections, tumors, discitis or spinal tuberculosis; (4) recurrent disc herniation; and (5) lumbar instability or spondylolisthesis in more than two levels. A total of 48 patients were included in the TPELD group and 58 in the FD group, with an average follow-up time of 16.7 months (12 – 25) e 17.3 (12.5 – 23.5), respectively for each group. In the TPELD group, compared to the FD group, we found lower blood loss (in ml, 13.8 ± 3.6 vs 87.2 ± 32.3; MD = -74; CI95% -83.2 to -64.8; p<0.01), shorter hospitalization time (days, 7.2 ± 1.6 vs 12.8 ± 3.8; MD = -5; CI95% -5.8 to -4.10; p<0.01), lower risk of complications (ARR = 0.14; CI95% 0.019 to 0.269; NNT = 7, CI95% 4 to 52) in 6 months after the surgery. In TPELD, in comparison with FD, the pain was reduced (VAS) on the legs (p<0.05) and lumbar spine (p<0.05), at the 6-month analysis; however, there was no difference for these comparisons at 12 months. As for the postoperative ODI score, there was no difference between both groups at 6 and 12 months of follow0up (all p<0.05). Based on the modified MacNab, at the end of the follow-up, 95.84% of the patients in the TPELD group and 94.82% in the FD group were classified as excellent or good, with no significant difference between both groups (p>0.05).[4]**(B)** (This RCT is not included in the RSs mentioned here.)

A total of 1,092 adult patients (<70 years) with symptomatic lumbar herniation was included in a systematic review with a meta-analysis that compared endoscopic discectomy (ED) and open discectomy (OD). Out of the 15 studies assessed in its integrity (search from August 2014), 9 RCTs with sample size ranging from 40 to 240 patients were meta-analyzed. Studies that included patients with acute vertebral fracture, infection, tumor, or rheumatoid arthritis were excluded. The studies included in the meta-analysis were heterogeneous in patient selection, surgery techniques, instruments used, and follow-up time (minimum of 1 year and loss <20% for all studies). The authors observed that the studies had good methodological quality. The instrument used to measure clinical outcomes (primary outcome) was the MacNab criteria ("global perceived effect" or "global improvement"). There is no reference to the instrument used to assess the "patient satisfaction", considered a secondary outcome along with intraoperative blood loss and length of hospital stay.[5]**(B)**

The meta-analysis of the 9 RCTs showed the results below.[5]**(B)**

EFFECTIVENESS - There was no difference with statistical significance (ED vs OD)

- in the "global improvement" (MacNab criteria) between the ED (95.7%) and OD (80%), (3 studies, n = 165, OR = 3.72, CI95% [0.76 to 18.14], p = 0.10, I^2 = 62%).
- in the comparison of recurrence between ED (5.04%) and OD (3.35%), [7 studies; n = 417; OR = 1.62; CI95% [0.84, 3.12]; p = 0.15, I^2 = 0 %];
- in the comparison of reoperation rates between ED (6.82%) and OD (6.93%), [8 studies; n = 440; OR = 0,98, CI95% [0.60, 1.61]; p = 0.93, I^2 = 0 %]

There was a difference with statistical significance (ED vs OD)

- in the proportion of satisfied patients (does not specify the evaluation instrument), being 93.2% in the ED group and 86.5% in the OD, (4 studies; n = 221; OR = 2.19, CI95% [1.09 to 4.40]; p = 0.03, I^2 = 0 %);
- in the volume of intraoperative blood loss, fa-

voring ED (3 studies; n = 190; WMD: –123.71, CI95% [–173.47, –73.95], p<0.00001, I^2 = 99%);

- in the length of hospital stay, favoring ED (4 studies; n = 220; WMD: –144.45, CI95% [–239.54 to –49.37], p = 0.003, I^2 = 99 %)

SAFETY - There was no difference with statistical significance (ED vs OD)

- in the comparison of complication rates, Ed (16.11%) *vs* OD (20.12%), [8 studies; n = 447; OR = 0.73, CI95% (0.34 a 1.57); p = 0.41, I^2 = 75 %).

The high heterogeneity (I^2) between the studies, in the analysis of the outcomes evaluated in this meta-analysis, affects some results.[5]**(B)**

This systematic review of RCTs compared microendoscopic discectomy (MED) with open discectomy (OD) or microdiscectomy (MD), evaluating their effectiveness and safety in patients with symptomatic lumbar herniated disc. Out of the 109 studies analyzed, the authors found only four randomized clinical trials that met the eligibility criteria (Huang et al.[7], Righesso et al.[8], Teli et al.[9] and Garg et al.[10]) and reported the Oswestry Disability Index (ODI) as a result. Three studies compared MED and OD, and one compared OD, MD and MED (three groups). The eligibility criteria were studies that included adult patients with symptoms of sciatic pain, who did not respond to conventional treatment and with no previous lumbar herniated disc surgery. Endoscopic surgery by any method of MED that involved the use of an endoscopic tool was considered a surgical intervention, as well as the comparison between any OD and MD method. All four studies showed significant methodological flaws, especially referring to the low score in the CONSORT questionnaire. No significant differences were observed in the results between conventional microdiscectomy and endoscopic discectomy in the Oswestry Disability Index (ODI) scores in any period of time, thus showing similar effectiveness. However, Teli et al.[9] reported a higher rate of complications in patients who underwent endoscopic discectomy. That study, obviously, has a profound impact on this analysis, being one of the largest randomized series reported (total N = 212).[6]**(B)**

A total of 8,396 adult patients with symptomatic lumbar herniated disc (39 studies reported in 45 articles) was included in this review, with search until 2008; being six prospective controlled studies (one RCT and five non-randomized; n = 920 [412 transforaminal percutaneous endoscopic lumbar discectomy (TPELD) versus 508 controls]), two retrospective controlled studies (n = 962 [325 transforaminal percutaneous endoscopic lumbar discectomy versus 637 controls] and 31 before and after studies (n = 6.514). The inclusion and exclusion criteria varied between the studies (often not clearly described). Thirty-six studies specified radiculopathy in inclusion criteria. In most studies, the patients received some kind of conservative preoperative treatment for a few months. The duration of symptoms varied; some included all types of hernia and other just some specific types. Therefore, several techniques were used (including intradiscal and intracanal), as well as different instruments. The follow-up time ranged from six weeks to 108 months. Sixteen studies had an average follow-up of over two years. The studies included in this review were heterogeneous in patient selection, surgical indication, surgery techniques, follow-up time and outcome measures. The authors observed that the studies had poor methodological quality. The studies used different instruments (validated and not validated) to measure the results. Pain was measured by the Visual Analog Scale (VAS) or visual numeric scale. The functional status was measured by the Oswestry Disability Index (ODI) or Roland Morris Disability Scale. The ODI measures the degree of disability in a person with lumbar pain. The index score ranges from 0 to 100, 0 indicating no disability and 100 maximum disability. The "global perceived effect" was measured using the MacNab score or the percentage of patients with improvement. Patient satisfaction was generally reported using a Likert scale . In two series of cases included, the intervention was the "endoscopic laser foraminoplasty" (n = 250). None of the studies included was designed to assess adverse events.[11]**(B)**

A review of the eight studies with a control group showed the results below.[11]**(B)**

EFFECTIVENESS - There was no difference with statistical significance

- in the reduction of leg pain (VAS) between the group of transforaminal endoscopic surgery (89%) and the open microdiscectomy group (87%), (1 study, n = 200);
- in the median score of "global improvement" (MacNab criteria) between transforaminal endoscopic surgery and open lumbar microdiscectomy (84% versus 78% satisfactory, 5 studies, n = 1,102). The sum of the "excellent" and "good"

scores were reported as "satisfactory";

- the median rates of recurrence between transforaminal endoscopic surgery (5.7%) and open lumbar microdiscectomy (2.9%; 4 studies, n = 1,182);
- in the median rates of reoperation between transforaminal endoscopic surgery (6.8%) and open lumbar microdiscectomy (4.7%; 6 studies, n = 1,302). The most common cause of reoperation was the persistence of symptoms due to unresolved lateral stenosis and remaining fragments;

SAFETY - There was no difference with statistical significance

- in the median rates of complications between transforaminal endoscopic surgery (1.5%) and open lumbar microdiscectomy (1.0%; 6 studies, n = 1,302). The most reported complications were transient dysesthesia or hypoesthesia.

The results of TPELD (effectiveness and safety) in 31 "before and after studies" included in this review are listed below with the results in median % (max-min).[11]**(B)**

EFFECTIVENESS OF TPELD

- leg pain (VAS) - an improvement of 88% (65%-89%) - 7 studies, n = 1558,
- lumbar pain (VAS) - an improvement of 74% (13%-84%) - 5 studies, n = 1401,
- "global improvement" (MacNab criteria) - an improvement of 85% (72%-94%) - 15 studies (n = 2,544),
- functional state (ODI) - an improvement of 83% (74%-90%) - 3 studies, n = 624,
- returned to work - 90% (67%-95%) - 5 studies, n = 757,
- median rate of recurrence - 1.7% (0%-12%) - 13 studies, n = 2,612,
- median rate of reoperation - 7% (0-27%) - 28 studies (n = 4.135).

SAFETY OF TPELD

- median rate complications - 2.8% (0%-40%) - 28 studies, n = 6,336,

This study concluded that the results on the effectiveness of transforaminal endoscopic surgery were poor and did not provide valid information to support or refute its use in patients with a symptomatic lumbar herniated disc.[11]**(B)**

This systematic review assessed the effectiveness and safety of the percutaneous endoscopic lumbar discectomy (PELD) in the treatment of recurrent lumbar herniated discs (rLHD), second surgery. Three controlled studies were included (an RCT, one non-randomized CT and a retrospective cohort), in addition to five studies with no control group (before and after [2] and observational retrospective [3]), with searches in publications from 2002 to July 2015. Patients with recurrence confirmed by imaging exams with the failure of the conservative treatment and a pain-free interval of six weeks were included in the studies. The main exclusion criteria for PELD were: sequestrated or calcified discs, lumbar stenosis greater than moderate, instability of the spinal column, spondylolisthesis, cauda equina syndrome, and severe neurological deficit. The methodological rigor and scientific quality of the studies were considered in the analysis and conclusion of this review. In order to compare PELD and open discectomy (OD), a meta-analysis was carried out, including the three controlled studies, whose quality was considered high after the analysis. The quality of the five non-controlled studies was considered moderate/high.[12]**(B)**

An assessment of the eight studies (n = 475; three controlled and five non-controlled) included in this review showed the following results, expressed in mean and range (min-max).[12]**(B)**

PELD without comparison with a control group with a follow-up time ranging from 13 to 42 months, approximately:

EFFECTIVENESS

leg pain improvement (VAS) of 66.92% (50.6%-89.87%), 7 studies (n = 457),

back pain improvement (VAS) of 54.91% (29%-67.95%), 5 studies (n = 339),

improvement in the McNab score/patient satisfaction percentage of 75.77% (60%-95%), 5 studies (n = 391),

- functional state improvement (ODI) of 60.9% (40.7%-75%), 4 studies (n = 111),
- presented a rate of recurrence of 6.3% (4%-10%) assessed in 6 studies (n = 414),
- presented a rate of reoperation of 3.66% (2.33%-4.8%), 3 studies, (n = 110)

SAFETY

- the global average of the rate of complications was 4.89% (0%-9,76%),
- the rate of dural tears was of 0.1% (0%-4.9%).

A meta-analysis including the three studies with a control group, with a total of 197 patients (93 PELD versus 104 OD), presented the results below.[12]**(B)**

PELD compared with OD (result in mean differ-

ence), with a follow-up time that ranged from 24 to 34 months between the studies:

EFFECTIVENESS

- reduced surgical time (3 studies [n = 197, 68 PELD vs 65 OD]; DM = -59.08, CI95% -98.03 -20.13; p = 0.003), but with significant heterogeneity among the studies (I^2 = 94%, p<0.00001),
- there was no difference in intraoperative bleeding (ml) (2 studies [n = 143; 68 PELD vs 75 OD]; (DM = -161.73, CI95% -418.46 to 95.01, p = 0.22); significant heterogeneity among the studies (I^2 = 96%, p = 0.0001),
- there was no difference in length (days) of hospital stay (2 studies [n = 97; 43 PELD vs 54 D], DM = -6.49, CI95% -13.83 to 0.84, p = 0.08), with significant heterogeneity among the studies (I^2 = 96%, p<0.00001),
- there was no difference in leg pain reduction (VAS) (3 studies [n = 184; 88 PELD *vs* 96 OD], DM = 2.03, CI95% −1.38 a 5.44, p = 0.24); significant heterogeneity among the studies (I^2 = 80%, p = 0.007),
- there was no difference in lumbar pain reduction (VAS) (2 studies [n = 141; 70 PELD *vs* 71 OD], DM = −0.28, CI95% −3.90 a 3.33, p = 0.88); with significant heterogeneity among the studies (I^2 = 91%, p<0.00007),
- there was no difference in functional state (ODI), [2 studies, n = 141; 70 PELD *vs* 71 OD], DM = −3.62, CI95% −13.93 a 6.70, p = 0.49); with no heterogeneity among these studies (I^2 = 0%, p = 0.92),
- there was no difference in recurrence risk (3 studies, n = 184; 85 PELD *vs* 99 OD), RR = 0.53, CI95% 0.13 a 2.22, p = 0.39), with no heterogeneity among these studies (I^2 = 0%, p = 0.66).

SAFETY - PELD versus OD

- there was no difference in risk of infection of the surgical wound, RR = 0.38, CI95% 0.06 a 2.45; p = 0.31; with no heterogeneity among the studies, I^2 = 0%.
- there was no difference in risk of dural tears, RR = 0.27, CI95% 0.06 a 1.30; p = 0.10; with no heterogeneity among the studies, I2 = 0%,
- reduced the risk of complications considered serious in this study (surgical wound infection, dural tear, damage to nerve roots, cauda equina syndrome, cerebrospinal fluid fistula, transient dysesthesia of the leg (RR = 0.24, CI95% 0.08 to 0.71, p = 0.01); composite outcome.12(B)

DISCUSSION

The results of this review showed that the bleeding and length of hospital stay were lower with the percutaneous lumbar discectomy in comparison with MD/OD. The differences were small and did not reach the standard threshold for clinically significant differences in the assessment of outcomes, such as: global improvement (McNab criteria), function improvement (Oswestry Disability Index), recurrences, reoperations, and complications (clinical outcomes). A RCT (Teli et al.[9]) included in a systematic review (Smith et al.[6]) and, therefore, not separately described in this review, showed an increase in the number of complications; however, another RCT (Pan Z et al.[4]) showed a reduction. Another study that showed a decrease in the number of complications assessed the composite outcome and, when the analysis was carried out separately, by outcome (infection and dural tears), it did not find any differences.[12](B)

It is important to consider that this review grouped different surgical and instrumental techniques, according to the type of lumbar disc herniation. For this review, the results of the meta-analysis with high heterogeneity (I^2>80%) were not considered consistent. The analysis was deemed to be consistent when it had low heterogeneity (R^2 = 0%) for the outcomes: recurrence, reoperation, improvement in functional status. The general opinion of the authors, reported in the discussion/conclusion sections of most studies, is that the results for endoscopic microdiscectomy are comparable to that of a standard microdiscectomy.

RECOMMENDATION

For patients with lumbar herniated disc (recurrent or not) and surgical indication, the endoscopic lumbar discectomy, when compared with the microdiscectomy or open discectomy:

- had similar results in "global improvement" (MacNab criteria), functional status (Oswestry Disability Index), leg pain (VAS), lumbar pain (VAS), recurrence, reoperation and complications.
- reduced the bleeding (in ml, MD = -74, CI95% -83.2 To -64.8, p<0.01), and the length of hospital stay (in days, MD = -5, CI95% -5.8 to -4.10, p<0.01).

STRONG RECOMMENDATION GRADE / MODERATE LEVEL OF EVIDENCE (GRADE 1B)

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APPENDIX I

Clinical question

Is endoscopic lumbar discectomy effective and safe when compared with microdiscectomy and open discectomy for patients with lumbar herniated disc and surgical indication?

Structured question

P – Patients with a lumbar herniated disc with surgical indication
I – Endoscopic lumbar discectomy
C – Microdiscectomy or open discectomy
O – Outcomes related to clinical effectiveness and safety

Methodology for evidence search

PubMed-Medline

#1 – (Intervertebral Disk Displacement OR Disc, Herniated OR Discs, Herniated OR Disk, Herniated OR Disks, Herniated) AND (Surgical Procedures, Endoscopic OR Surgical Procedure, Endoscopic OR Surgical Endoscopy OR Endoscopy OR endoscopic OR Percutaneous Endoscopic Discectomy OR endoscopic discectomy)

#2 – (Diskectomies OR Discectomy OR Discectomies OR Diskectomy) AND (Surgical Procedures, Endoscopic OR Surgical Procedure, Endoscopic OR Surgical Endoscopy OR Endoscopy OR Percutaneous Endoscopic Discectomy OR endoscopic discectomy)

#1 OR #2

Cochrane Library

disc herniation AND discectomy

Returned studies

The literature review was carried out until December 10, 2016 in the databases Medline/PubMed and Cochrane Library. The studies were identified in terms of MeSH vocabulary and free text (**Table 1**).

The evidence used was retrieved by the following steps: elaboration of the clinical question, structuring of the question, search for evidence, presentation of results, and recommendations.

TABLE 1 - NO. OF PAPERS RETURNED FROM THE SEARCH METHODOLOGY USED IN EACH OF THE SCIENTIFIC DATABASES

DATABASE	NUMBER OF PAPERS
Medline/PubMed	**886**
Cochrane Library	**174**

Inclusion criteria for the selected papers

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted by two researchers with expertise in the development of systematic reviews, in total accordance with the inclusion and exclusion criteria established and described in the PICO. Finally, the studies with potential relevance were separated.

5.1 According to the designs of the studies

Systematic Reviews (SRs) were included, with or without meta-analysis that did not include the same studies, and RCTs published *a posteriori*.

The evidence retrieved was selected based on a critical assessment that used the Amstar (A Measurement Tool to Assess Reviews) tool for SRs and the Jadad[14] and Grade[15] discriminatory instruments (scores) for the RCTs.

The Type II Error was not used in the selection of RCTs in order to avoid greater limitation.

5.2 Language

Studies available in Portuguese, English, Italian or Spanish were included.

5.3 According to the publication

Only studies with texts available in its entirety were considered for critical evaluation.

Method for critical evaluation

From the databases, after the initial critical evaluation, were selected: Medline/PubMed (5 studies), Cochrane Library (0) (**Appendix II**).

The papers considered for complete reading were critically evaluated following the inclusion and exclusion criteria, based on study performance, PICO, language and availability of the text in its entirety.

Out of the five papers considered for critical evaluation, none was excluded for not being complete.

Amstar[13] was used to evaluate the quality of the systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, in which 11 represents a review of the highest quality. Quality categories were determined as follows: low (0 to 3 score), medium (4 to 7 score) and high (8 to 11 score). SRs of low and medium quality were excluded (**Appendix III**)

When, after the inclusion and exclusion criteria

were applied, the evidence selected was classified as Randomized Controlled Trial (RCT), it was subjected to a suitable critical evaluation check-list Table 2).

The critical evaluation of RCT allows to classify it according to the Jadad score[14], considering Jadad trials < 3 (three) as inconsistent, and those with score ≥ 3 (three) consistent.

During the critical evaluation, the Grade[15] (Grading of Recommendations Assessment, Development and Evaluation) discriminatory instrument was also applied, using evidence of high and moderate quality **(Table 3)**.

TABLE 2 - GUIDE FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, level of evidence	**Sample size calculation** Estimated differences, power, significance level, the total number of patients
Patient selection Inclusion and exclusion criteria	**Patients** Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	**Patient follow-up** Time, losses, migration
Treatment protocol Intervention, control, and blinding	**Analysis** Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	**Results** Benefit or harm in absolute data Survival analysis

Presentation of the results of the evidence selected

The results regarding the intervention considered in the clinical question will be exposed individually, by means of the following items: clinical question, number of selected works (according to the criteria of inclusion), main reasons for exclusion and synthesis of the evidence available.

References related to studies included and excluded will be arranged in the item References and the reasons for exclusion in **Appendix IV.**

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be specifically defined whenever possible.

Matters related to costs will not be included in the results, and the outcomes considered will be limited to the clinical effectiveness and safety of the interventions.

Recommendations

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of evidence, and will subject to validation by all authors who participated in creating the Guideline.

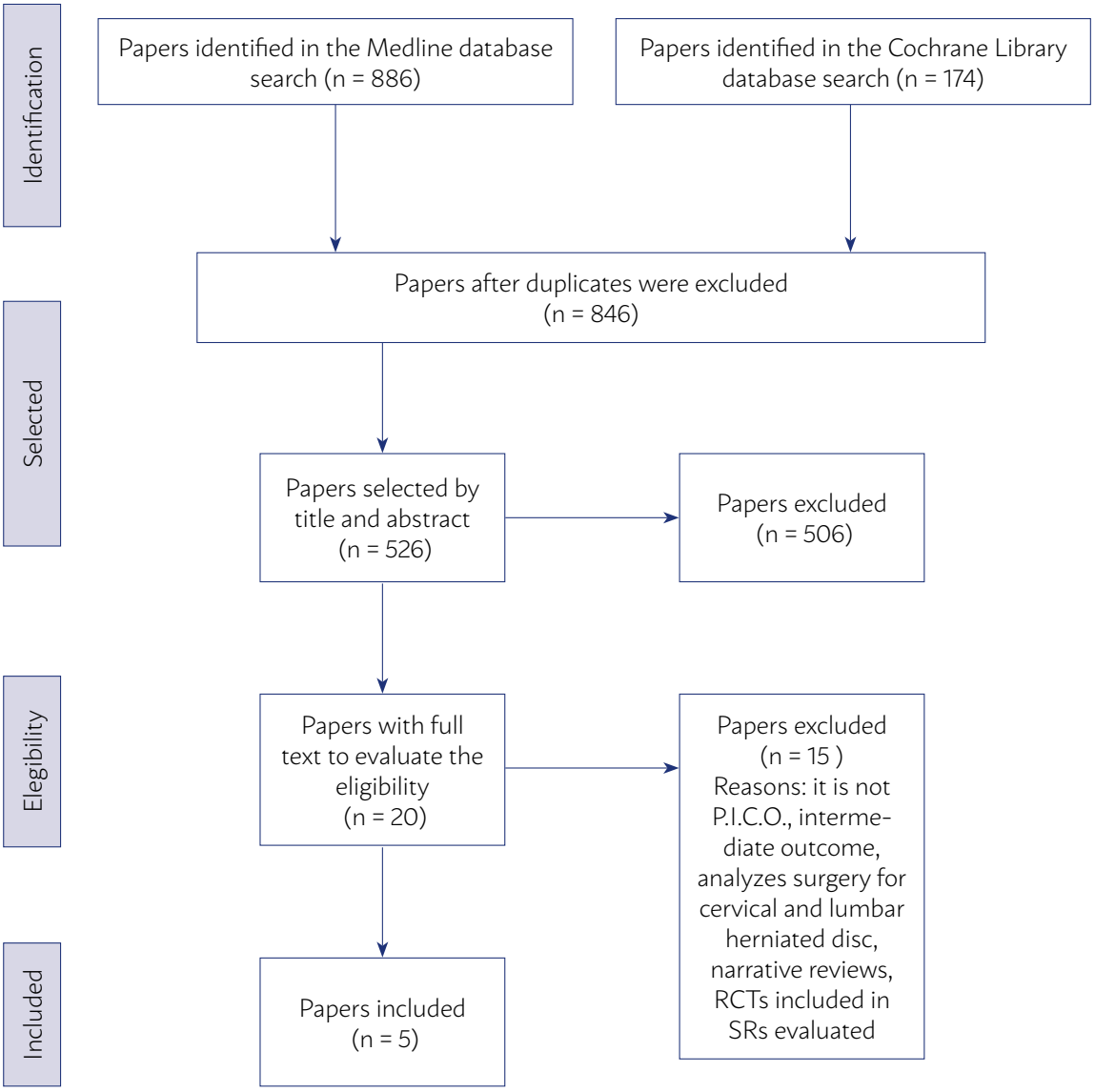
The level of recommendation used comes directly from the power available in the studies included in Oxford[16] and the use of the Grade system[15].

TABLE 3 - DESCRIPTIVE TABLE OF THE BIASES IN THERAPEUTIC STUDIES

STUDY	QUESTION	RANDOMIZATION	ALLOCATION	BLINDING	LOSSES	PROGNOSIS	OUTCOMES	ITT
Pan Z 2016[10]	Yes. Suitable	There was randomization, but no description	No description	Blinding of the outcome evaluator	There was none	No difference between the groups	Short follow-up time. Adequate scores	No

ITT = analysis by intention to treat / Jadad = 3 / Sample size calculation = There was none

APPENDIX II
Diagram of recovery and initial selection of papers



APPENDIX III

Amstar (a measurement tool to assess reviews)

	Cong L et al. (2016)[5]	Smith N et al. (2013)[6]	Nellensteijn J et al. (2010)[11]	Li X et al. (2016)[12]
Was a project received a priori?	Y	Y	Y	Y
Were there duplicates in the study selection and data extraction?	Y	Y	Y	Y
Was a comprehensive bibliographic search/research conducted?	Y	Y	Y	Y
Was the publication status (i.e., gray literature) used as an inclusion criterion?	Y	Y	Y	Y
Was a study list (included and excluded) provided?	N (only included)	N (only included)	N (only included)	N (only included)
Were the characteristics of the studies provided?	Y	Y	Y	Y
Was the scientific quality of the studies included assessed and documented?	Y	Y	Y	Y
Was the scientific quality of the studies included used properly in formulating the conclusions?	Y	Y	Y	Y
Were the methods used to combine the studies results appropriate?	Y	Y	Y	Y
Was the probability of publication bias assessed?	Y	Y	Y	Y
Were conflicts of interest informed?	Y	Y	Y	Y
Total score	10	10	10	10

Y = yes / N = no / NS = not sure / NA = not applicable . Maximum score = 11 points

APPENDIX IV

Studies excluded and the reason for exclusion

STUDY	REASON
Anichini G 201517	It is not a SR
Lee DY 200918	Included in meta-analysis evaluated
Birkenmaier C 201319	SR includes cervical and lumbar herniation
Garg B 201110	Included in SR evaluated
Huang TJ 20057	Included in SR
Hussein M 201420	Included in SR
Li XC 201621	Includes cervical and lumbar
Pan L 201422	Intermediary outcome
Rasouli MR 201423	Partially answers PICO and more recent SRs include all its studies
Righesso O 20078	Included in SR evaluated
Ruetten S 200824	Included in SR evaluated
Ruetten S 200925	Does not answer to PICO (cervical hernia)
Ruetten S 200926	Included in SR evaluated
Teli M9	Included in SR evaluated
Ruan W 201627	Medium quality in Amstar

APPENDIX V

RESULTS - using studies that allow for the comparison of both procedures

STUDY	TYPE OF STUDY AND POPULATION INCLUDED (N)	OUTCOMES - ENDOSCOPIC DISCECTOMY COMPARED TO MICRODISCECTOMY OR OPEN DISCECTOMY								
		MacNab Criteria	Oswestry Disability Index	Leg pain	Lumbar pain	Recur-rence	Reoper-ation	Bleeding	Length of hospital stay	Complica-tions
Cong L 2016[5]	RS N = 1.092	ND				ND	ND	I	I	ND
Smith N 2013[6]	RS N = 414		ND							
Nellensteijn J 2010[9]	RS N = 8.396	ND		ND		ND	ND			ND
Li X 2016[12] (Recurrent lumbar herni-ated disc - 2nd surgery)	RS N = 579		ND					I	I	B (for the composite outcome - serious compli-cations) ND = for infection of surgical wound and dural tear
Pan Z 2016[4]	RCT N = 106	ND	ND	B in 6 M ND in 12 M	B in 6 M ND in 12 M			B: in ml (MD = −74 CI95% −83.2 a −64.8); p<0.01	B: in days (MD = −5 CI95% −5.8 a −4.10); p<0.01	B: in 6 M (NNT = 7 CI95% 4-52

B = benefit favoring endoscopic discectomy, D = damage with endoscopic discectomy, ND = no difference between procedures (ED *vs* OD), I = inconclusive due to the high heterogeneity of the meta-analysis (I^2 > 80%), NNT = number needed to treat, M = months, DM = mean difference

w

Tuberculous peritonitis following intestinal perforation in malignancy

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SUMMARY

Tuberculous peritonitis is one of the most common causes of exudative ascites, especially in the young, and is an important cause of extra-pulmonary disease. However, tuberculous peritonitis is challenging to diagnose because there are no pathognomonic clinical features or imaging findings. Therefore, it is commonly misdiagnosed as another type of peritoneal disease, especially so in elderly patients with malignant disease. In this report, we described two cases of tuberculous peritonitis that were observed after intestinal perforation in elderly patients with malignancies. These diagnoses were established by laparoscopic peritoneal biopsy or AFB cultures of the ascitic fluid. Both patients were treated with anti-TB medications.

KEYWORDS: *Peritonitis. Tuberculosis. Intestinal Perforation. Neoplasms. Multidetector Computed Tomography.*

INTRODUCTION

The peritoneum is a common site for tuberculosis involvement of the abdomen.[1] Tuberculous peritonitis accounts for 2% of all extrapulmonary infections.[2] This diagnosis, however, is difficult to reach in the absence of any pathognomonic clinical features or imaging findings. The radiologic features of tuberculous peritonitis can be easily confused with those of other peritoneal diseases, including peritoneal carcinomatosis, primary peritoneal mesothelioma, peritonitis, and rarely lymphoma.[3-7] Therefore, it is difficult to identify tuberculous peritonitis, especially in elderly patients with malignant disease and a recent history of intestinal perforation. In this study, we report two cases of tuberculous peritonitis that were observed after intestinal perforation in patients with malignancies.

CASE REPORT

The first patient was a 66-year-old man was admitted for epigastric pain, poor oral intake, and a 6-kg weight loss over 2 months. He had under-

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gone endoscopic submucosal dissection (ESD) for pathologically-proven gastric cancer, 2 months prior to the presentation. The diagnosis was confirmed as early gastric cancer (pT1a according to the American Joint Committee on Cancer staging system 8th edition). Subsequently, abdominal radiographs and contrast-enhanced abdominal CT revealed a localized perforation at the ESD site. The patient had a history of pulmonary tuberculosis 30 years prior to his current presentation. Laboratory findings were unremarkable, except for an elevated CRP of 6.49 mg/dl (normal, 0.0–0.5). Physical examination revealed no tenderness or rebound tenderness of the abdomen. Contrast-enhanced abdominal CT obtained 8 days after ESD showed segmental, layered wall thickening with a hemoclip at the greater curvature side of the gastric antrum. There was a small amount of associated extraluminal free air, fluid collection, and minute soft tissue stranding in the surrounding fat. Otherwise, there was no abnormal lymphadenopathy, free ascetic fluid or peritoneal thickening. Contrast-enhanced abdominal CT obtained 2 months later revealed a new large-volume ascites and irregular nodular thickening of the parietal peritoneum (Fig. 1a). Enhancing nodules and soft tissue stranding were also identified in the omentum (Fig. 1b). There were multiple low-attenuated nodules <1 cm in diameter in the left lateral segment of the liver (Fig. 1c). Extraluminal free air in the perigastric area had resolved. These findings were worrying and could indicate liver metastasis and peritoneal carcinomatosis. Therefore, an ultrasound-guided liver biopsy and paracentesis were performed. There were no malignant cells on the histopathological analysis. Both ascitic fluid culture, and staining for acid-fast bacilli (AFB) were negative. The adenosine deaminase (ADA) level was 90 units/L. Finally, a laparoscopic peritoneal biopsy was ultimately in the peritoneum and omentum. Intraoperative findings included multiple whitish nodules in the peritoneum, omental cake, and a large volume of ascites. The histopathological results revealed chronic granulomatous inflammation. The final diagnosis was confirmed to be tuberculous peritonitis. The patient was treated with anti-tuberculous medications for 9 months.

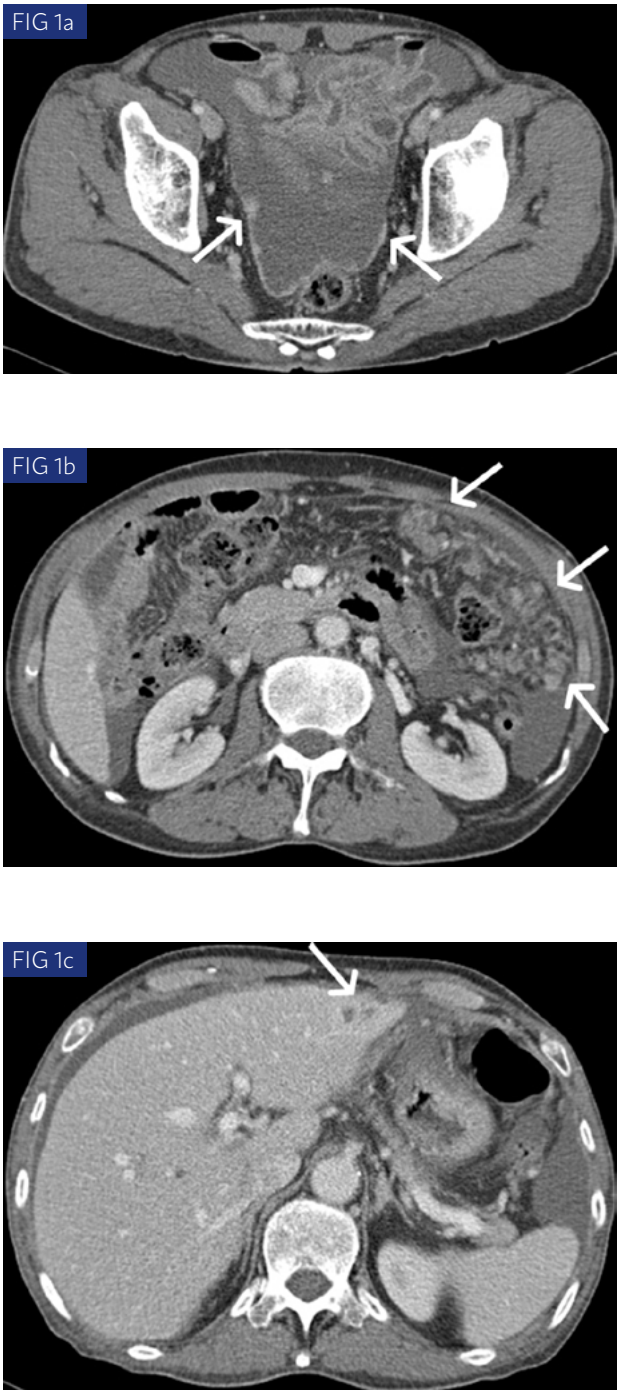

FIGURE 1. A 66-year-old man with tuberculous peritonitis. a-c. Contrast-enhanced abdominal CT images show a large volume of ascites with irregular and nodular thickening of the parietal peritoneum (arrows in a), enhancing nodules (arrows in b), soft tissue stranding in the omentum, and small low-attenuation lesions in the left lateral segment of the liver (arrow in c).

The second patient was a 76-year-old man who presented abdominal pain and poor oral intake. This patient had a surgical history of a pylorus-preserving pancreatoduodenectomy for distal bile duct cancer. He was also treated with hormone therapy for prostate cancer 8 years prior to presentation.

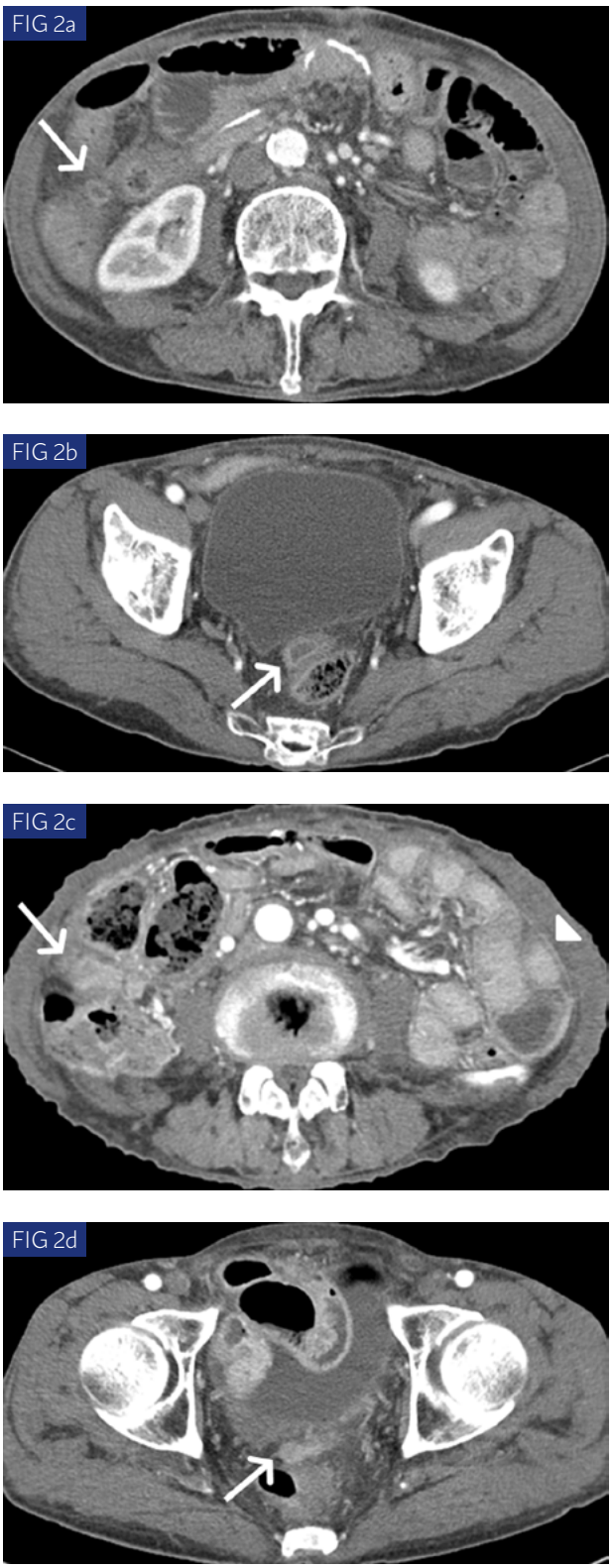

FIGURE 2. A 76-year-old man with tuberculous peritonitis. a, b. Contrast-enhanced abdominal CT images obtained 2 weeks after revision of the gastrojejunostomy for marginal ulcer perforation show a few small fluid collections confined within an enhancing rim in the abdomen and pelvis (arrows in a,b).
c, d. Abdominal CT images obtained 6 weeks later demonstrate enhancing soft tissue lesions replacing the fluid collections (arrow in c, d) and a moderate amount of ascites with diffuse peritoneal thickening (arrowhead in c).

Two months prior to presentation, the patient underwent revision gastrojejunostomy for marginal ulcer perforation with panperitonitis. Physical examination revealed no tenderness or rebound tenderness of the abdomen. Laboratory findings on presentation were only remarkable for a mild elevation of CRP to 1.20 mg/dl (normal, 0.0 – 0.5), and anemia with a hemoglobin level of 10.0 g/dL (normal, 13-17) and hematocrit 31.2% (normal, 29-52). Tumor markers, including CA19-9 (7.75 U/mL; normal, 2-37), CEA (0.38 ng/mL; normal, 0-6.0) and PSA (0.01 ng/mL; normal 0-40) were within normal range. Contrast-enhanced abdominal CT obtained 2 weeks later (after revision of gastrojejunostomy for marginal ulcer perforation) showed a few small fluid collections confined within an enhancing rim in the abdomen and pelvis (Fig. 2a, b). A follow-up abdominal CT obtained 6 weeks later demonstrated a complex fluid collection, evidenced by an enhancing soft tissue lesion, with an interval increase in size (Fig. 2c, d). There was also a moderate amount of new ascites, diffuse thickening of the peritoneum, and nodules (Fig. 2c). Ultrasonography-guided biopsy of the peritoneal nodule and diagnostic paracentesis were performed. The tissue biopsy revealed a foreign body reaction to the suture material. There were no malignant cells on the tissue biopsy or ascitic fluid. The ADA level in the ascitic fluid was 40 units/L. The AFB culture of the ascitic fluid was positive for Mycobacterium tuberculosis. Thus, the patient was diagnosed with tuberculous peritonitis and treated with anti-tuberculous medications.

DISCUSSION

Both of these patients had nonspecific and complicated presentations, which made it difficult to accurately diagnose tuberculous peritonitis. It was challenging to distinguish tuberculous peritonitis from other differential diagnoses, including peritoneal carcinomatosis, and other peritonitis. Most cases of tuberculous peritonitis result from the reactivation of long-latent foci of tuberculous infection in the peritoneum. Other mechanisms of pathogenesis include hematogenous spread from an adjacent, or distant active primary site. For instance, tuberculosis can spread in the blood from primary pulmonary lesions or directly from caseous abdominal lymph nodes, abscesses, intes-

tinal segments, or fallopian tubes.[1, 8-10] Neither of the two patients had active tuberculosis infection, although one had a remote history of pulmonary tuberculosis. Several known risk factors for TB include old age, male gender, previous anti-TB treatment, gastrectomy, and chemotherapy treatments for malignancy.[11, 12] There is an increased risk of TB incidence after chemotherapy in patients with a history of TB.[11] Therefore, we hypothesize that tuberculous peritonitis develops from the reactivation of long-latent foci of a tuberculous infection in patients with risk factors for tuberculosis. Interestingly, in our cases, tuberculous peritonitis was observed approximately 2 months after the intestinal perforation. There have been many reported cases in which there was intestinal perforation secondary to intestinal tuberculosis. There are also a few cases in which intestinal perforation was related to tuberculous peritonitis. However, to the best of our knowledge, tuberculous peritonitis that develops after intestinal perforation (without intestinal tuberculosis) has not been previously reported. In the cases presented here, the association of tuberculous peritonitis and intestinal perforation is uncertain. However, we hypothesize that the decreased immunity after an intestinal perforation with associated peritonitis could increase the risk of tuberculosis reactivation. [11, 13]

Tuberculous peritonitis is one of the most common causes of exudative ascites. It presents a variable amount of exudative ascites, soft-tissue infiltration, and thickening of the peritoneum, mesentery, and omentum. There also may be caseous lymph nodes. Relative characteristic features of tuberculous peritonitis include smooth thickening and strong contrast enhancement of the parietal peritoneum, soft-tissue infiltration of the mesenteric leaves, and a smudged or dirty appearance of the omentum. In contrast, nodular peritoneal thickening and a nodular or caked appearance are more suggestive of peritoneal carcinomatosis. However, these CT findings can overlap between the two diseases, it difficult to distinguish them.[5-7, 14] Peritoneal carcinomatosis is unusual in patients with EGC, despite its occurrence in our first case; however, nodular peritoneal thickening and a nodular or caked appearance on CT images made it more challenging to diagnose the tuberculous peritonitis.

There are no pathognomonic clinical features of tuberculous peritonitis. Abdominal swelling and malaise are the most frequent symptoms, while ascites is the most frequent sign at presentation. [1, 8, 15] Although the presence of thoracic tuberculosis may be suggestive of associated abdominal tuberculosis, only 15% of patients with abdominal TB have evidence of pulmonary disease.[16] Therefore, the differential diagnosis between tuberculous peritonitis and peritoneal carcinomatosis remains challenging, especially in elderly patients with malignancies because of their variable presentations and the limitations of available diagnostic tests. Therefore, one must have a high level of suspicion in patients with unexplained ascites and thickening of the peritoneum, mesentery, and omentum. This is particularly true in high-risk patients because the two diseases require entirely different treatment pathways and prognoses.

Definitive diagnosis of tuberculous peritonitis can only be made by identification of caseating granulomas, positive AFB, culture for *Mycobacterium tuberculosis*, or polymerase chain reaction. The rates of positive AFB and positive ascitic fluid culture vary significantly in different series. There is a relatively high rate of false-negative results.[1, 17] Although ADA activity in the ascitic fluid is a helpful marker of tuberculous peritonitis, it may be insufficient to distinguish tuberculous peritonitis from peritoneal carcinomatosis. Therefore, early diagnosis with tissue biopsy or laparoscopic exploration may be needed.[1, 17, 18]

In conclusion, there are no pathognomonic clinical features or imaging findings for tuberculous peritonitis. Therefore, one must have a high level of suspicion in patients with unexplained ascites and thickening of the peritoneum, mesentery, and omentum. The suspicion should be even greater for high-risk patients, since early diagnosis is critical for the appropriate management and improved of prognosis for patients with tuberculous peritonitis.

ACKNOWLEDGMENTS

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PALAVRAS-CHAVE: *Peritonite. Tuberculose. Perfuração intestinal. Neoplasias. Tomografia computadorizada multidetectores.*

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Osteoma of the cochlear promontory

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KEYWORDS: *Osteoma. Cochlea. Otolaryngology.*

The authors describe the case of a 21-year-old patient with a history of recurrent otitis media and placement of transtympanic tubes during childhood. The patient consulted the otorhinolaryngology professional because of muffled hearing and otalgia in the right ear that had been occurring for 6 months. During the objective examination, the otoscopy revealed a rounded structure, visible through the transparency of the tympanic membrane (Figure 1). The audiometry test showed thresholds within the normal range. A computed tomography scan of the ear showed a nodular bone lesion, with bilateral implantation in the cochlear promontory (Figures 2 and 3), compatible with the diagnosis of osteoma of the

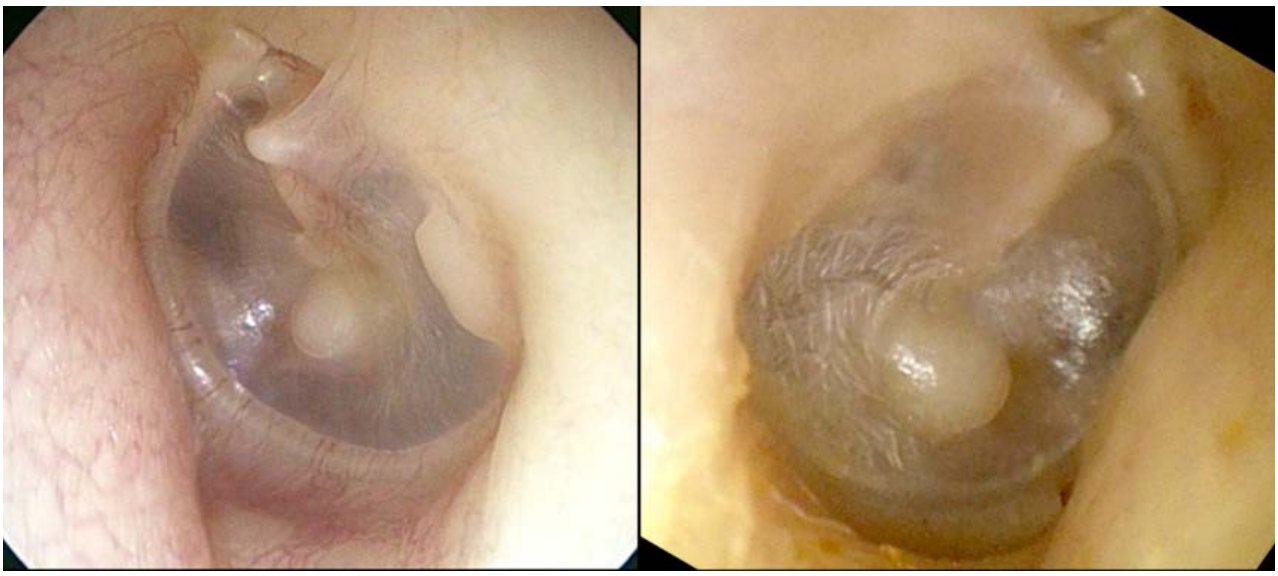

FIGURE 1

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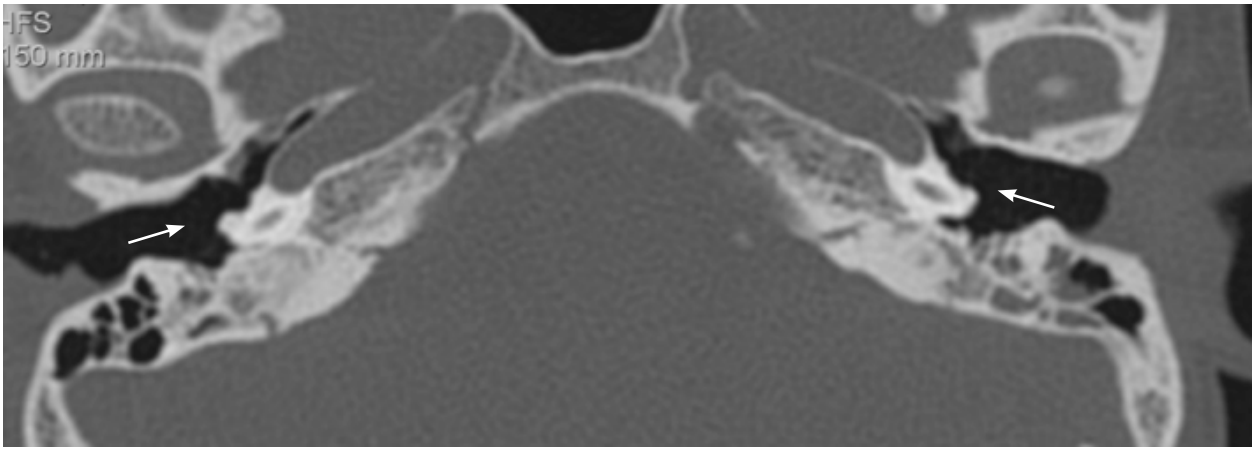

FIGURE 2

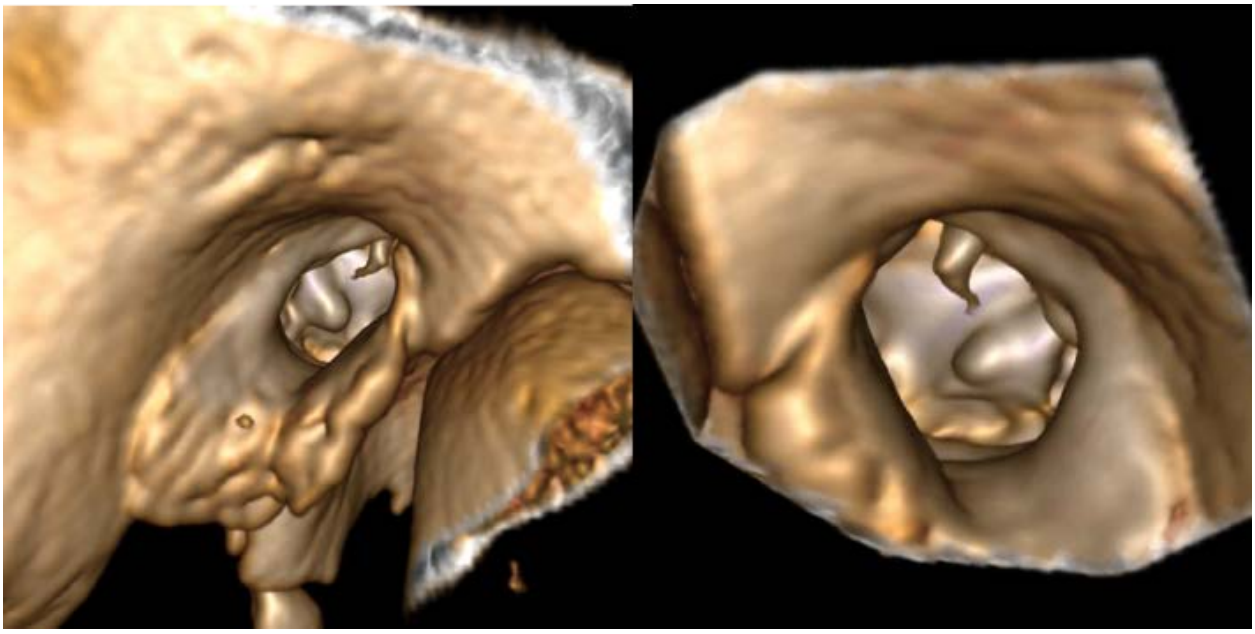

FIGURE 3

promontory. The patient has been under follow-up for 18 months, without further complaints.

The osteoma of the middle ear is a rare benign tumor.[1] The most frequent initial symptom is the hypoacusis of transmission,[2] however, in most cases it is asymptomatic. These are lesions of slow growth, and the conservative treatment[3] is recommended with periodic monitoring in the absence of associated symptoms.

PALAVRAS-CHAVE: *Osteoma. Cóclea. Otorrinolaringologia.*

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Hand-foot syndrome due to hepatitis C therapy

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SUMMARY

INTRODUCTION. *Direct-acting antivirals are new drugs for chronic hepatitis C treatment. They are usually safe and well tolerated, but can sometimes cause serious adverse effects and there is no consensus on how to treat or prevent them. We described a case of hand-foot syndrome due to hepatitis C virus interferon-free therapy.*

METHODS. *We report the case of a 49-year-old man with compensated liver cirrhosis due to chronic hepatitis C genotype 1, treatment-naïve, who started viral treatment with sofosbuvir, simeprevir and ribavirin for 12 weeks.*

RESULTS. *At the sixth week of treatment he had anemia, requiring a lower dose of ribavirin. At the tenth week, he had erythematous, pruritic, scaly and flaky lesions on hands and feet, which showed a partial response to oral antihistamines and topical corticosteroids. It was not necessary to discontinue antiviral treatment, but in the first week after the end of treatment, there was worsening of injuries, including signs of secondary infection, that required hospitalization, antibiotics and oral corticosteroid, with progressive improvement. Biopsy of the lesions was consistent with pharmacodermia. The patient had sustained a virological response, despite the side effect. He had a history of pharmacodermia one year ago attributed to the use of topiramate, responsive to oral corticosteroid.*

CONCLUSION. *Interferon-free therapies can rarely lead to severe adverse reactions, such as skin lesions. Patients receiving ribavirin combinations and those who had a history of pharmacodermia or skin disease may be more susceptible. There is no consensus on how to prevent skin reactions in these patients.*

KEYWORDS: *Hepatitis C. Antiviral Agents. Drug-related Side Effects and Adverse Reactions. Hand-Foot Syndrome.*

INTRODUCTION

Hepatitis C virus (HCV) infection are one of the leading causes of chronic liver disease worldwide[1]. The inflammation caused by the virus leads to liver fibrosis, cirrhosis, and complications, such as hepatocellular carcinoma. Treating the disease is essential, because it blocks the inflammation, reducing the fibrosis progression and the mortality associated with the infection[2].

For many years, HCV therapy has consisted of the combination of pegylated interferon and ribavirin for 24 or 48 weeks. With this regimen, genotype 1 patients had a around 50%[2] of chance to sustain virological response (SVR). However, this treatment was

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accompanied by many side effects, such as anemia, leukopenia, thrombocytopenia, flu-like symptoms, blood glucose changes, alterations in thyroid function, anxiety and mood disorders, teratogenicity and autoimmunity[2-4].

New drugs that act against the virus replication were developed, known as DAAs, or direct-acting antiviral agents. Their use without interferon improved treatment efficacy and safety, reducing the adverse effects, especially in cirrhotic patients, a more susceptible population[2-4]. In Brazil, the most used DAAs are sofosbuvir (a nucleotide analog inhibitor of RNA polymerase), daclatasvir (a NS5A inhibitor) and simeprevir (a NS3-4A protease inhibitor)[5].

There are few reports of side effects due to interferon-free therapy[6]. They are usually mild and do not require discontinuation of treatment. However sometimes they can be severe and there are scarce data on how to avoid them. Here, we report a case of hand-foot syndrome due to HCV interferon-free treatment.

CASE REPORT

A 49 year-old man with HCV related liver cirrhosis, genotype 1 and alcohol abuse was referred to our outpatient clinic for HCV therapy assessment. He was HCV treatment naïve, with arterial hypertension, diabetes, anxiety disorder and a tobacco user. He denied previous gastrointestinal bleeding, ascites or hepatic encephalopathy. He had a compensated liver function (Child-Pugh A, MELD 6), with a liver stiffness by Fibroscan® of 47.2 kPascal, compatible with Metavir F4 (cirrhosis). The upper digestive endoscopy revealed portal hypertension with esophageal varices. Baseline exams were as follows: hemoglobin: 15 mg/dL, leukocytes: 8,710/mm^3, platelet count: 193,000/mm^3, total bilirubin: 0.99 mg/dL [reference value (RV) < 1.2], urea: 41 mg/dL (RV < 43), creatinine: 0.9 mg/dL (RV < 1,2) , alanine aminotransferase: 82 IU/L (RV < 50), aspartate aminotransferase: 48 IU/L (RV < 50), alkaline phosphatase: 117 IU/L (RV < 120), gamma glutamyl transferase: 300 IU/L (RV < 38), albumin: 4.0 g/dL (RV 3.5-5.2), INR: 0.9 (RV

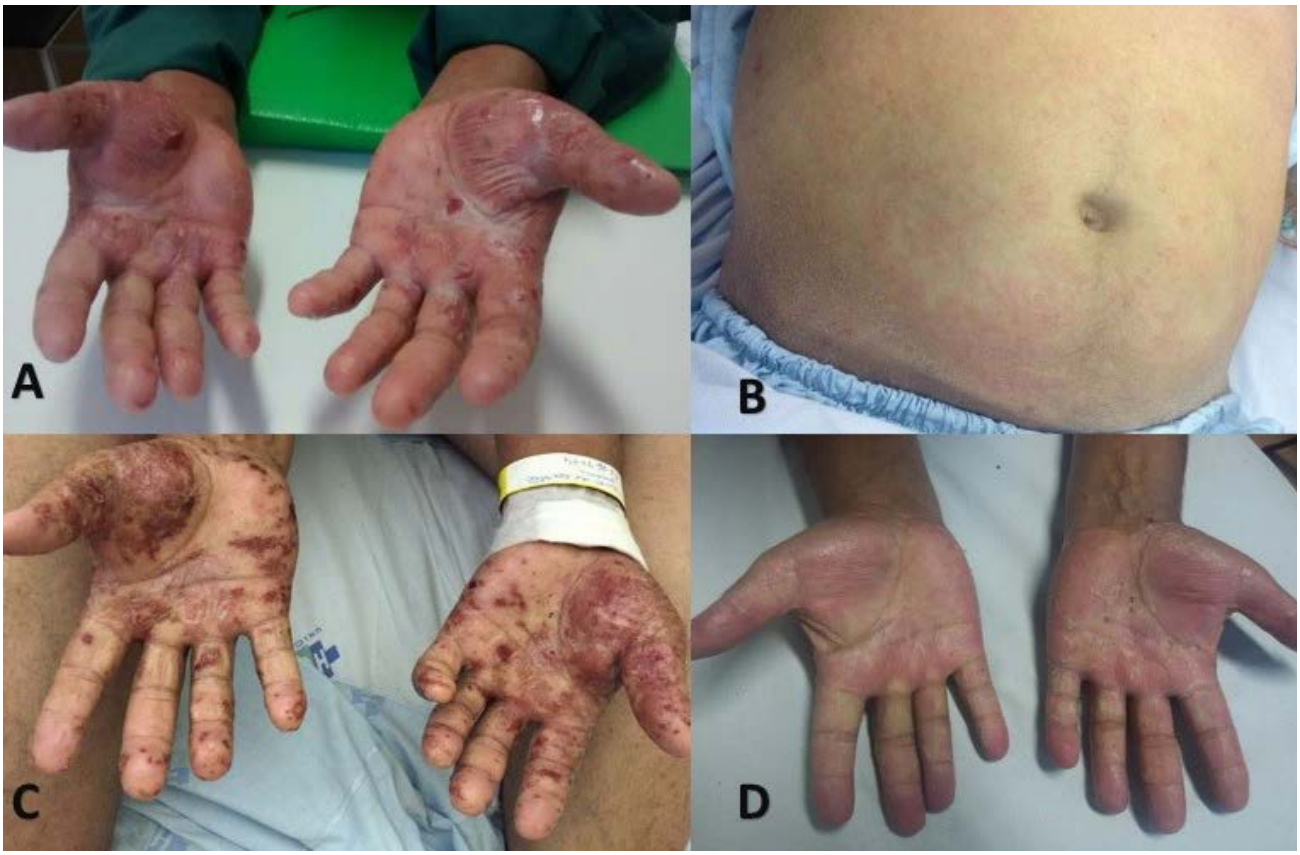

FIGURE 1. A) Erythematous, pruritic, scaly and flaky lesions on hands and B) abdomen (at tenth week of HCV treatment). C) Peeling areas, break blisters, skin fissures with bleeding and signs of secondary infection on hands (one week after the end of HCV treatment). D) Improvement of skin lesions after one week of a higher dose of prednisone and intravenous antibiotic.

< 1.25). The HCV Viral load was of 6.91 log and serum cryoglobulin was positive, without previous clinical manifestations.

He started the all oral HCV treatment with sofosbuvir 400mg / day + simeprevir 150mg /day + ribavirin 1g /day (14 mg/kg), planned for twelve weeks. At the sixth week of treatment, the hemoglobin level was 9.5 mg/dL and ribavirin dose was reduced to 500 mg per day (7 mg/kg). At the 10th week of treatment, he complained of pruritus in palms, feet soles, bending regions and abdomen, accompanied by scaly lesions in the abdomen and upper limbs. He denied fever, respiratory symptoms, or other complaints. On physical examination, erythematous, pruritic, scaly and flaky lesions on hands, feet and abdomen could be noted (Figures 1A and 1B). A topical corticosteroid and an oral antihistaminic were prescribed, with partial improvement.

One week after the end of treatment, he had diffuse erythroderma, a progression of lesions, blistering in upper and lower limbs, especially in the hands and feet with peeling areas, break blisters, skin fissures with bleeding and signs of secondary infection (Figure 1C).

We started outpatient treatment with oral prednisone 40 mg daily and cephalexin (a first generation cephalosporin) 2g daily. However, the skin lesions worsened, and the patient was referred to the hospital. There were no mucosal injuries, fever, eosinophilia or lymphadenopathy. Hepatic and renal functions were not compromised. He received treatment with intravenous amoxicillin-clavulanate and oral prednisone 60 mg daily (0.8 mg/kg) because of suspected pharmacodermia with infection of skin lesions.

A skin biopsy performed on the left arm injury showed squamous-crust dermatitis, subcorneal spongiform pustule, psoriasiform epidermal hyperplasia and moderate superficial mixed inflammatory infiltrate composed of mononuclear lymphocytes and eosinophils (Figure 2). These findings were compatible with pharmacodermia. There was a progressive improvement of the skin lesions after one week of the intravenous antibiotic therapy and the higher dose of oral prednisone (Figure 1D). The patient was discharged and prednisone was tapered to 10 mg per week until withdrawal.

When actively asked, the patient informed a previous history of pharmacodermia attributed to topiramate one year ago, that was responsive to its suspension combine with oral prednisone 60 mg daily. The HCV RNA was undetectable at the 4th and 12th week after treatment, setting up a sustained virological response.

DISCUSSION

We reported a case of a skin adverse event (AE) during the interferon-free treatment of HCV with sofosbuvir, simeprevir and ribavirin. Adverse events, especially skin related ones, were commonly seen with interferon and the first wave protease inhibitors telaprevir and boceprevir. Real life cohort studies reported an overall severe adverse event rate of 12%, and skin manifestations could be found in up to 57% of patients treated with this interferon-based regimen[7].

Some differential diagnosis should be considered

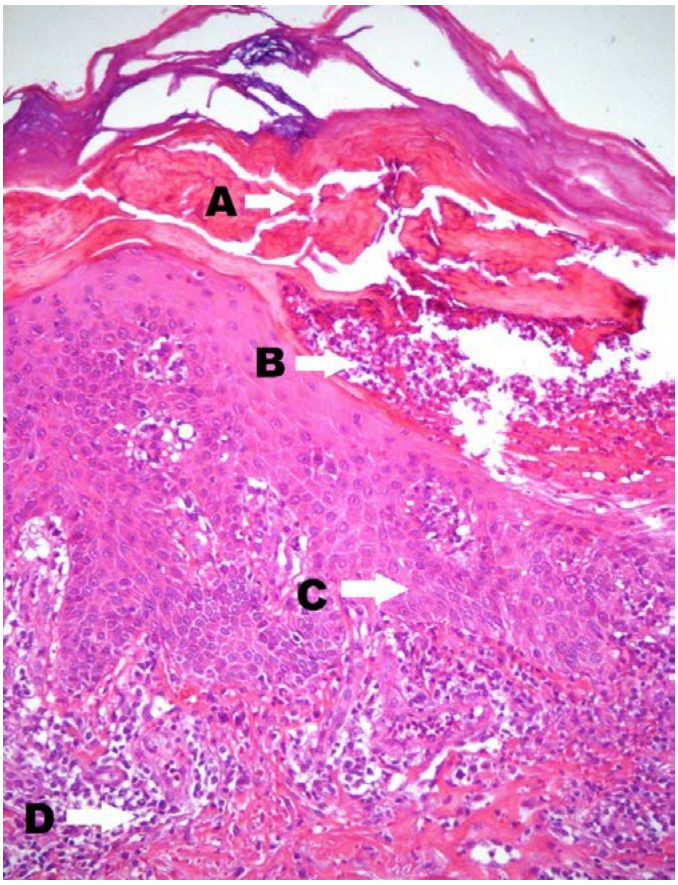

FIGURE 2. Skin biopsy showing squamous-crust dermatitis (arrow A), subcorneal spongiform pustule (arrow B), psoriasiform epidermal hyperplasia (arrow C) and moderate superficial mixed inflammatory infiltrate (arrow D) composed by mononuclear lymphocytes and eosinophils (H&E, 125x). These findings suggest pharmacodermia.

when an HCV patient has cutaneous manifestations, such as cryoglobulinemia, porphyria cutanea tarda, lichen planus, psoriasis, urticaria, erythema multiforme and other types of vasculitis. During antiviral treatment, the possibility of adverse reaction should always be considered, and if there is any doubt, skin biopsy must be performed[8].

A meta-analysis with 4,187 patients treated with pegylated interferon plus ribavirin and one more DAA (telaprevir, boceprevir, simeprevir or sofosbuvir) showed an incidence of skin AE of 44.5%, 25.4%, 23.1% and 20.5%, respectively[3]. New DAAs without interferon are well tolerated and have fewer side effects. Occasionally, it is difficult to assign a symptom to a drug or another. Some adverse effects were related with to sofosbuvir, such as fatigue, headache and renal impairment. With daclatasvir, the most frequent side effects are fatigue, headache and nausea. Simeprevir can lead to skin reactions, photosensitivity and indirect hyperbilirrubinaemia[9]. When ribavirin is associated with these drugs, anemia may be more frequent, as well as skin lesions. Drug interactions are frequent and must be evaluated before prescribing these treatments[2].

In an American real life study with 836 HCV genotype 1 patients treated with sofosbuvir combined with simeprevir, with or without ribavirin, anemia occurred in 29.6%, and fatigue in 26.5%, both more common in the ribavirin group. Serious adverse events occurred in 5.3%, more frequent in cirrhotic patients, which were almost 60% of the study population. No serious skin adverse events were identified. Discontinuation of treatment occurred in 3%[10]. In a Mexican real life study with 81 patients treated with DAAs, 35.8% experienced AEs, mainly anemia, asthenia, and headache. There was no treatment discontinuation due to AEs[11].

Simpson et al.[12] reported two cases of photo-distributed lichenoid eruption attributed to sofosbuvir and simeprevir use (two and four weeks after treatment initiation). One of the patients had a history of vitiligo and allergy to ampicillin and seafood, and none of them had ribavirin on their HCV treatment schedule. Eyre et al.[13] recently also reported a photo-induced skin lesion at the second week of sofosbuvir plus simeprevir treatment in an HCV transplanted patient. She received topical steroids with improvement in the following 14 days and resolution of skin lesions after HCV treatment completion. Wang et al.[14] showed a case of erythema multiforme drug eruption induced by sofosbuvir and daclatasvir in an HCV patient with psoriasis vulgaris and previous history of sulfamethoxazole–trimethoprim allergy. These few case reports highlight skin lesions secondary to DAAs, mainly to sun-exposed areas, and in patients with a history of drug allergy or skin disease prior to HCV therapy initiation.

The management of skin reactions encompasses oral antihistamines and topical corticosteroids. Limited sun exposure, skin hydration and sunscreen use are also important measures. There is usually no need to stop treatment, except in the case of severe adverse reactions, when hospital admission and systemic corticosteroids may be necessary[3]. The risk of anaphylaxis should be previously evaluated, but there is no objective evidence of benefit for prophylactic corticosteroids[15].

Some therapeutic measures have been adopted in different groups of patients with pharmacodermia unrelated to HCV treatment, but we do not know whether these measures can be extrapolated to HCV patients with skin AE due to DAAs. It has been reported that in patients with hand-foot syndrome caused by docetaxel for breast cancer, the use of topical vitamin E was effective, and perhaps the use of oral vitamin E could be promising[16,17]. There are reports of pyridoxine replacement in preventing skin reactions caused by chemotherapy, but a recent meta-analysis concluded that its use is not effective[18]. Instead, celecoxib was effective in preventing moderate to severe skin reactions[18]. In patients with hepatocellular carcinoma treated with sorafenib, vitamin E was able to improve skin lesions without reducing chemotherapy dose[19].

There are no reports of adopting these strategies to prevent skin reactions due to DAAs for HCV treatment. The best approach is not yet known. Physicians should conduct detailed research on the previous history of allergies to choose a safe treatment against HCV.

CONCLUSION

Interferon-free therapies significantly improved HCV management in the recent years. They are usually safe, but can on rare occasions lead to serious adverse reactions, such as skin lesions. Patients receiving ribavirin combinations and those who had a history of pharmacodermia or skin disease may be more susceptible. There is no consensus on how to prevent skin reactions in these patients.

RESUMO

INTRODUÇÃO: *Antivirais de ação direta são as novas drogas utilizadas no tratamento da hepatite C crônica. São geralmente seguros, com boa tolerância, mas eventualmente podem causar efeitos adversos graves, e não há consenso sobre como tratá-los ou preveni-los. Descrevemos um caso de síndrome mão-pé secundária à terapia livre de interferon para hepatite C crônica. Materiais e métodos: Relatamos o caso de um paciente de 49 anos com cirrose hepática compensada secundária à hepatite C crônica, genótipo 1, virgem de tratamento, que iniciou terapia com sofosbuvir, simeprevir e ribavirina por 12 semanas. Resultados: Na sexta semana de tratamento, apresentou anemia, sendo necessária redução de dose da ribavirina. Na 20ª semana, apresentou lesões eritematosas e descamativas, com prurido em mãos e pés, que teve resposta parcial ao uso de anti-histamínico oral e corticoide tópico. Não foi necessário descontinuar os antivirais, mas na primeira semana após o término do tratamento, houve piora das lesões, com sinais de infecção secundária, sendo necessárias hospitalização e terapia com antibiótico e corticoide oral, com melhora progressiva. Biópsias das lesões foram compatíveis com farmacodermia. O paciente teve resposta virológica sustentada, apesar dos efeitos adversos. Tinha história de farmacodermia há um ano, atribuída ao uso de topiramato, responsiva a corticoterapia oral. Conclusão: Os tratamentos livres de interferon raramente causam eventos adversos graves, como lesões cutâneas. Pacientes em uso de ribavirina e com história de farmacodermia ou doença cutânea prévia podem ser mais susceptíveis. Não existe consenso sobre como prevenir reações cutâneas nesses pacientes.*

PALAVRAS-CHAVE: *Hepatite C. Antivirais. Efeitos colaterais e reações adversas relacionados a medicamentos. Síndrome mão-pé.*

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ORIGINAL ARTICLE

Functionality, comorbidity, complication & surgery of hip fracture in older adults by age distribution

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SUMMARY

BACKGROUND: *Hip fractures may be the greatest complication secondary to osteoporotic disorder. The objective of this study was to determine the influence of age distribution in the functionality, comorbidity, complications and surgical features of older adults with hip fractures.*

METHODS: *A prospective cohort study was carried out from 2013 to 2014. A sample of 557 adults over 75 years old with osteoporotic hip fractures was recruited from the Orthogeriatric Unit of the León University Hospital (Spain). Age distributions of 75–84, 85–90 and >90 years old were considered. Firstly, sociodemographic data, fracture type and hospital staying days were collected. Secondly, baseline functionality (Barthel index), ambulation, cognitive impairment and comorbidities were described. Thirdly, surgical intervention, urgency, type, American Association of Anesthesiologists (ASA) scores, non-surgical cause, and baseline pharmacologic treatments were determined. Finally, complications and features at hospital discharge were observed.*

RESULTS: *The age ranges did not show any statistically-significant differences ($P<.05$; $R^2=.000–.005$) for gender, fracture type, or number of hospital staying days. Statistically-significant differences ($P<.05$; $R^2=.011–.247$) between age groups were observed for Barthel index, cognitive impairment, dementia, osteoporosis, Parkinson's disease, aortic stenosis, surgery type, ASA–score, non-surgical cause, benzodiazepines, antidementia, anti-osteoporosis, insulin, pharmacologic treatments, renal function alteration, heart failure, destination and ambulation features. All other measurements did not show statistically-significant differences ($P>.05$; $R^2=.000–.010$).*

CONCLUSION: *Age distributions greater than 75 years old may determine the functionality, comorbidities, surgical features, baseline pharmacologic treatments, complications and features at hospital discharge for older adults who suffer a hip fracture.*

KEYWORDS: *Age Distribution. Frail Elderly. Hip Fractures. Musculoskeletal Diseases.*

INTRODUCTION

Worldwide, hip fractures may be considered as the major complication in terms of morbid-mortality and economic burden secondary to the osteoporotic disorder.[1] Regarding the southern European population, a high prevalence and incidence were observed in Spain, especially regarding trochanteric fractures, female gender and ages over 85 years.[2,3] the community with the highest incidence of HF in Spain. Methods data about age, gender, type of fracture and month of hospitalisation among patients aged 65 years and older discharged with a diagnosis of HF were collected. Crude and age-standardised annual incidence rate were reckoned. To analyse HF trend, the age/sex-adjusted average annual change in incidence (incidence rate ratio, IRR Furthermore, the relationship between age and mortality after a hip fracture in older adults may reach 5.5% and can be associated with several comorbidities, such as con-

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gestive heart failure, metastasis, fluid and electrolyte disorders, coagulation deficiencies, or liver disease.[4]

Indeed, older adults who suffered hip fractures in a hospital may present a worse surgical (grade III and IV of the American Association of Anesthesiologists – ASA score) and mortality risk than those who suffered hip fractures in the community.[5] Medical treatments associated to hip fracture can comprise conservative or invasive procedures.[6] The conservative treatment may produce a high rate of mobility, mortality and local complications.[7] Whereas, surgical intervention (overall hemiarthroplasty and total hip arthroplasty) may be the first line of treatment in older adults with a hip fracture, since it allows for an earlier mobilization and reduces complications such as respiratory, infection, circulatory or wound conditions.[8]

After a hip fracture, older adults showed the reductions in quality of life and functionality due to associated balance and mobility impairments. Consequently, this suggested that the majority of these older adults did not return to their pre-fracture lifestyle.[9] Therefore, the objective of this study was to determine the influence of age distribution in the functionality, comorbidity, complications and surgical features of hip fractures in older adults.

METHODS

Design

A prospective cohort study was carried out from December 2013 to November 2014. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were considered.[10]

Ethical considerations

The study was approved by the Clinical Research Ethics Committee of the León University (Spain; code ÉTICA-ULE-004-2015). An informed written consent form was obtained from all participants before their inclusion in the research study. Furthermore, the Helsinki Declaration, Protection Data Organic Law (15/1999) and ethical standards in human experimentation were respected.

Sample size

Based on the hip fracture incidence in Spain, Azagra et al.[11] showed a similar rate of 517 new hip fractures from 100,000 older adults per year. Considering the assumed 4% error for a possible loss in follow-up, 534 participants were necessary to justify the sample size.

Participants

A sample of 557 older adults with hip fracture was recruited from the Traumatology Unit of the León University Hospital, León (Spain). A consecutive sampling method was used to select the participants in the present study.

The inclusion criteria were: adults over 75 years old who suffered an osteoporotic hip fracture from December 1st of 2013, to November 31 of 2014 recruited from the Orthogeriatric Unit of the León University Hospital.[1]

The exclusion criteria were: pathological fractures secondary to other conditions different from osteoporosis (such as neoplasia or osteomyelitis),[12] traumatic fractures,[13]treatment type, and inpatient mortality of traumatic hip fractures are important health policy issues. We showed that insurance status and treatment in university hospitals were significantly associated with treatment type (i.e., primary hip replacement or periprosthetic fractures.[14]

Procedure ant outcomes

All data were extracted from the medical records by the same authorized investigator (SJM). Age distributions of 75-84, 85-90 and > 90 years old were considered.[4] Firstly, data on sociodemographic (age and gender), fracture type (subcapital or pertrochanteric fractures), total number of hospital staying days and before the surgery were collected.[8]

Secondly, baseline functionality, based on the Barthel index (total, severe, moderate, slight or no dependence),[15] ambulation (independence/1 stick; walker/2 sticks; high assistance; not walk),[16] and cognitive impairment (severe, moderate, slight and no impairment),[17]65 years or older, with a hip fracture. Mobility and Cognitive status were measured by Tinetti Performance-Oriented Mobility Assessment and Pfeiffers' Scale (Short Portable Mental State Questionnaire as well as comorbidities (cardiopathy, hypertension, depression, dementia, diabetes, osteoarthritis, atrial fibrillation, visual impairment, ictus, chronic renal failure, chronic obstructive pulmonary disease, cancer, multiple falls, anemia, osteoporosis, peripheral vascular disease, ischemic heart disease, prior hip fracture, Parkinson's disease, dysphagia and aortic stenosis) were described.[4]

Thirdly, surgical features such as surgical intervention, surgical urgency, surgery type (nail, partial bipolar prosthesis, monopolar prosthesis, total prosthesis and screws),[8] ASA scores (II – Moderate Systemic Disease; III – Severe Non-disabling Systemic Disease; IV – Severe Vital-risk Systemic Disease),[18] and non-surgical cause (death, orthopedic care, high surgical risk and hospital transfer),[5] as well as baseline pharmacologic treatments (anti-hypertensives, benzodiazepines, antidepressants, proton-pump inhibitors, antiplatelets, anticoagulants, oral antidiabetic agents, analgesics, antidementia, neuroleptics, anti-osteoporosis, bronchodilators, domiciliary Oxygen, anti-Parkinsonians and Insulin) were determined.[19]

Finally, complications (anemia, transfusion, delirium, constipation, renal function alteration, urinary tract infection, infection or respiratory insufficiency, malnutrition, heart failure, acute retention of urine, ischemic heart disease, death, pressure ulcers, seroma, surgical wound infection, ictus, venous thrombosis or thromboembolism),[20] and features at hospital discharge (destination, home move, ambulation and discharge) were observed.[21]

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package SPSS 22.0 (IBM SPSS Inc., Chicago. IL, USA). A confidence interval (CI) of 95% and a *P*-value < .05 were considered statistically significant. The sample was divided into 3 age distributions (75-84, 85-90 and > 90 years old) in order to determine differences between these groups.[4] Initially, normality analysis were performed by the Kolmogorov-Smirnov test. Then, a descriptive analysis of the data was carried out. For the quantitative variables, the mean and standard deviation (SD) as well as the one-factor analysis of variance (ANOVA) were calculated for the total number of hospital staying days and before surgery. For the rest of qualitative outcomes, percentage and frequency as well as the Chi-square (χ^2) test were used. The effect size was calculated by the R^2 coefficient (slight ~ .050; moderate ~ .150; high ~ .250; large ~ .360; and very large ~ .450).[22]

RESULTS

A sample of 557 participants with hip fractures were received during the follow-up. Periprosthetic fractures (n = 19) and pathological fractures (n = 4) were excluded. From the remaining participants (n = 534), 31 (5.8%) older adults expired during admission, and 6 (1.1%) were referred to a different hospital for the intervention (n = 497). Age distributions of 75-84 (n = 189; 46 men and 143 women; 94 subcapital and 95 pertrochanteric fractures), 85-90 (n = 180; 47 men and 133 women; 78 subcapital and 102 pertrochanteric fractures) and > 90 (n = 165; 42 men and 123 women; 68 subcapital and 97 pertrochanteric fractures) did not show any statistically-significant differences for gender (χ^2 = 0.16; *P* = .924; R^2 = .000) or fracture type (χ^2 = 2.87; *P* = .238; R^2 = 0.005), as well as for total of hospital staying days (F = 0.08; *P* = .921; R^2 = .000), mean (SD) varied from 11.15 (6.12) to 11.43 (7.84) days, and before surgery (F = 0.32; *P* = .726; R^2 = .001), mean (SD) varied 5.76 (3.52) from to 6.13 (4.70) days.

Regarding baseline functionality and comorbidities (Table 1), statistically-significant differences between age distributions were observed for Barthel index (χ^2 = 35.06; *P* < .001; R^2 = .062), cognitive impairment (χ^2 = 31.28; *P* = < .001; R^2 = .055), dementia (χ^2 = 8.60; *P* = .014; R^2 = .016), osteoporosis (χ^2 = 6.07; *P* = .048; R^2 = .011), Parkinson's disease (χ^2 = 6.35; *P* = .048; R^2 = .012) and aortic stenosis (χ^2 = 7.08; *P* = .029; R^2 = .013). All other measurements did not show any statistically-significant difference (*P* > .05; R^2 = .000 – .007).

Considering surgical features and baseline pharmacologic treatments (Table 2), statistically-significant differences between age ranges were found for surgery type (χ^2 = 88.34; *P* < .001; R^2 = .151), ASA score (χ^2 = 12.22; *P* = .016; R^2 = .023), non-surgical cause (χ^2 = 14.53; *P* = .024; R^2 = .247), benzodiazepines (χ^2 = 13.29; *P* = .001; R^2 = .025), antidementia (χ^2 = 6.77; *P* = .034; R^2 = .013), anti-osteoporosis (χ^2 = 5.60; *P* = .049; R^2 = .011) and insulin (χ^2 = 9.51; *P* = .009; R^2 = .018) pharmacologic treatments. The rest of measurements did not show any statistically significant difference (*P* > .05; R^2 = .000 – .010).

With respect to complications and features at hospital discharge (Table 3), statistically-significant differences between age groups were observed for renal function alteration (χ^2 = 8.99; *P* = .011; R^2 = .017), heart failure (χ^2 = 7.08; *P* = .029; R^2 = .013), destination (χ^2 = 19.22; *P* = .004; R^2 = .038) and ambulation (χ^2 = 19.14; *P* = .004; R^2 = .037) features. All other measurements did not show any statistically significant difference (*P* > .05; R^2 = .001 – .009).

TABLE 1. BASELINE FUNCTIONALITY AND COMORBIDITIES OF OLDER ADULTS WITH HIP FRACTURE BY AGE DISTRIBUTION.

Outcomes	Category (N=189) 75 – 84	Age distribution (y) (N=180) 85 – 90	(N=165) > 90		χ^2	Df	P†	Effect size R^2
Functionality								
BARTHEL	Total dependence	8.5% (16)	15.6% (28)	12.1% (20)	35.06	8	.000**	.062
	Severe dependence	16.4% (31)	22.8% (41)	17.6% (29)				
	Moderate dependence	26.5% (50)	26.1% (47)	37.6% (62)				
	Slight dependence	3.7% (7)	6.1% (11)	11.5% (19)				
	Independence	45.0% (85)	29.4% (53)	21.1% (35)				
Ambulation	Independence/1 stick	68.8% (130)	62.2% (112)	61.8% (102)	5.76	6	.451 NS	.011
	Walker/2 sticks	24.3% (46)	25.6% (46)	28.5% (47)				
	High assistance	3.7% (7)	7.2% (13)	7.3% (12)				
	Not walk	3.2% (6)	5.0% (9)	2.4% (4)				
Cognitive impairment	No impairment	70.4% (133)	43.9% (79)	49.1% (81)	31.28	6	.000**	.055
	Slight	11.6% (22)	25.0% (45)	25.5% (42)				
	Moderate	14.8% (28)	25.0% (45)	21.8% (36)				
	Severe	3.2% (6)	6.1% (11)	3.6% (6)				
Comorbidities								
Cardiopathy	400	72.5% (137)	77.2% (139)	75.2% (124)	1.11	2	.575 NS	.002
Hypertension	377	67.7% (128)	71.1% (128)	73.3% (121)	1.37	2	.504 NS	.003
Depression	158	29.1% (55)	31.7% (57)	27.9% (46)	0.63	2	.731 NS	.001
Dementia	132	18.0% (34)	31.1% (56)	25.5% (42)	8.60	2	.014 *	.016
Diabetes	127	27.5% (52)	24.4% (44)	18.8% (31)	3.77	2	.152 NS	.007
Osteoarthritis	117	24.9% (47)	20.6% (37)	20.0% (33)	1.51	2	.470 NS	.003
Atrial fibrillation	107	21.2% (40)	21.1% (38)	17.6% (29)	0.90	2	.637 NS	.002
Visual impairment	89	13.8% (26)	18.3% (33)	18.2% (30)	1.79	2	.410 NS	.003
Ictus	85	16.4% (31)	15.6% (28)	15.8% (26)	0.05	2	.973 NS	.000
Chronic renal failure	83	13.2% (25)	18.3% (33)	15.2% (25)	1.86	2	.395 NS	.003
COPD	82	18.0% (34)	16.7% (30)	10.9% (18)	3.76	2	.153 NS	.007
Cancer	72	13.2% (25)	11.7% (21)	15.8% (26)	1.25	2	.535 NS	.002
Multiple falls	62	13.2% (25)	11.7% (21)	9.7% (16)	1.07	2	.585 NS	.002
Anemia	61	10.1% (19)	10.0% (18)	14.5% (24)	2.30	2	.317 NS	.004
Osteoporosis	58	14.8% (28)	10.6% (19)	6.7% (11)	6.07	2	.048 *	.011
Peripheral vascular disease	56	11.1% (21)	7.8% (14)	12.7% (21)	2.37	2	.306 NS	.004
Ischemic heart disease	46	9.5% (18)	8.9% (16)	7.3% (12)	0.59	2	.743 NS	.001
Prior hip fracture	38	6.3% (12)	7.2% (13)	7.9% (13)	0.32	2	.854 NS	.001
Parkinson's disease	28	5.8% (11)	7.8% (14)	1.8% (3)	6.35	2	.042 *	.012
Dysphagia	17	2.1% (4)	3.9% (7)	3.6% (6)	1.10	2	.577 NS	.002
Aortic stenosis	13	4.8% (9)	1.7% (3)	0.6% (1)	7.08	2	.029 *	.013

NS = Non statistically significant different with P > .05. *Statistically significant differences with $P < 0.05$. ** = Statistically significant differences with $P < 0.01$. † = Chi square test (χ^2) was applied, Bold numbers determine the most significant contribution. Abbreviations: COPD, chronic obstructive pulmonary disease; Df, degrees of freedom.

DISCUSSION

The present study supports novel evidence on functionality, comorbidity, complications and surgical features of hip fractures in older adults over 75 years old by age distribution. It determines the key points to consider in the aging process of older adults during and after hip fracture. All sociodemographic data, fracture type and hospital staying days were representative of the general population of Spain and in accordance to prior studies.[11,23,24]

Considering baseline functionality and comorbidities (Table 1), there were only slight effects observed for the Barthel index, cognitive impairment, dementia, osteoporosis, Parkinson's disease and aortic stenosis. Therefore, independence, osteoporosis, aortic

TABLE 2. SURGICAL FEATURES AND BASELINE PHARMACOLOGIC TREATMENTS OF OLDER ADULTS WITH HIP FRACTURE BY AGE DISTRIBUTION.

Outcomes 75 – 84	Category / n 85 – 90	Age distribution (y) > 90			χ^2	Df	P†	Effect size R^2
Surgical characteristics								
Surgery	Sí	92.6% (175)	96.1% (173)	91.5% (151)	3.32	2	.190 NS	.006
Surgical urgency	Sí	12.7% (24)	14.4% (26)	12.1% (20)	0.45	2	.798 NS	.001
Surgery type	Nail	49.7% (87)	56.5% (98)	59.6% (90)	88.34	8	.000**	.151
	Partial bipolar prosthesis	28.6% (50)	34.1% (59)	19.9% (30)				
	Monopolar prosthesis	1.1% (2)	5.2% (9)	17.9% (27)				
	Total prosthesis	16.0% (28)	0.6% (1)	--				
	Screws	4.6% (8)	3.5% (6)	2.6% (4)				
ASA scores	II – Grade	31.9% (60)	21.7% (39)	18.2% (30)	12.22	4	.016 *	.023
	III – Grade	53.7% (101)	67.2% (121)	68.5% (113)				
	IV – Grade	14.4% (27)	11.1% (20)	13.3% (22)				
Non-surgical cause	Death (n=15)	28.6% (4)	42.9% (3)	57.1% (8)	14.53	6	.024 *	.247
	Orthopedic care (n=7)	7.1% (1)	42.9% (3)	21.5% (3)				
	High surgical risk (n=7)	28.6% (4)	0%	21.4% (3)				
	Hospital transfer (n=6)	35.7% (n=5)	14.3% (n=1)	0%				
Pharmacologic treatments at baseline								
Anti-hypertensives	390	68.3% (129)	75.6% (136)	75.8% (125)	3.40	2	.183 NS	.006
Benzodiazepines	189	30.7% (58)	30.0% (54)	46.7% (77)	13.29	2	.001**	.025
Antidepressants	171	32.8% (62)	35.6% (64)	27.3% (45)	2.80	2	.247 NS	.005
Proton-pump inhibitors	157	28.0% (53)	30.6% (55)	29.7% (49)	0.29	2	.865 NS	.001
Antiplatelets	150	24.3% (46)	33.9% (61)	26.1% (43)	4.65	2	.098 NS	.009
Anticoagulants	100	20.1% (38)	21.1% (38)	14.5% (24)	2.80	2	.246 NS	.005
Oral antidiabetic agents	96	21.2% (40)	15.6% (28)	17.0% (28)	2.13	2	.345 NS	.004
Analgesics	94	22.2% (42)	15.0% (27)	15.2% (25)	4.31	2	.116 NS	.008
Antidementia	63	12.7% (24)	15.6% (28)	6.7% (11)	6.77	2	.034 *	.013
Neuroleptics	52	8.5% (16)	11.7% (21)	9.1% (15)	1.19	2	.552 NS	.002
Anti-osteoporosis	44	12.2% (23)	6.1% (11)	6.1% (10)	5.60	2	.049 *	.011
Bronchodilators	40	7.9% (15)	7.8% (14)	6.7% (11)	0.24	2	.888 NS	.000
Domiciliary Oxygen	28	4.8% (9)	6.7% (12)	4.2% (7)	1.16	2	.561 NS	.002
Anti-Parkinsonians	28	6.3% (12)	7.2% (13)	1.8% (3)	5.78	2	.056 NS	.010
Insulin	24	7.9% (15)	3.9% (7)	1.2% (2)	9.51	2	.009**	.018

NS = Non statistically significant different with $P > .05$. *Statistically significant differences with $P < 0.05$. ** = Statistically significant differences with $P < 0.01$. † = Chi square test (χ^2) was applied, Bold numbers determine the most significant contribution. Abbreviations: ASA, American Association of Anesthesiologists – ASA scores (II – Moderate Systemic Disease; III – Severe Non-disabling Systemic Disease; IV – Severe Vital-risk Systemic Disease); Df, degrees of freedom.

stenosis and Parkinson's disease may be more frequent in younger age distributions of older adults, while cognitive impairment and dementia seemed to be presented in older adults over 85 years old, coinciding with previous researches.[4,15,17] Furthermore, Parkinson's disease may decrease in the older elderly patients, since it may be considered a neurodegenerative condition with associated life expectative reduction.[25]

Regarding surgical features and baseline pharmacologic treatments (Table 2), high effects were observed for surgery type, non-surgical cause, and insulin pharmacologic treatment, while slight effects were determined for ASA score, benzodiazepines, antidementia and anti-osteoporosis drugs. Partial bipolar prosthesis and monopolar prosthesis seemed to be more common in older adults over 90.[8] Moreover, the IV – ASA score did not seem to variate with age distribution. Nevertheless, the II and III – ASA scores may be associated with 75-84 and 85-90 age groups, respectively. Therefore, increased age is not associated with higher surgical risk in geriatric hip fracture patients.[24] Anti-dementia and benzodiazepines may be more frequent in nonagenarian patients, while anti-osteoporosis and insulin seemed to be more common in the 75-84 age group. In this

TABLE 3. COMPLICATIONS AND FEATURES AT HOSPITAL DISCHARGE OF OLDER ADULTS WITH HIP FRACTURE BY AGE DISTRIBUTION.

Outcomes	N (N=189) 75 – 84	Age distribution (y)			χ^2	Df	P†	Effect size R^2
		(N=180) 85 – 90	(N=165) > 90					
Complicaciones								
Anemia	469	88.4% (167)	85.0% (153)	90.3% (149)	2.34	2	.310 NS	.004
Transfusion	208	36.5% (69)	40.0% (72)	40.6% (67)	0.75	2	.688 NS	.001
Delirium	196	30.7% (58)	38.9% (70)	41.2% (68)	4.76	2	.093 NS	.009
Constipation	117	24.9% (47)	17.2% (31)	23.6% (39)	3.57	2	.168 NS	.007
Renal function alteration	94	13.2% (25)	15.6% (28)	24.8% (41)	8.99	2	.011 *	.017
Urinary tract infection	81	12.7% (24)	16.1% (29)	17.0% (28)	1.44	2	.488 NS	.003
Infection / Respiratory insufficiency	79	13.2% (25)	13.3% (24)	18.2% (30)	2.18	2	.337 NS	.004
Malnutrition	74	14.8% (28)	12.2% (22)	14.5% (24)	0.61	2	.736 NS	.001
Heart failure	64	9.5% (18)	9.4% (17)	17.6% (29)	7.08	2	.029 *	.013
Acute retention of urine	50	8.5% (16)	10.0% (18)	9.7% (16)	0.29	2	.866 NS	.001
Ischemic heart disease	39	9.5% (18)	7.8% (14)	4.2% (7)	3.72	2	.156 NS	.007
Death	31	4.8% (9)	3.9% (7)	9.1% (15)	4.84	2	.089 NS	.009
Pressure ulcers	21	5.3% (10)	2.2% (4)	4.2% (7)	2.36	2	.307 NS	.004
Seroma	9	2.6% (5)	0.6% (1)	1.8% (3)	--	--	--	--
Surgical wound infection	4	1.1% (2)	0.6% (1)	0.6% (1)	--	--	--	--
Ictus	3	1.1% (2)	0%	0.6% (1)	--	--	--	--
Venous thrombosis/Thromboembolism	2	0%	0%	1.2% (2)	--	--	--	--
Features at hospital discharge								
Destination	Concerted care center	31.6% (55)	27.6% (47)	37.3% (56)	19.22	6	.004**	.038
	Nursing home	25.3% (44)	33.5% (57)	35.3% (53)				
	Family home	17.2% (30)	22.9% (39)	17.3% (26)				
	Own home	25.9% (45)	15.9% (27)	10.0% (15)				
Home move	Yes	10.3% (18)	11.1% (19)	8.0% (12)	4.35	4	.361 NS	.009
	No	58.6% (102)	62.0% (106)	54.7% (82)				
	Hospital concerted center	31.0% (54)	26.9% (46)	37.3% (56)				
Ambulation	Independence/1 stick	1.7% (3)	0%	0%	19.14	6	.004**	.037
	Walker/2 sticks	41.1% (72)	32.0% (55)	22.7% (34)				
	High assistance	22.9% (40)	25.6% (44)	29.3% (44)				
	Not walk	34.3% (60)	42.4% (73)	48.0% (72)				
Discharge	Yes	14.9% (26)	9.3% (16)	16.0% (24)	3.71	2	.157 NS	.007

NS = Non statistically significant different with $P > .05$. *Statistically significant differences with $P < 0.05$. ** = Statistically significant differences with $P < 0.01$. † = Chi square test (χ^2) was applied, Bold numbers determine the most significant contribution. Abbreviations: Df, degrees of freedom.

sense, some authors have claimed a higher risk of hip fracture in older adults with hypnotic pharmacologic treatment.[26]

Finally, complications and features at hospital discharge (Table 3) showed only slight effects for renal function alteration, heart failure, destination and ambulation features. Coinciding with this, other authors reported kidney function alteration as a frequent complication in older adults with hip fracture.[27] Additionally, ambulation and lifestyle characteristics may be more dependent in the nonagenarian patients as it was reported by previous authors.[28]

Some limitations should be considered in the present study; despite the age distributions over 75 years old seemed to show the greatest prevalence of hip fracture and presented a similar number among participants in our study, the considered age ranges were not equal.[1] Indeed, the follow-up after hospital discharge was not carried out. Therefore, rehabilitation, complications and pharmacologic treatments

after hospital discharge were not collected. New cohort studies may be necessary in order to describe the status of older adults with hip fracture during the rehabilitation phase.[29] Furthermore, this study did not consider the presence of musculoskeletal alterations in the lower limb such as the myofascial pain syndrome associated to hip fracture.[30] Further interventional studies may be necessary to improve the clinical features of older adults with muscle conditions associated to hip fracture, according to prior studies in other body regions.[31]

In conclusion, age distributions over 75 years old may determine the functionality, comorbidities, surgical features, baseline pharmacologic treatments, complications and features at hospital discharge for older adults who suffer a hip fracture.

RESUMO

CONTEXTO:*As fraturas do quadril podem ser a maior complicação secundária à doença osteoporótica. O objetivo deste estudo foi determinar a influência da distribuição etária na funcionalidade, comorbidade, complicações e características cirúrgicas de idosos com fratura de quadril.*

MÉTODOS: *Um estudo prospectivo de coorte foi realizado de 2013-2014. Uma amostra de 557 adultos mais velhos, com mais de 75 anos, com fratura de quadril osteoporótica foi recrutada na Unidade Ortogeriátrica do Hospital Universitário de León (Espanha). As distribuições de idade de 75-84, 85-90 e >90 anos foram consideradas. Em primeiro lugar, foram coletados dados sociodemográficos, tipo de fratura e dias de permanência hospitalar. Em segundo lugar, foram descritas funcionalidades de base (índice Barthel), ambulação, comprometimento cognitivo e comorbidades. Em terceiro lugar, determinaram-se a intervenção cirúrgica, a urgência, o tipo, os resultados da Associação Americana de Anestesiologistas (ASA), a causa não cirúrgica e os tratamentos farmacológicos iniciais. Finalmente, foram observadas complicações e características na alta hospitalar.*

RESULTADOS: *As faixas etárias não mostraram diferenças estatisticamente significativas (P <,05; R^2 = ,000-,005) para sexo, tipo de fratura ou dias de permanência hospitalar. Foram apresentadas diferenças estatisticamente significativas (P <,05; R^2 = ,011-,247) para o índice de Barthel, comprometimento cognitivo, demência, osteoporose, doença de Parkinson, estenose aórtica, tipo de cirurgia, pontuação ASA, causa não cirúrgica, benzodiazepínicos, antidementia, antiosteoporose, insulina, tratamentos farmacológicos, alteração da função renal, insuficiência cardíaca, destino e características de ambulação entre grupos etários. O restante das medidas não apresentou diferença estatisticamente significativa (P> 0,05; R^2 = ,000-,010).*

CONCLUSÃO: *As distribuições de idade após 75 anos podem determinar a funcionalidade, comorbidades, características cirúrgicas, tratamentos farmacológicos de base, complicações e características na alta hospitalar de adultos mais velhos que sofrem fratura de quadril.*

PALAVRAS-CHAVE: *Distribuição por idade. Idosos fragilizados. Fraturas do quadril. Doenças musculoesqueléticas.*

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ORIGINAL ARTICLE

Mecobalamin and early functional outcomes of ischemic stroke patients with H-type hypertension

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SUMMARY

OBJECTIVE: *To analyze the effect of mecobalamin on the early-functional outcomes of patients with ischemic stroke and H-type hypertension.*

METHODS: *From October of 2014 to October of 2016, 224 cases of ischemic stroke and H-type hypertension were selected. The patients were randomly divided into treatment control groups, with 112 patients in each group. The control group was treated with the conventional therapy. The observation group was treated with 500 μg of mecobalamin three times a day in addition to the conventional therapy. We compared serum homocysteine (Hcy), hs-CRP levels, carotid plaques, and NIHSS scores between the two groups on the 2nd day and at 4 weeks, 8 weeks, 3 months, and 6 months.*

RESULTS: *After 4 weeks, 8 weeks, 3 months and 6 months, the difference of serum Hcy level between the two groups was statistically significant (t = 4.049, 3.896, 6.052, 6.159, respectively. All P <0.05). After the treatment, at 4 weeks, 8 weeks, 3 months and 6 months, the levels of hs-CRP in the treatment group were significantly lower than those in the control group (t = 37.249, 28.376, 26.454, 20.522, respectively. All P <0.01). After 3 months and 6 months, the carotid artery plaques were significantly reduced in the treatment group compared to those in the control group (t = 2.309 and 2.434. All P <0.05). After 3 months and 6 months, the NIHSS score was significantly higher in the treatment group compared to those in the control group (t = 2.455 and 2.193. All P <0.05).*

CONCLUSION: *Mecobalamin can reduce the level of plasma homocysteine, then lead to reductions of levels of plasma inflammatory factors and volume of carotid artery plaques, resulting in more significant functional recovery.*

KEYWORDS: *Stroke. Homocysteine. Hypertension. Vitamin B 12/Analogs & Derivatives.*

1. INTRODUCTION

H-type hypertension is defined as hypertension with plasma homocysteine (Hcy) levels over 10 μmol / L [1-3]. Previous studies have shown that only 5% of the average population has an increase in plasma Hcy levels. However, in the stroke patient population, approximately 30-40% has Hcy level increases[4]. In addition, H-type hypertension is closely related to ischemic stroke and cerebral infarction [5]. As a common neurological disease, ischemic stroke has high incidence, recurrence, mortality rates and has become a serious threat to patient's health and life in recent years. Previous studies have shown that the underlying relationship mechanism between a high plasma Hcy level and ischemic stroke is that Hcy causes inflammation and increases carotid artery plaques [6,7].

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Mecobalamin (methyl-vitamin B12) belongs to the vitamin B group and is one of the active analogs of vitamin B12. It is the essential cofactor for methionine synthase. Deficiency in folic acid and vitamin B12 leads to the elevation of the plasma homocysteine level, which is considered an independent risk factor in the pathogenesis of atherosclerosis [8], acute myocardial infarction [9], stroke [10], and hypertension [11]. However, to date, there is no study investigating the effects of mecobalamin on the early functional outcomes of ischemic stroke patients with H-type hypertension. In the present study, in order to analyze the impact of mecobalamin on the prognosis of patients with H-type hypertension and ischemic stroke, we enrolled a total of 400 patients with H-type hypertension and ischemic stroke from October of 2014 to October of 2016. The data were analyzed and reported as follows.

2. PATIENTS AND METHODOLOGY

2.1 Patients

We selected 400 cases of hypertension and ischemic stroke from October of 2014 to October of 2016 in our hospital. Out of the patients selected, 220 were male and 180 female, with an average age of 78. Then, 224 cases of ischemic stroke and H-type hypertension were randomly divided into the treatment and control groups, with 112 cases in each. The inclusion criteria were: (1) Age ≥ 60 years old; (2) Blood pressure ≥ 140 / 90mmHg; (3) Have education of junior high school or above; (4) No history of stroke; (5) No infection within 2 weeks. Exclusion criteria were: (1) Other neurological disorders that can cause dementia, such as epilepsy, Parkinson, brain trauma, intracranial tumors, infections, or toxic encephalopathy; (2) History of depression confirmed with the American Psychiatric Association Mental Disorders Diagnostic and Statistical Manual (DSM-IV); (3) Family history of other mental diseases; (4) History of alcohol and psychoactive drug abuse and dependence; (5) Use of drugs that affect brain function within two weeks.

In the treatment group, 62 patients were male and 50 were female, aged between 61 and 92, with an average of 77.8 years old. In the control group, 62 patients were male and 50 were female, aged between 62 and 79, with an average age of 78.1 years old. There was no significant difference in gender, age, and other clinical characteristics between the two groups (all P> 0.05).

2.2 Methodology

All patients in both groups were routinely given drugs to inhibit platelet aggregation, to stabilize and reduce plaques, and to improve cerebrovascular circulation and perfusion. The treatment group was treated with mecobalamin (Nippon Eisai Co., Ltd. Tokyo, Japan. Batch number: 111068) with 500 μg, 3 times a day, for 6 months.

2.3 Measurements

All patients were drawn morning fasting venous blood on the 2nd day, at 4 weeks, 8 weeks, 3 months, and 6 months to measure plasma levels of Hcy and hs-CRP. In addition, carotid artery plaques were measured using carotid intima-media thickness (IMT) by ultrasound examination (ATL HDI 3000 color Doppler ultrasound system, Philips Co., Ltd, Amsterdam, Holland). The carotid IMT is defined as the distance between the endometrial lumen interface and the media external membrane interface. The bilateral carotid arteries were measured at 10, 20, and 30 mm from the proximal end of the common carotid artery bifurcation, both for the anterior and posterior walls. A total of 12 measurement values were obtained and the average value was calculated as the IMT of the common carotid artery. IMT <1.0 mm was consider normal; IMT 1.0 ~ 1.1 mm was considered intimal thickening; IMT> 1.2 mm was considered plaque. In addition, according to ultrasound characteristics, the plaques were classified into soft, hard, and mixed. The soft plaque was defined as medium or weak echo with intimal convexing to the cavity; The hard plaque was defined as strong echo accompanied by significant sound shadow; The mixed plaque was defined as strong echo, weak or no echoes, with irregular shape and rough surface. Soft and mixed plaques are considered unstable, while hard plaque is considered stable. In addition, the National Institute of Health stroke scale (NIHSS) and Barthel index (BI) were measured [12].

2.4 Statistical analysis

IBM SPSS 17.0 statistical software was used to analyze data. Continuous data were expressed as the mean ± standard deviation (SD). Categorical data were expressed as percentages. All the tests were performed using a two-sided test of difference, where the inspection level α of 0.05 and a difference with P < 0.05 were considered statistically significant.

3. RESULTS

3.1 Comparison of plasma Hcy levels before and after treatment in both groups

There was no significant difference in plasma Hcy level in the control group (all P > 0.05). After 4 weeks, 8 weeks, 3 months and 6 months, the difference in plasma Hcy levels between the two groups were statistically significant. The plasma Hcy levels in the treatment group were significantly lower than those in the control group (t = 4.049, 3.896, 6.052, 6.159, respectively. All P <0.05). See Table 1.

TABLE 1 THE COMPARISON OF PLASMA HCY LEVELS BETWEEN THE CONTROL AND TREATMENT GROUPS (X±S, μMOL / L)

Group	2nd day	4th week	8th week	3rd month	6th month
Control	26.5±9.1	27.0±8.6	25.8±9.5	25.7±10.2	24.9±11.3
Treatment	27.0±9.2	18.2±6.3	16.6±6.6	11.5±5.3	8.6±6.2
t	0.189	4.044	3.896	6.052	6.195
p	0.851	0.000	0.000	0.000	0.000

3.2 Comparison of plasma hs-CRP levels before and after treatment in both groups

There was no significant difference in plasma hs-CRP levels in the control group (all P > 0.05). After 2 days, 4 weeks, 8 weeks, 3 months and 6 months, the difference in plasma hs-CRP levels between the two groups were statistically significant. The plasma hs-CRP levels in the treatment group were significantly lower than those of the control group (t =4.330, 37.249, 28.376, 26.454, 20.522, respectively. All P <0.05). See Table 2.

3.3 Comparison of IMTs before and after treatment in both groups

There was no significant difference in IMTs in the control group (all P > 0.05). After3 months and 6 months, the difference of IMTs between the two groups were statistically significant. The IMTs in the treatment were significantly lower than those of the control group (t = 2.309 and 2.434, respectively. All P <0.05). See Table 3.

3.4 Comparison of NIHSS and BI scores before and after treatment in both groups

After 3 months and 6 months, the difference of NIHSS and BI scores between the two groups were statistically significant. After 3 and 6 months of treatment, the NIHSS scores of the treatment group were 17.68 ± 5.28 and 15.45 ± 5.45, respectively, which were significantly better than those of the control group (22.12 ± 6.65 and 20.45 ± 5.18, respectively). The differences were statistically significant (all P <0.05). After 3 and 6 months of treatment, the BI scores of the treatment group were 82.86 ± 10.41 and 85.45 ± 11.45, respectively, which were significantly better than those of the control group (68.64 ± 8.27 and 70.19 ± 10.20, respectively). The differences were statistically significant (all P <0.05). See Tables 4 and 5.

4. DISCUSSION

Ischemic stroke is the most common type of stroke in the elderly population accounting for approximately 60-70% of all strokes, with high recurrence and mortality rates. A large number of studies have shown that high plasma Hcy level is an independent risk factor for ischemic stroke [1,13]. Its underlying mechanisms include participating in oxidative stress, initiating endothelial and lipid peroxidation and promoting nitric oxide synthase, thereby reducing the endothelium-derived relaxation factor, causing dysfunction of vascular endothelial cells. Serum Hcy causes damages to the blood vessels and endothelial functions, therefore decreasing the elasticity of the arterial wall [14]. It also can cause accumulation of calcium within vascular smooth muscle cells (VSMCs) and proliferation of VSMCs [15]. In addition, Hcy also

TABLE 2 THE COMPARISON OF PLASMA HS-CRP LEVELS BETWEEN THE CONTROL AND TREATMENT GROUPS (X±S, MG / L)

Group	2nd day	4th week	8th week	3rd month	6th month
Control	16.5±0.25	15.3±0.38	14.9±0.78	10.9±0.58	8.9±0.69
Treatment	15.7±0.87	9.9±0.6	9.2±0.6	6.8±0.49	4.6±0.76
t	4.330	37.249	28.376	26.454	20.522
p	0.000	0.000	0.000	0.000	0.000

TABLE 3 THE COMPARISON OF IMTS BETWEEN THE CONTROL AND TREATMENT GROUPS (X±S, MM)

Group	2nd day	4th week	8th week	3rd month	6th month
Control	1.68±0.16	1.45±0.39	1.28±0.32	1.12±0.46	1.01±0.64
Treatment	1.69±0.21	1.36±0.45	1.12±0.60	0.82±0.36	0.65±0.43
t	0.168	0.673	1.036	2.309	2.431
p	0.868	0.505	0.307	0.027	0.019

TABLE 4 THE COMPARISON OF NIHSS BETWEEN THE CONTROL AND TREATMENT GROUPS (X±S, MM)

Group	2nd day	4th week	8th week	3rd month	6th month
Control	28.23±5.45	25.45±2.34	23.28±2.45	22.12±6.65	20.45±5.18
Treatment	28.34±5.45	26.45±4.56	22.41±2.65	17.68±5.28	15.45±5.45
t	0.145	0.645	1.045	2.455	2.193
p	0.845	0.577	0.345	0.025	0.024

TABLE 5 THE COMPARISON OF BI BETWEEN THE CONTROL AND TREATMENT GROUPS (X±S, MM)

Group	2nd day	4th week	8th week	3rd month	6th month
Control	56.23±10.34	61.34±10.56	71.12±10.45	82.86±10.41	85.45±11.45
Treatment	56.43±10.25	62.36±10.81	72.61±10.56	68.64±8.27	70.19±10.20
t	0.133	0.383	1.339	2.292	2.383
p	0.455	0.577	0.345	0.018	0.014

causes an increase in platelet adhesion and aggregation and thrombin production, therefore resulting in the formation of atherosclerotic thrombosis [16].

A number of previous studies have shown that the course of hypertension is accompanied by local and systemic inflammation [17-19]. The previous studies have found that H-type hypertension patients are more prone to have cerebral infarction, suggesting that Hcy has a high probability of causing ischemic strokes [20]. In addition, a recent study has shown that plasma Hcy level in stroke patients is significantly higher than that in a healthy population, suggesting that the plasma Hcy level is associated with an increased risk of stroke [21].

In the present study, we found that plasma hs-CRP level increased in patients with H-type hypertension, indicating that the increased Hcy level is one of the causes of systemic inflammatory response in patients with H-type hypertension. The possible mechanisms of hs-CRP on carotid artery plaques are as follows.

Elevated levels of inflammation in the body lead to vascular endothelial dysfunction. Increased expression of monocyte chemoattractant protein-1 (MCP-1), endothelial cell adhesion molecules, and proinflammatory cytokines can lead to vascular inflammation, VSMCs proliferation, vascular endothelial cell injury, thus leading to plaque formation. In addition, hs-CRP can increase vascular permeability, induce VSMCs sclerosis to expand the arteriosclerosis plaque and cause leukocyte to release protease to break fibrous thrombus cap leading to thrombosis. Furthermore, hs-CRP can cause thrombosis by promoting endothelial cell-induced plasminogen inhibitor and damage arterial endothelium [22]. Clinical studies have found that high level of Hcy is accompanied by a high level of hs-CRP [23]. Therefore, drugs to reduce the level of Hcy can help reduce the level of hs-CRP in patients with H-type hypertension, which is consistent with the data of our study.

Hcy metabolic process requires cofactors including vitamin B12, vitamins B6, and folic acid, whose deficiencies will affect the activity of enzymes and the metabolic process of Hcy. A previous study has shown that there was a negative correlation between plasma Hcy level and vitamin B12, vitamin B6 and folic acid [24]. Therefore, the decrease in plasma Hcy level can be achieved by adding vitamin B12, vitamin B6, and folic acid in order to treat ischemic stroke.

The mechanisms of the therapeutic effects of mecobalamin are as follows: it will participate in the sulfur pathway and methylation metabolism and reduce plasma Hcy levels, which will delay cerebral artery atherosclerosis [25]. At the same time, mecobalamin can also effectively promote the protease, lipid and nerve tissue metabolism and myelin lipid lecithin synthesis, therefore repairing the damages to the central nervous system, improving the metabolism and transmission of nerve tissue, and ultimately promoting the functional recovery after an ischemic stroke [26].

In the present study, the oral administration of mecobalamin in the treatment group effectively reduced the patient's plasma Hcy and hs-CRP levels, decreased carotid artery IMTs, and improved NIHSS and BI scores. For patients with H-type hypertension and ischemic stroke, mecobalamin treatment can not only effectively reduce the patients' plasma Hcy and hs-CRP levels, but also effectively improve the prognosis of patients.

RESUMO

OBJETIVO: *Analisar o efeito de mecobalamin sobre os primeiros resultados funcionais de pacientes com AVC isquêmico e hipertensão H-type.*

MÉTODOS: *De outubro de 2014 a outubro de 2016, 224 casos de AVC isquêmico e hipertensão H-type foram selecionadas. Os pacientes foram divididos aleatoriamente em grupo de tratamento e grupo controle, com 112 doentes em cada grupo. O grupo controle foi tratado com a terapia de rotina. O grupo de observação foi tratado com 500 μg de mecobalamin três vezes por dia, além da rotina de tratamento. No segundo dia, 4 semanas, 8 semanas, 3 meses e 6 meses, comparamos níveis séricos da homocisteína (Hcy) e de hs-CRP, placas da carótida e pontuações NIHSS entre os dois grupos.*

RESULTADOS: *Após 4 semanas, 8 semanas, 3 meses e 6 meses, a diferença dos níveis séricos de Hcy entre os dois grupos foi estatisticamente significativa (t= 4,049, 3,896, 6,052, 6,159, respectivamente. Todos os P<0,05). Após o tratamento de 4 semanas, 8 semanas, 3 meses e 6 meses, os níveis de hs-CRP no grupo de tratamento foram significativamente inferiores aos do grupo controle (t=37,249, 28,376, 26,454, 20,522, respectivamente. Todos os P<0,01). Depois de 3 meses e 6 meses, as placas da artéria carótida foram significativamente reduzidas no tratamento, em comparação com os do grupo controle (t=2,309 e 2,434. Todos os P<0,05). Depois de 3 meses e 6 meses, as pontuações NIHSS foram significativamente mais elevadas no tratamento em comparação com as do grupo controle (t=2,455 e 2,193. Todos os P<0,05).*

CONCLUSÃO: *Mecobalamin pode reduzir o nível de homocisteína plasmática, o que conduz à redução dos níveis de plasma inflamatórios e do volume das placas na artéria carótida, resultando em maior recuperação funcional.*

PALAVRAS-CHAVE: *Acidente vascular cerebral. Homocisteína. Hipertensão. Vitamina B12/análogos & derivados.*

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ORIGINAL ARTICLE

Evaluation of plaque characteristics in coronary artery patients with impaired glucose tolerance through optical coherence tomography

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SUMMARY

OBJECTIVE: *With the adoption of optical coherence tomography (OCT), this study targets the impacts on plaque characteristics brought about by impaired glucose tolerance (IGT) in patients with coronary artery disease.*

METHODS: *For this study, 150 patients with coronary artery disease were recruited. Regarding glycosylated hemoglobin (HbAlc), the patients were sectioned into normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus (DM) groups. Coronary angiography (CAG) and OCT were conducted for 150 patients.*

RESULTS: *There were 186 plaques discovered in 150 patients (37, 40, 44, and 65 in the NGT, IFG, IGT, and DM groups, respectively). Compared to the NGT group, the lipid core size, which is presented as the average angle of the lipid arc, was markedly larger in the IFG,IGT and DM groups (135.7 ± 32.7 Ê, 161.2 ± 55.7 Ê, 162.5 ± 55.8 Ê, and 170.2 ± 59.7 Ê, respectively, all P values< 0.05). Meanwhile, the fibrous cap over the lipid core in the NGT group was remarkably thicker than that in the IFG, IGT, and DM groups (115.7 ± 47.7 μm vs. 77.7 ± 23.5 μm, 75.1 ± 23.2 μm, 71.2 ± 22.1 μm, all P values<0.05).*

CONCLUSION: *Coronary plaques in coronary artery patients with NDT are more stable than in those with IGT and DM.*

KEYWORDS: *Tomography, Optical Coherence. Diabetes Mellitus. Coronary Disease. Coronary Artery Disease. Atherosclerosis.*

In recent years, the prevalence and mortality of coronary heart disease (CAD) were increasing. In addition, two of its highest risk factors are diabetes mellitus (DM) and impaired glucose tolerance (IGT)[1, 2]. Diabetic patients are 2 to 4 times more likely to suffer from cardiovascular disease than non-diabetic patients. Furthermore, the stability of the coronary plaque is also considered to be a significant risk factor for cardiovascular events [3,4]. According to previous studies, unstable coronary plaques are closely related to acute coronary syndrome (ACS) [5-7]. Optical coherence tomography (OCT) is a high-definition intravascular image modality that is able to conduct a detailed evaluation of the coronary plaque [8-10]. This study aims to explore the impacts of blood glucose control on coronary plaque on patients with type-2 diabetes mellitus (T2DM). In this study, the glycosylated hemoglobin (HbAlc) test was used to determine the blood glucose control in diabetic patients. OCT was used to assess the characteristics of the

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atherosclerotic plaque and the thickness of the lipid plaque fibrous cap, so as to determine the plaque morphology.

1. RESEARCH PARTICIPANTS AND METHODOLOGY

1.1 Research participants

A total of 150 patients with unstable angina (UA) and T2DM were included in this study between January of 2011 and December of 2014, out of which 79 were males and 71 females, with a mean age of 64.68 ± 7.89 years. According to CAG examination results, one or more coronary artery with stenotic lesion(s) ≥ 50% diameter of the lumen was selected as a diagnostic criterion for CAD. WHO (1999) diagnostic criteria were chosen for T2DM diagnosis [11]. Exclusion criteria included history of smoking, hypertension, congenital heart disease, pulmonary heart disease, rheumatic heart disease, cardiomyopathy, acute heart myocardial infarction, heart failure, severe anemia, aortic dissection, acute cerebrovascular disease, and severe liver and kidney dysfunction.

1.2 Image-producing and analyzing of OCT

The technique of OCT was utilized to generate pictures on OCT. The 6-Fr guiding catheter that can access radial line or femoral artery was also employed. The contrast media was injected into coronary arteries at 4 mL per second. The OCT started to record images with a speed of 15 mm per second. Those captured images were them studied with C7-XR Imaging Program by two independent radiologists. A thin-cap fibroatheroma or TCFA was taken as the sheerest fibrous cap. Its thickness was no more than 65 μm in a fat-ample condition on interconnected image-producing. Macrophage infiltration refers to signal-ample discrete punctuate areas that outweigh the concentration of background fleck noise[12-14]. Plaque disruption refers to fibrous cap incoherence with significant creation of hole in the condition[15]. Microchannel structures mean signal-bad cavities that are marked in several adjoining settings[14]. Calcification refers to well-marked and low backscattered mixed areas[14]. A thrombus is a well-marked substance with good signal connected to the luminal surface or moving inside the lumen[14, 15].

1.3 Grouping

Based on the outcomes of a 75-g oral glucose lenience trial, four groups of patients were formed. In such trial, NGT was prescribed with a fasting plasma glucose (FPG) level that was no more than 110 mg/dL and 2-h plasma glucose (PG) level no more than 140 mg/dL. IFG was observed with a 2-h PG level higher than 110 mg/dL, but lower than 126 mg/dL. IGT has a 2-h PG level higher than 140 mg/dL, but lower than 200 mg/dL. DM was observed as a prefigure of DM, hemoglobin A1c value no less than 6.5%, and FPG level no less than 126 mg/dL or 2-h PG level no less than 200 mg/dL[11].

1.4 Statistical studies

IBM SPSS 17.0 statistical program was employed to analyze the data. Continuous data were represented as the mean ± standard deviation (SD). And categorical stats were described as proportions. All the trials were performed using a two-sided test of difference, in which the inspection level α of 0.05 and a difference with $P < 0.05$ were seen as statistically relevant.

TABLE 1 - ESSENTIAL FEATURES OF THE FOUR GROUP PATIENTS.

Factors	NGT (n=37)	IFG (n=31)	IGT (n=40)	DM (n=42)	P
Age (years)	64.45±9.8	62.56±5.7	66.30±5.5	65.48±8.5	0.566
Sex (male/female)	30/7	24/7	34/6	35/7	0.733
BMI (kg/m^2)	25.5±2.7	24.7±3.1	25.0±3.0	24.6±4.5	0.455
Hypertension [n (%)]	34(91.2)	28(90.3)	36(90.0)	38(90.5)	0.956
Smoking [n (%)]	19(51.4)	17(54.8)	24(60.0)	26(60.5)	0.984
LDL-C (mg/dL)	101.2±32.0	99.5±23.8	98.3±27.7	110.9±31.4	0.488
HDL-C (mg/dL)	51.4±13.5	51.0±11.5	49.4±12.8	50.5±15.5	0.393
HbA1c (%)	5.4±0.5	5.5±0.5	5.6±0.8	7.5±0.5	<0.01
FPG (mg/dL)	90.4±7.7	95.5±10.5	96.3±13.8	107.5±10.9	<0.05

2. OUTCOMES

2.1 Essential features

Gender, age, BMI, blood pressure, level of LDL-C and HDL-C, as well as statin intake barely differs in the 4 units. The HbA1c level was significantly higher in the DM unit compared to those in IFG, IGT as well as NGT units. The FPG standards were significantly higher in DM, IFG, and IGT units compared to that in the NGT unit.

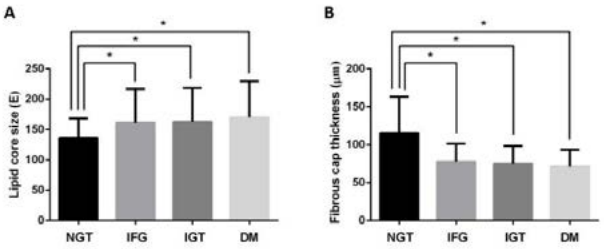

FIG. 1. Comparison of plaque parameters from OCT findings. A. Lipid core's size; B. The fibrous cap thickness

2.2 The characteristics of coronary plaques from OCT findings

A total of 186 plaques were discovered among 150 diseased patients (37, 40, 44, and 65 in NGT, IFG, IGT, and DM units, respectively). The percentages of calcification plaques, fat-ample plaques, as well as fibrous plaques were the same (Table 2).

2.3 Plaque quantitative analysis

For 186 lesions, IGT group MLA < NGT group, and EEMA, PA and PB were significantly more than in the group NGT ($P < 0.05$), RMAL was substantially less than in group NGT, RPB > NGT ($P < 0.05$)

2.4 Comparison of plaque parameters from OCT findings

The lipid core's size represented as the norm point of the lipid arc is remarkably larger in IFG, IGT, and DM units in comparison to that in the NGT unit (161.2 ± 55.7 Ê, 162.5 ± 55.8 Ê, 170.2 ± 59.7 Ê, and 135.7 ± 32.7 Ê, respectively, all P values < 0.05). The thickness of the fibrous cap on the lipid core is smaller in the former units than in the latter one (77.7 ± 23.5 μm, 75.1 ± 23.2 μm, 71.2 ± 22.1 μm vs. 115.7 ± 47.7 μm, all P values<0.05) .

3. DISCUSSION

A previous analysis found that the proportion of CAD patients combined with DM and IGT is as high as 30.0% and 40.0%, respectively. In addition, the incidence of abnormal glucose metabolism among CAD patients in China is approximately 80.0%, which is much higher than that in the Western population. Previous studies have shown that about 60.0~75.0% of diabetic patients' mortality is caused by cardiovascular complications. Furthermore, CAD brings about the highest death rate among people with diabetes. Yeboah et al.[16] have found that approximately 3/4 of diabetic patients without CAD clinical symptoms have a reduction of more than 75.0% of the cross-sectional area of the coronary artery lumen. Even after the coronary artery revascularization, CAD causes more death among people suffering from DM than of those with no diabetes.

The HbA1c test result can accurately reflect the normal levels for the past 60 to 90 days for diabetic patients. It is not affected by diet, insulin injections and lifestyle changes, thus making it a reliable clinical indicator for assessing long-term glycemic control in diabetic patients. OCT can produce intravascular images with high resolutions, which has a significant correlation with pathological study results. It can clearly show the structural features of atherosclerotic conditions as well as accurately gauge the fatness of the fibrous cap, which is known as "*in vivo* histology microscopy" [17].

In the present study, we found that the percentages of calcification plaques, fat-ample plaques, as well

TABLE 2 - THE CHARACTERISTICS OF CORONARY PLAQUES FROM OCT FINDINGS

Variable	NGT (n=37)	IFG (n=40)	IGT (n=44)	DM (n=65)	X^2	P
Calcification plaques [n (%)]	13 (35.1)	10 (25.0)	17 (38.6)	22 (33.8)	0.58	0.75
Lipid-rich plaques [n (%)]	8 (21.6)	9 (22.5)	13 (29.5)	22 (33.8)	0.76	0.98
Fibrous plaques [n (%)]	16 (43.3)	21 (52.5)	14 (31.9)	21 (32.4)	0.64	0.77

TABLE 3 - QUANTITATIVE ANALYSIS OF CORONARY PLAQUES IN 4 GROUPS

Group	NGT	IFG	IGT	DM	P
EEMA(mm^2)	13.86±0.56	14.12±0.74	14.26±0.95	14.45±0.37	0.016
MLA(mm^2)	5.86±0.46	5.53±0.34	5.49±0.66	5.32±0.48	0.002
PA(mm^2)	8.0±0.67	8.56±0.78	8.76±1.08	8.93±0.87	0.000
PB(%)	57.59±3.48	60.26±4.73	61.15±4.93	62.28±5.36	0.000
REEMA(mm^2)	13.74±1.14	13.62±1.03	13.54±1.08	13.46±1.06	0.351
RMAL(mm^2)	10.08±0.9	9.32±0.49	9.20±0.82	8.94±0.73	0.000
RPA(mm^2)	3.66±1.31	4.07±1.26	4.33±1.17	4.57±1.02	0.008
RPB(%)	31.90±8.19	31.89±7.46	31.90±7.22	31.91±7.06	0.001
RI	1.01±0.78	1.04±0.78	1.06±0.78	1.07±0.78	0.008

as fibrous plaques are the same. However, IFG, IGT, and DM units have larger lipid cores than those of the NGT unit. Additionally, the thickness of fibrous cap on the lipid core in the IFG, IGT, and DM groups decreases compared with that of the NGT unit. If the lipid core grows and the fibrous cap becomes thinner, it can lead to the instability of atherosclerotic plaques and, eventually, result in the onset of ACS. This research used 75g OGTT to identify those with IFG and IGT aiming to determine whether atherosclerotic plaques are more unstable in CAD patients combined with IFG and IGT, compared to those with NGT using OCT. The results showed that, compared to CAD patients with NGT, those with IFG and IGT have significantly larger lipid cores and a thinner fibrous cap.

Kato et al. [18] found that, in comparison to diseased patients with no diabetes, people with diabetes have plaques that are more fat-rich fibrous, which does not coincide with the results from the present study. This can be due to the fact that the present analysis has a limited sample size. However, studies also found that the lipid core grows, and the fibrous cap becomes thinner among IFG, IGT, and DM patients, which is consistent with the results from Kato et al. [18]. The underlying development structures of unstable atherosclerotic conditions in diabetic patients have not been fully recognized. The reason may be that long-term hyperglycemia can cause coronary artery vascular endothelial dysfunction, the loss of balance between contraction and relaxation of the coronary artery, and increased plaque local inflammatory cell activities, therefore increasing the vulnerability and instability of atherosclerotic plaques [19, 20].

It is concluded that the instability of CAD victims suffering from atherosclerotic conditions combined with IFG, IGT, or DM presents more advantages than when compared to that of CAD patients with NGT. These findings may indicate that patients with abnormal glucose metabolism might be more prone to cardiovascular-related diseases, in comparison to CAD patients with healthy glucose metabolism.

RESUMO

OBJETIVO: *Com a adoção da tomografia de coerência óptica (OCT), o presente estudo visa as características dos impactos na placa trazidos pela tolerância diminuída à glicose (IGT) em pacientes com doença na artéria coronária.*

MÉTODOS: *Cento e cinquenta doentes com doença arterial coronária foram recrutados para este estudo. De acordo com a hemoglobina glicosilada (HbAlc), os pacientes foram divididos em grupos: tolerância normal à glicose (NGT), diminuição da glicemia de jejum (IFG), diminuição da tolerância à glicose (IGT) e diabetes mellitus (DM). Angiografia coronária (CAG) e OCT foram conduzidas para 150 doentes.*

RESULTADOS: *Existem 186 placas descobertas em 150 doentes (37, 40, 44 e 65 nos grupos NGT, IFG, IGT e DM, respectivamente). Em relação ao grupo NGT, o tamanho do núcleo lipídico, que é apresentado como o ângulo médio do arco lipídico, foi significativamente maior nos grupos IFG, IGT e DM (135,7 ± 32,7 Ê, 161,2 ± 55,7 Ê, 162,5 ± 55,8 Ê, e 170,2 ± 59,7 Ê, separadamente, os valores de P<0,05). Entretanto, a tampa sobre o núcleo de lipídios fibrosos no grupo NGT estava bem mais grossa do que nos grupos IFG, IGT e DM (115,7 ± 47,7μm* **vs.** *77,7 ± 23,5 μm, 75,1 ± 23,2 μm, 71,2 ± 22,1 μm, todos os valores de P<0,05).*

CONCLUSÃO: *Placas coronárias na artéria coronária de pacientes com NDT são mais estáveis do que em doentes com IGT e DM.*

PALAVRAS-CHAVE: *Tomografia de coerência óptica. Diabetes mellitus. Doença das coronárias. Doença da artéria coronariana. Aterosclerose.*

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ORIGINAL ARTICLE

The serum homocysteine level in patients with acute ischemic stroke (AIS) after thrombolysis and its relationship with clinical outcomes

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SUMMARY

OBJECTIVE: *The present study aims to investigate whether hyperhomocysteinemia (HHcy) affects the outcomes of the thrombolytic treatment for patients with AIS.*

METHODS: *A sample of 120 AIS patients were recruited and grouped according to their serum homocysteine (Hcy) levels. The National Institute of Health Stroke Scale (NIHSS) was obtained before treatment and 7 days after it to evaluate neurological outcomes; modified Rankin Scale (mRS) was obtained 12 weeks later to assess functional outcomes. Receiver operating characteristic curve (ROC) was used to demonstrate the relationship between serum Hcy level and the outcomes after tPA treatment.*

RESULTS: *The serum Hcy level of 120 patients was of 27.57±20.17μmol/L. The NIHSS scores of the patients in the low Hcy level group were remarkably lower compared to those in the high-level group ($p<0.05$), after 7 days of treatment. In addition, the mRS scores of the patients in the low Hcy level group, after 12 weeks, were remarkably lower compared to those in the high-level group ($p<0.01$). ROC demonstrated that the serum Hcy level is related to the clinical outcomes of thrombolytic treatment with moderate specificity (80.3%) and sensitivity (58.2%).*

CONCLUSION: *In conclusion, higher serum Hcy levels can indicate poorer clinical outcomes of thrombolytic treatment in patients with AIS.*

KEYWORDS: *Homocysteine. Stroke. Thrombolytic Therapy.*

Nowadays in China, AIS is one of the leading causes of disability and death. It brings tremendous financial burden to patients' families [1]. Intravenous thrombolysis (IVT) and alteplase (t-PA) has been widely used in AIS patients within 4.5 hours after the onset[2–4]. However, its possible complications i.e. symptomatic intracerebral hemorrhage (sICH) require appropriate precautions. To the best of our knowledge, reliable methods and indexes to predict sICH and evaluate treatment outcomes of IVT still lack in clinical practice. Therefore, an accurate predictor with reasonable sensitivity and specificity is needed.

Previous investigations have indicated that hyperhomocysteinemia (HHcy) is related to a higher risk of AIS and poor prognosis of patients with AIS, with a possible underlying mechanism in which increased serum homocysteine (Hcy) may result in endothe-

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lial dysfunction, neurotoxicity, and upregulation of prothrombotic factors [5–7]. However, the possibility to also use HHcy to predict clinical outcomes after tPA treatment has not been comprehensively studied. The present study aims to retrospectively research the possible relationship between HHcy and clinical outcomes of tPA for patients with AIS.

MATERIAL AND METHODOLOGY

Ethical approvals were obtained from the Ethics Review Committee of the West China Hospital (Chengdu, Sichuan, China). We collected and analyzed data from consecutive AIS patients treated in the Department of Neurology of the West China Hospital between January of 2011 and December of 2014. All patients provided written informed consent.

Criteria for inclusion: (1) Age≥18 years; (2) Diagnosis of AIS validated by head CT scanning; (3) Beginning of tPA treatment within 4.5 h after the onset.

Criteria for exclusion: (1) Prior stroke within 12 weeks; (2) History of intracranial hemorrhage; (3) Recent intraspinal or intracranial surgery; (4) Active internal bleeding; (5) Hypertension (systolic BP >185mmHg or diastolic BP >110mmHg); (6) Blood glucose concentration < 2.7mmol/l; (7) Multiple lobar infarction demonstrated by head CT; (8) Unwillingness to participate.

Upon admission, a head CT was performed on all patients, and clinical characteristics including sex, age, history of smoking and alcohol consumption, systolic and diastolic BP, hypertension, diabetes mellitus, coronary atherosclerotic cardiovascular disease, previous stroke, atrial fibrillation, time of thrombolysis, and stroke subtypes were gathered. The NIHSS scores were evaluated upon admission and 7 days after tPA treatment in order to assess the severity of AIS and the outcomes of tPA treatment. The mRS was performed after 12 weeks to evaluate the long-term outcomes. In addition, laboratory tests including platelet count, hemoglobin level, fasting blood-glucose and uric acid level, fibrinogen level, serum homocysteine level, and serum lipid profile were conducted on admission.

TREATMENT

The patients were given intravenous alteplase (0.9mg/kg, maximum 90mg, Boehringer-Ingelheim Pharmaceuticals, Germany) within 4.5h of onset (10% in pellet within 1min, remaining 90% was intravenously infused within 1h) [2–4].

CLINICAL OUTCOMES

The NIHSS score was performed on admission and 7 days after tPA treatment to assess the severity and progression of AIS. All patients underwent head CT or MRI scan within 1 day after the tPA treatment. The secondary endpoint was Symptomatic Intracerebral Hemorrhage (sICH). The sICH was defined as a detectable hemorrhage and parenchymal hematoma on the head CT or MRI with a neurological deterioration (NIHSS score≥4) [8]. All patients were reevaluated at 12 weeks after tPA treatment using the mRS score.

STATISTICAL ANALYSIS

IBM SPSS version 17.0 was used to conduct statistical analysis. A t-test was performed to compare the continuous variables. The Pearson chi-square test and Fisher exact test were performed to compare the categorical variables. Possible predictors of poor prognosis were evaluated by using multiple logistic regression analysis. The ability of serum Hcy level to predict patient prognosis was investigated by calculating the area under the receiver operating characteristic curve (AUC).

RESULTS AND ANALYSIS

A sample of 120 patients which included 87 males and 33 females with mean age of 65.7±12.7 years were recruited for this study. The serum Hcy level was 27.57±20.17μmol/L. The serum Hcy levels were divided into quartiles of 1, 2, 3, and 4 with ranges of 2.26 to 11.50μmol/L, 11.50 to 17.70μmol/L, 17.70 to 23.85μmol/L, and 23.85 to 138.90μmol/L, respectively. The serum Hcy median level was 17.70μmol/L. Patients with Hcy<17.70μmol/L were assigned to the low concentration group and the other patients were assigned to the high concentration group.

Different clinical characters of patients in the two groups are presented in Table 1. There were more male patients in the high concentration group ($P<0.01$). Additionally, the univariate analysis demonstrated that smoking, alcohol consumption, uric acid level, hemoglobin level, and diabetes mellitus were related to a higher concentration of Hcy ($P<0.05$).

TABLE 1. CLINICAL CHARACTERS AND OUTCOMES OF PATIENTS IN LOW AND HIGH HCY CONCENTRATION GROUPS.

	Hcy level		P-value
	Low concentration (n=63)	High concentration (n=57)	
Age, y	65.67±11.50	62.55±15.02	0.556
Male [n (%)]	44(69.84)	43(75.44)	<0.001
Alcohol consumption [n (%)]	17 (26.98)	14 (24.56)	0.017
Current smoking status [n (%)]	44 (69.84)	31 (54.40)	<0.001
Hypertension [n (%)]	33 (52.38)	37 (64.91)	0.577
Diabetes mellitus [n (%)]	23 (36.50)	9 (15.79)	0.015
Coronary atherosclerotic cardiovascular disease [n (%)]	27 (42.86)	20 (35.09)	0.75
Atrial fibrillation [n (%)]	6 (9.52)	9 (15.79)	0.157
Previous stroke [n (%)]	13 (20.63)	11 (19.30)	0.205
Hemoglobin (g/L)	135.45±15.25	141.55±19.41	0.05
Platelet count ($x10^9$/L)	212.27±61.75	225.95±73.55	0.25
Fibrinogen level (g/L)	3.00±0.75	3.01±0.95	0.997
Uric acid (μmol/L)	259.22±82.57	302.67±97.77	<0.001
Blood glucose level (mmol/L)	6.35±2.27	6.07±2.77	0.487
Triglyceride (mmol/L)	1.55±1.05	1.77±1.10	0.577
Low-density lipoprotein (mmol/L)	2.77±0.05	2.87±1.17	0.557
High-density lipoprotein (mmol/L)	2.77±0.87	2.87±1.07	0.557
Total cholesterol (mmol/L)	2.75±0.87	2.80±1.17	0.507
sICH (%)	13 (20.63)	44 (77.19)	0.017
NIHSS on admission	7.97±2.77	8.09±3.02	0.55
NIHSS 7-day after treatment	4.57±5.57	6.87±7.70	0.007
mRS 12-week after treatment	1.77±1.50	2.37±1.70	0.007

TABLE 2. MODIFIED RANKIN SCALE AND ODDS RATIO WITH RESPECT TO HCY QUARTILES.

	OR	95% CI	P-value
Q1	nr	nr	nr
Q2	1.83	0.49-6.81	0.370
Q3	2.29	0.62-8.43	0.241
Q4	13.75	3.57-51.77	<0.001
Male	0.711	0.181-2.80	0.626
Age	1.00	0.966-1.04	0.965
Alcohol consumption	1.65	0.495-5.48	0.415
Current smoking status	0.468	0.138-1.59	0.223
Diabetes mellitus	0.981	0.324-2.97	0.974
Hemoglobin	1.00	0.978-1.03	0.771
Uric acid	0.999	0.994-1.00	0.598
NIHSS on admission	1.61	1.38-1.86	<0.001

nr: not relevant

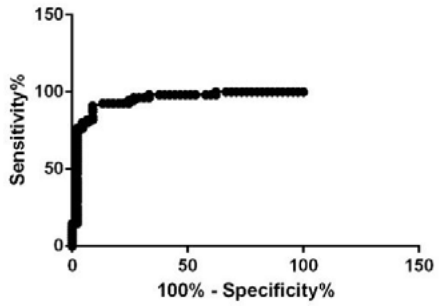

FIG.1. The ability of serum Hcy level to predict prognosis of AIS was assessed by conducting ROC analysis.

No significant difference was observed between the 2 groups regarding NIHSS scores obtained on admission. However, the scores of the low concentration group were significantly lower than those of the high concentration group, 7 days after tPA treatment (P<0.05). The sICH was found in 57 (47.50%) patients within 24 h after initiation of tPA. There were significantly more patients with sICH in the high concentration group (P<0.05). In addition, mRS scores indicated poor prognosis after 12 weeks (P<0.01).

Univariate analysis demonstrated that Hcy level, NIHSS score on admission, uric acid level, and diabetes mellitus were related to the prognosis. That NIHSS score on admission and Hcy level were independent predictors of poor prognosis (P<0.001) was demonstrated by multiple logistic regression analysis (Table 2). The fourth quartile (23.85 to 138.90μmol/L) of the Hcy level was considered to be an independent predictor of poor prognosis (OR 13.75, 95% CI 3.57–51.77, P<0.001). The risk of poor prognosis gets higher as Hcy level increases, as illustrated in Fig.1. ROC analysis showed an AUC value of 0.685 (95% CI 0.603–0.768) and a cut-off value of 17.75μmol/L with a sensitivity of 58.2% and specificity of 80.3%.

DISCUSSION

The IVT with t-PA has been widely used in AIS patients within 4.5 hours after the onset [2–4]. However, sICH is a fatal complication of tPA and limits its clinical application. Therefore, it is useful to discover an index that can predict the risk of sICH after tPA treatment. Previous studies have reported that serum Hcy level might be able to predict the occurrence of AIS [5–7]. Zhou et al.[9] have discovered that higher serum Hcy level was related to a larger volume of hematoma of AIS patients, with the possible underlying mechanism of disruption of the cerebral vessel wall integrity caused by elevated Hcy [10-12]. Our study aimed to research the potential relationship between serum Hcy level and sICH.

This study has demonstrated that 17.7μmol/L is the cut-off value to determine whether the serum Hcy level of a patient is higher than average. Patients with high Hcy concentrations tended to have worse clinical outcomes after tPA treatment, compared to patients with low concentrations. This was demonstrated by NIHSS and mRS scores after 7 days and 12 weeks. The results suggested that high Hcy levels predicted poor prognosis after tPA treatment.

Although some recent studies have demonstrated the relationship between high Hcy level and elevated risk of AIS, the predicative value of patients' Hcy level following tPA treatment has not been studied comprehensively. Several studies have shown that high Hcy level is an independent risk factor for both long and short-term poor prognosis, which is consistent with our results [5–7, 13, 14]. Toole et al. [15] have shown that the stroke risk decreases by 10% as the serum Hcy level decreases by 3μmol/L. The cut-off value was determined to be 17.75μmol/L based on the ROC model. It was close to the cut-off value (17.64μmol/L) reported from Yan et al. [16]. Therefore, we have shown that the cut-off value of 17.75μmol/L is a reliable predictor of poor prognosis in patients with AIS following tPA treatment. As far as we know, this was the first retrospective study to report the relationship between high Hcy level and poor prognosis after tPA treatment.

Several limitations exist in the present study. First of all, this is a retrospective analysis with relatively small sample size which did not include AIS patients without thrombolytic treatment as a control group. Therefore, a multicenter randomized controlled study should be conducted in the future to validate and confirm the results of the present study. Secondly, multiple factors affect the serum Hcy level, including genetic background, general nutrition, health, and various comorbidities such as nephropathy, diabetes mellitus, etc.[17]. Therefore, it was impossible to eliminate all the confounding factors during the follow-up, which inevitably affected the results.

In conclusion, the present study suggested that increased serum Hcy level was an independent risk predictor of sICH and poor prognosis in AIS patients who underwent tPA treatment. The cut-off value of 17.75μmol/L provided a valuable reference point for Chinese patients.

RESUMO

OBJETIVO: *O presente estudo tem por objetivo investigar se a hiperhomocisteinemia (HHcy) afeta os resultados do tratamento trombolítico em pacientes com AVCI agudo.*

METODOLOGIA: *Uma amostra de 120 pacientes AVCI agudo foi recrutada e agrupada de acordo com os níveis séricos de homocisteína (Hcy). Uma avaliação nos padrões do National Institute of Health Stroke Scale (NIHSS) foi obtida antes do tratamento e 7 dias após ele para avaliar desfechos neurológicos e a escala de Rankin modificada foi utilizada 12 semanas depois para avaliar os desfechos funcionais. A curva ROC (Receiver Operating Caracteristic) foi utilizada para demonstrar a relação entre os níveis séricos de Hcy e os desfechos após tratamento com t-PA.*

RESULTADOS: *Os níveis séricos de Hcy de 120 pacientes foi de 27,57±20,17μmol/L. Os escores NIHSS dos pacientes no grupo de baixo nível de Hcy foram notavelmente mais baixos em comparação àqueles do grupo de nível mais alto (p<0,05), após 7 dias de tratamento. Além disso, os escores mRS dos pacientes no grupo de baixo nível de Hcy, após 12 semanas, foram consideravelmente mais baixos em comparação com os do grupo de alto nível (p<0,01). A curva ROC demonstrou que o nível sérico de Hcy tem relação com os desfechos clínicos do tratamento trombolítico com especificidade moderada (80,3%) e sensibilidade (58,2%).*

CONCLUSÃO: *Podemos concluir então que níveis séricos mais altos de Hcy podem prever desfechos clínicos piores para o tratamento trombolítico em pacientes com AVCI agudo.*

PALAVRAS-CHAVE: *Homocisteína. Derrame. Terapia trombolítica.*

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ORIGINAL ARTICLE

Success of promotion strategies for a stroke rehabilitation protocol

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SUMMARY

OBJECTIVE: *To prospectively evaluate the success of promotion strategies for a protocol of motor rehabilitation strategies for patients with stroke at Albert Einstein Hospital.*

METHODS: *In a clinical trial of neuromodulation and rehabilitation for patients with stroke, conventional methods of dissemination and publications about the research protocol in social networks or on the hospital's website were performed. Frequencies of types of advertisements that reached potentially eligible subjects were calculated.*

RESULTS: *Data from 80 potentially eligible patients were analyzed. The types of ads that motivated contacts more frequently were social media (38.8%) and information provided to physicians from other hospitals (23.8%) (p=0,288). The frequencies of contacts motivated by publications on the internet (53%) and conventional strategies (47%) were similar. Facebook was the digital strategy associated with the higher number of contacts, followed by the hospital's website.*

CONCLUSION: *Social networks and websites can be as effective as traditional methods of advertisement, in order to reach patients for stroke rehabilitation protocols. These results may have an impact on the planning of clinical trials, including studies that evaluate effects of rehabilitation interventions in patients with stroke.*

KEYWORDS: *Internet. Social media. Social networking. Neurology. Stroke. Physical therapy modalities.*

INTRODUCTION

Epidemiological studies have revealed an incidence of cerebrovascular accidents (CVA) of 105.4/100,000 inhabitants/year in Joinville, Santa Catarina and 137/100,000 in Matão, in the interior of São Paulo.[1, 2] In a study carried out in Fortaleza, 72.3% of the patients hospitalized for stroke showed functional dependence defined by a score higher than 2 in the modified Rankin Scale, at the time of discharge.[3] In Matão, one year after a first stroke, 61% of the survivors presented some degree of functional dependence, defined by a score lower than 100 in the Barthel Index.[1] The individual and social burden of strokes are expected to grow even more in the coming decades, due to the increased life expectancy and decreased mortality in the acute phase of the disease.[4, 5]

Therefore, rehabilitation strategies aimed at the reduction of disability in stroke victims should be developed in parallel with efforts in prevention and emergency treatment. The recruitment of patients is a substantial challenge for trials in general[6] and for

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rehabilitation in particular.[7-12] An alternative to improve recruitment is the use of social networks for the promotion of research projects.

From 2000 until 2008, there was a growth of around 342% in access to the internet and there are estimates that over 1.5 billion people, or 23.8% of the world population, use it in their daily lives.[13]

The use of digital media and social networks for participant recruitment in research protocols was identified in studies on the health of children, adolescents,[14, 15] and pregnant women,[16, 17] as well as in projects for smoking cessation,[18, 19] promotion of physical activity,[20, 21] assessment of the relationship between cognitive function and diabetes mellitus,[22] or in clinical trials on osteoporosis[23] and breast cancer.[24] We did not identify the use of these tools in studies on the rehabilitation of stroke patients, a condition with high individual, social and economic impact worldwide.

In Brazil, we identified only two studies that described the effectiveness of different promotion strategies for research in rehabilitation aimed to stroke patients with stroke.[9, 10] Only one of them[9] reported the use of electronic brochures on hospital websites. Social networks were not used as communication tools in these projects.

OBJECTIVES

The objectives of this study were: to assess the success of promotion strategies that involve the use of digital media and social networks for patients with cerebrovascular diseases, in a rehabilitation protocol in progress at the Hospital Israelita Albert Einstein; to compare the success of conventional promotion strategies with publications in social networks and the hospital website.

METHODOLOGY

Study design

We prospectively assessed the recruiting strategies for the study "Safety of transcranial stimulation by a continuous current in the subacute phase after an ischemic cerebrovascular accident". This project consisted of a randomized clinical trial on transcranial direct current stimulation (tDCS) applied in the subacute phase (72 hours at 6 weeks) in patients with paresis of the upper limb after an ischemic cerebrovascular accident (stroke). This type of intervention has been used in studies with the objective of potentiating the effects of rehabilitation.[25, 26] The clinical trial was approved by the Research Ethics Committee of the Hospital Israelita Albert Einstein (HIAE) in April 2015, registered in the website Clinicaltrials.gov (NCT024555427) and is currently ongoing. This project was exempted from approval of the Research Ethics Committee of the HIAE because it aims at improving processes.

The criteria for inclusion in the study are: age between 18 and 80 years; ischemic stroke of any etiology occurred between 72 hours and 6 weeks before the start of the protocol, leading to unilateral paresis of the upper limb, measured by the stroke scale of the National Institutes of Health (minimum of 1 in item 5a or item 5b; maximum score on the scale between 5 and 15);[27] informed consent in writing, as a specific term; radiological confirmation of the ischemic stroke by structural magnetic resonance or computed tomography of the skull without contrast.

The criteria for exclusion criteria were: other neurological diseases prior to the ischemic stroke (with the except of migraines); a history of seizures, psychiatric disorders; advanced systemic disease, such as cancer in advanced stage or kidney disease, clinical and/or hemodynamic instability; contraindication to physiotherapy; presence of pacemaker, uncontrolled arrhythmias or decompensated heart disease; score on the modified Rankin Scale[27] greater than 2 before the ischemic stroke; dementia reported by the patient and/or by a companion, such as loss of memory prior to the event and at least one other cognitive domain, with social or occupational harm;[28] pregnancy; aphasia in understanding; prior ischemic stroke compromising the corticospinal pathway in the unaffected hemisphere.

PROMOTION

Five promotion methods were used to recruit research voluntaries:

- Printed signs posted on communication boards and on the intranet accessed by HIAE employees.
- Emails e-mails sent to physicians, physical therapists and researchers from the HIAE, as well as for the Integrated Program of Neurology;
- Emails sent to doctors and researchers external to the HIAE;
- publications of research promotion in social networks (Facebook, LinkedIn, Twitter);

Publications in the HIAE site through the links:

- http://www.einstein.br/Pages/Home.aspx,
- http://medicalsuite.einstein.br/Paginas/home.aspx) and http://medicalsuite.einstein.br/pesquisa/Paginas/.

During the promotion, the primary requirements for the candidate to participate were informed: Ischemic stroke and paresis in one hand. In case of interest, the patient or their family/guardian should contact the research team of the hospital via email or telephone to verify other inclusion and exclusion criteria.

Between October 07, 2015 and September 09, 2016, five promotion attempts were made by means of printed signs displayed at the internal employee communication boards of HIAE, four by emails to physicians and researchers from the HIAE, another four by emails to physicians and researchers from other hospitals, in addition to a permanent posting on the HIAE website, three on the LinkedIn page, two on the institutional profile on Twitter and six on the HIAE page on Facebook. In one of the Facebook posts, the target audience was segmented according to place of residence, age, educational level and interests. The other five publications were made in the traditional way, without segmentation.

The promotion methods by which patients were made aware of the project were stored in a database in Excel, version 2010.

The emails sent to internal and external doctors, physiotherapists and researchers and the printed signs posted on boards were classified as conventional promotion methods.

STATISTICAL ANALYSIS

For the characterization of patients, the mean age and standard deviation were calculated, as well as the percentage of male and female individuals. In addition, the proportions on the degree of relationship between the patient and the individual who contacted the research team were calculated.

The binomial test was used to test the equality of the proportion of digital and non-digital contact occurrences. The analysis was performed with SPSS (version 24), considering a significance level of 5%.

RESULTS

In total, 88 individuals contacted the research team. For eight of them, it was not possible to define how the individuals became aware of the project. For this reason, we analyzed data from 80 individuals (40 men). The mean age (± standard deviation) was 55±17 years (p=0.115). In the majority of cases (79.6%), it was not the patient who contacted the research team, but a relative.

The most frequent means of promotion that motivated contact (Table 1) were social networks and information supplied by external doctors. Forty-three individuals (53.8%) were reached by posts about the project in social networks or on the HIAE website, and 37 by conventional methods (47%). There was no statistically significant difference between the scope of both methods of promotion (p=0.288).

In relation to online publications, Facebook promotion was the most effective (29/43; 67.4% of all contacts), followed by the HIAE website (12/43; 27.9%), Twitter (1/43; 2.3%) and LinkedIn (1/43; 2.3%). The impact of the directed posting on Facebook was more significant than the traditional ones. On average, each conventional post via Facebook was responsible for the contact of four individuals (13.7%), while the post directed at specific segments reached nine, 31% of the total number of people informed about the research through this social network.

So far, 12 patients were included in the project. Of these, five (41.7%) were made aware of the research by physicians outside the HIAE, two (16.7%) by printed signs, two (16.7%) by internal HIAE doctors, two (16.7%) by Facebook and one (8.3%) by Twitter.

DISCUSSION

The main result of this research is that little more than half of the individuals who contacted the research team to receive information or participate in the project were reached by online publications (Facebook, Twitter, LinkedIn, and HIAE website). To this moment, this is the first study to demonstrate

TABLE 1. PROMOTION METHODS THAT LED TO CONTACT WITH THE RESEARCH TEAM.

Promotion methods	n	%
Social networks.	31	38.8
HIAE website	12	15.0
Internal doctor (emails)	6	7.5
External doctor (emails)	19	23.8
Signs on employee communication boards	12	15.0
Total	80	100

Notes: (n = number, % = percentage). HIAE: Hospital Israelita Albert Einstein.

the role of this form of communication in the recruitment of participants for a clinical trial on rehabilitation. Most participants, however, received information from their physicians. It is possible that health professionals promoted the protocol to individuals with higher potential of eligibility, rather than lay individuals informed about the research by social networks. Even so, both conventional methods of communication and postings on social networks have contributed to the inclusion of participants.

In Brazilian studies on rehabilitation that detailed the recruitment of patients, different strategies were used. In a research on the use of neuromodulation combined with physical therapy in the first weeks after a stroke, the protocol was individually presented to patients treated in the acute phase in a tertiary hospital.[10] In another study focused on the effects of motor training up to six months after a stroke, the promotion was done by means of leaflets distributed in public places, electronic brochures distributed in non-governmental organizations or hospital websites, communication with neurologists who worked in private clinics, physical therapists who worked in rehabilitation clinics or hospitals, and other researchers.[9] The most successful strategy was the referencing by physical therapists responsible for the patients' hospital treatment (75%). Electronic Brochures motivated contact with researchers in only 1% of the cases. Other digital forms of research promotion were not used.

In other studies, 15% to 100% of the individuals who sought information about research protocols were reached by publications on websites. In addition, between 9% and 91% of the individuals included were reached by these promotion methods.[14, 18-20, 22] In some studies, in fact, the promotion was done exclusively on social networks.[15-17]

Therefore, our results and those of other authors indicate that the online publication of protocol information can contribute to the reaching of potentially eligible individuals. The promotion on Facebook through segmented profiles was more effective than the traditional posting in this social network, according to our data and in line with what was reported by other authors.[29] Therefore, targeting ads to specific audiences can facilitate the recruitment of participants.

In almost 80% of the cases, the individuals who contacted the HIAE researchers were not the individuals who had suffered a stroke, but a relative. This result was expected, considering that the neurological deficits may impair the ability of communication between patients and researchers, as well as the patient's access to the means of research promotion.

This study presents some limitations. The mean age of patients potentially eligible was lower than the ones described in epidemiological studies of population or hospital database in Brazil.[1-3] However, the ages of the individuals who contacted the researchers were not recorded. According to a survey conducted by the ComScore website in 2014, in the United States, the average age of social network users is 25-34 years (Facebook and Twitter) and 35-44 years (LinkedIn).[30] We do not know whether individuals of these age groups predominated among those who contacted the researchers by digital means or otherwise. In the same way, we cannot conclude whether there is a relationship between the age of these individuals and the lower mean age of the patients who motivated the contact.

CONCLUSION

Online postings can be as useful for the promotion of a research protocol on rehabilitation as conventional strategies, such as the use of posted signs or sending emails to health professionals. The communication with health professionals can facilitate the recruitment of individuals with a higher probability of eligibility than the promotion on social networks, but both traditional methods and online postings can contribute to the inclusion of participants. These results may have an impact on the planning of clinical trials on the effects of rehabilitation interventions in individuals with cerebral vascular accidents and of research projects in general, in places where access to social networks or hospital websites is part of the everyday life of the population.

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RESUMO

OBJETIVO: *Avaliar prospectivamente o sucesso de estratégias de divulgação de um protocolo de reabilitação motora para indivíduos com doenças cerebrovasculares no Hospital Israelita Albert Einstein (HIAE).*

MÉTODOS: *Um ensaio clínico de neuromodulação e reabilitação para indivíduos com acidente vascular cerebral (AVC) e paresia do membro superior utilizou meios de divulgação digitais e meios tradicionais, não digitais. Foram calculadas frequências das modalidades de divulgação que alcançaram indivíduos potencialmente elegíveis para o protocolo.*

RESULTADOS: *Foram analisados dados de 80 indivíduos que manifestaram interesse em participar da pesquisa. As formas de divulgação mais frequentes que motivaram o contato foram redes sociais (38,8%) e informações fornecidas a médicos externos ao HIAE (23,8%). As frequências de contatos motivados por publicações na internet (53%) foram semelhantes às de contatos motivados por divulgações convencionais (47%) (p=0,288). Em relação às publicações sobre a pesquisa na internet, a divulgação pelo Facebook foi a mais eficiente, seguida pelo site do HIAE.*

CONCLUSÃO: *A divulgação de um protocolo de pesquisa em reabilitação por meio de publicações em redes sociais e sites pode ser tão eficaz quanto estratégias convencionais de comunicação. Estes resultados podem ter impacto no planejamento de ensaios clínicos, incluindo os que têm por objetivo avaliar efeitos de intervenções de reabilitação em indivíduos com AVC.*

PALAVRAS-CHAVE: *Internet. Mídias sociais. Rede social. Neurologia. Acidente vascular cerebral. Modalidades de fisioterapia.*

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ORIGINAL ARTICLE

The cardiac profile and electrocardiographic standard of at-height workers

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SUMMARY

BACKGROUND: *The Medical Control Program for Occupational Health establishes the required supplementary exams, according to the activity exercised by the worker and its inherent risks. The Regulatory Norm No. 35, recently deployed, stipulates that at-height workers must undergo electrocardiogram exams as an additional routine examination.*

OBJECTIVE: *To evaluate the electrocardiographic standard in at-height.*

METHODOLOGY: *A cross-sectional study, developed from May 2014 to January 2015 with male at-height workers. Anthropometric and clinical data were collected after the electrocardiogram (ECG). The workers included in the program were evaluated by an occupational medicine service of Serra Gaúcha, responsible for medical assessment and occupational tests. All workers were assessed by the researcher.*

RESULTS: *A total of 561 at-height workers participated in the study. The average age was 35.9 ± 12.2 years. A total of 176 (31%) presented electrocardiographic changes in the analysis of the resting ECG. Regarding the amendments in the resting ECG, 15.7% were attributed to changes in ventricular repolarization, 8% as blocks conductions, and 5.8% as left ventricular overload. Demographic variables were not associated with changes in the electrocardiographic tracing*

CONCLUSION: *This study demonstrated the electrocardiographic alterations and the profile of at-height workers. These findings can help determine prevention strategies and provide warnings of possible future harms to the health of these workers.*

KEYWORDS: *Electrocardiography. Occupational Health. Occupational Medicine. Cardiovascular Diseases.*

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, totaling 30% of all deaths globally. The American Heart Association published that the overall rate for deaths attributed to CDV in 2013 was of 222.9/100,000 Americans, corresponding to 30.8% of all deaths in the United States.[1,2]

Ischemic Heart Disease (IHD) is the world leader in the cause for loss of years in life expectancy due to the premature death of individuals over 30 years old. Studies show that the estimates related to work and mortality caused by IHD, among the working age population, varies from 8% in Korea, to 17% in Denmark and Finland, with high costs to health systems.[3,4]

The WHO recommends a reduction in 25% of deaths caused by chronic non-communicable diseases (NCDs). In Brazil, actions are aimed at the pre-

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vention of CDV risk factors (RF).[5, 6] Among RFs, we can cite systemic arterial hypertension (SAH), cholesterol, smoking, diabetes mellitus, and others[7].

The Ministry of Labor and Employment, by means of guidelines and standards, defines mechanisms for the mitigation of risks and damages to the health of workers, which are of the responsibility of both employer and employee. Complementary exams, in accordance with the activity performed by the worker, are essential for the prevention of these scenarios, for which the company is liable from the activity and/or location of such worker.[8]

The Regulatory Norm (NR) No. 35, of 2012, concerns at-height workers involved in activities performed at least 2 meters above ground level. Periodic examinations and clinical evaluations are required of the workers. Among exams, the electrocardiogram (ECG) is required and considered a tool in the early diagnosis of CVDs that may cause sudden illnesses and falls from heights.

Falls are the leading cause of death from injuries in civil construction, presenting a considerable number of fatal accidents. Protective measures and early prevention, such as the use of personal protective equipment and accuracy in the diagnosis of diseases that lead to falls, have been implemented.[10-13]

With that in mind, the present study assessed the electrocardiographic standard and cardiac profile of a population of at-height workers.

METHODOLOGY

Study design and development

A cross-sectional study, conducted in a service of occupational medicine authorized to carry out periodic examinations in a municipality of the Serra Gaúcha, from May 2014 to January 2015.

Participants

A total of 561 male workers, >18 years old, who worked at heights with a resting electrocardiogram were included. Workers with low-quality ECG tracings and those who refused to participate in the study were excluded.

Study variables

The variables assessed were: ECG tracing, ethnicity, age, smoking habits, blood glucose, alcohol consumption, physical activity, body mass index (BMI), family history and arterial pressure values. The number of years of experience of the workers was not considered.

Study logistics

The resting ECG was performed in all the at-height workers who fit the NR 35 and had been referred by the doctor of the Occupational Medicine company. A digital ECG machine was used, Micromed Wincardio USB with 12 simultaneous leads. The 12 leads were recorded at a speed of 25 mm/s and standard calibration for 1.0 mV/cm. The electrocardiographic tracings were analyzed and reported by a cardiologist of the hired company, in accordance with the criteria and recommendations of the Brazilian Society of Cardiology Guidelines on the Electrocardiographic Analysis and Reporting of 2009.[14]

For data collection, were considered: smoking (>1 cigarettes/day), sedentary lifestyle (less than 30 minutes of physical activity/day or < 150 min/week), BMI (≥25,0 kg/m² for overweight and ≥30 kg/m2 for obesity), hypertension (≥140/90 mmHg), diabetes mellitus (> 126 mg/dl for fasting blood glucose), alcoholism (250 mg/week).[15-18]

Sample size calculation

For calculating the sample size, we used a Brazilian cross-sectional study[19], whose prevalence of ventricular repolarization was of 9.5% and overload of the left ventricle of 3.3%. A confidence level of 95% and a margin of error of 3 percentage points were considered, leading to 367 individuals necessary for the sample size calculation. We opted for a sample for a specified period of collection, resulting in 561 consecutive workers and a single ECG per worker. Only those with adequate technical standards were assessed.

Ethical aspects

The project was approved by the local Research Ethics Committee under the number CEP/IC-FUC UP 4.964/2014 and all participants in the study signed an Informed Consent Form (ICF).

Statistical analysis

For data analysis, we used the statistical software *Statistical Package for Social Science* (SPSS), version 23. The continuous variables were tested for normality by the Shapiro-Wilk test and described as a mean and standard deviation, and the categorical vari-

ables in absolute value and percentages. The Student t-test was used to compare the average ages between workers with and without electrocardiographic alterations. For the comparison of prevalences[19-21] of alterations in at-height workers against other samples from studies in the literature, we employed the chi-square test. An alpha of 0,05 was considered statistically significant.

RESULTS

Participated in the study a total of 561 at-height workers, male, white (86.9%), with an average age of 35.9 ±12.2 years. Sedentary lifestyle was the most prevalent RF (90.5%), followed by increased pressure levels (53.1%), and alcohol consumption (41%). The association between electrocardiographic alterations and the variables analyzed did not present any statistically significant difference (table 1).

In Figure 1, we can observe that out of the 561 workers, 31% (n=176) did not present a normal ECG tracing. A total of 222 electrocardiographic alterations were found, with more than one alteration present in some tracings. The diagnosis criteria for LVO used were the ones presented by Sokolow-Lyon, Cornell e Romhilt-Estes.

Electrocardiographic changes compared with other studies are as shown in Figure 2.

The prevalence of conduction blocks was of 9% among workers, and the most prevalent were LAHB (3.5%) and RBBB (2.8%).

TABLE 1 - ANALYSIS OF THE ASSOCIATION BETWEEN ELECTROCARDIOGRAPHIC ALTERATIONS AND THE VARIABLES ANALYZED

Variables	(%)	alterations ECG	p
Age (years)			
<30	31.0	65	0.925
≥30	31.7	111	
Ethnicity			
white	31.9	154	0.599
black	28.2	22	
Body Mass Index			
Up to 24.9 Kg/m²	31.2	83	
≥25 a 29.9 Kg/m²	29.9	63	0.618
≥30 Kg/m²	35.7	30	
Blood Pressure			
Up to 140x90mmHg	32.2	59	0.833
≥ 140x90mmHg	31.0	117	
Glycemia			
< 100 mg/dl	32.3	139	0.275
≥ 100 mg/dl	25.3	20	
Smoker			
yes	28.5	59	0.305
no	33.1	117	
Family History			
yes	32.7	66	0.687
no	30.6	110	
Sedentary Lifestyle			
yes	31.8	161	0.665
no	26.4	15	

DISCUSSION

The present study analyzed the profile and electrocardiographic alterations of at-height workers in a southern area of Brazil. National publications on profiles and ECG alterations for specific populations are scarce.

Among the workers, RF such as a sedentary lifestyle (83.7%), high blood pressure levels (53.1%), alcohol consumption (41%), smoking (37%) and family history (36%) were higher than in other national studies with RF of chronic diseases.[19, 23, 24] Gus et al.,[25] when analyzing RFs for CAD, found results lower than ours, with the exception of obesity/overweight and hypertension, whose prevalence rate was around 68% and 40%, respectively. The influence of cardiovascular RFs varies between men and women, which could justify our findings, since the samples of the other studies were formed mostly by women.[26, 27] The prevalence of SAH of 32.6% was similar to a study performed with male transport drivers from the state of Piauí.[28]

During the analysis of the ECG tracings, most (69%) at-height workers presented normal sinus rhythm. For the electrocardiographic alterations associated with workers' RFs, there was no correlation between the variables. Alterations in ventricular repolarization (VRA) (6.7%), followed by conduction blocks and left ventricular overload (LVO) (5.6%) were the most prevalent in our study. In a national study with 1,067 individuals, the RFs for ischemic disease in this population were correlated with high cholesterol and hypertension, and the most prevalent electrocardiographic alterations were VRA (9.5%) and LVO (3.3%). In comparison with the VRA found in our study, the percentage was higher.[19]

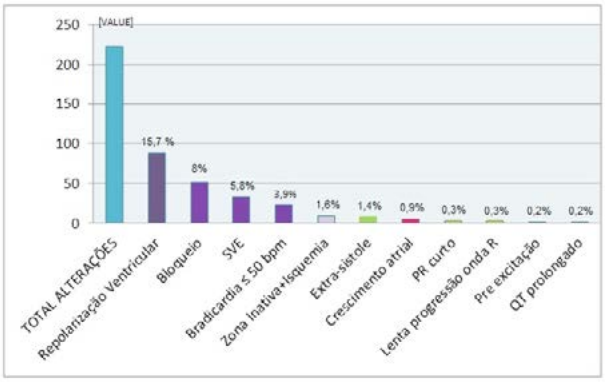
In the Framingham study,[20] the VRAs (14.1%) found in male participants were similar. The phenomenon of repolarization gained further attention after bringing contributions to the risk stratification of serious arrhythmic events and sudden deaths.[14] Among the repolarization alterations, the early repo-

larization pattern (ERP) was present in 4.5% of the at-height workers, a similar number to that found for the general population — something that is noteworthy, since recent studies have shown a correlation between this alteration and sudden cardiac deaths.[29]

The most significant clinical implication of the conduction blocks is its relationship with cardiac patients. In healthy individuals, blocks are considered trivial electrocardiographic abnormalities, thus justifying our findings. Among blocks, the left anterior fascicular block (LAHB) was the most prevalent, with 2.8%, surpassing the results found in the literature.[2]

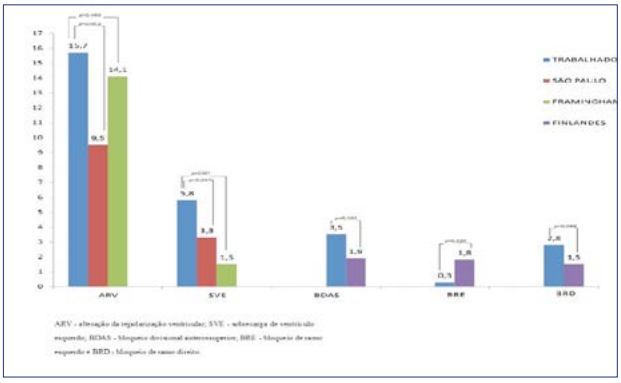
A Finnish population study with 6,315 participants assessed the prevalence of eight conduction blocks and their association with RFs and CVD by means of ECG. In this study, the most prevalent block, differently from what we found, was the right bundle branch block (RBBB), with 3.9%, followed by incomplete LBBB (1.8%), and left bundle branch block (LBBB), for which age and gender are intervening variables. Our sample was composed exclusively by men, younger than those in the Finnish study.[30-33] Emphasis should be given to the LBBB, since it is an electrocardiographic alteration associated with an increased risk of sudden cardiac death. The prevalence of LBBB was lower than in other studies with no heart disease basis.[34, 35]

FIGURE 1 - NUMBER OF ELECTROCARDIOGRAPHIC ALTERATIONS PRESENT IN WORKERS



SVE - sobrecarga de ventrículo esquerdo; bpm - batimento por minuto

FIGURE 2 - ELECTROCARDIOGRAPHIC ALTERATIONS, IN COMPARISON WITH OTHER STUDIES



Since the groundbreaking observations of the *Framingham Heart Study*, several epidemiological studies have highlighted LVO as one of the most important RFs for angina pectoris, myocardial infarction, cerebrovascular accident (CVA) and sudden death.[21] Despite the low sensitivity of the ECG for left ventricular hypertrophy (LVH), it is still the most widely used complementary examination in cardiology clinics and medical offices. After evaluating the influence of the ECG in LVO according to gender and cardiac mass, a Brazilian study concluded that the diagnostic sensitivity of the ECG is higher among males.[36] The results LVO results found in at-height workers coincide with the prevalence values reported in international studies, which vary from 3% to 14% in males. In studies with reference to Framingham, the ECG presented a 6.9% sensitivity and 98.8% specificity for LVO, finding a 2.9% LVO prevalence in ECG tracings for male individuals (n=2,042).[22, 37, 38]

The results found were compared with electrocardiographic alterations observed in other studies. The Framingham Heart Study (n=4.684), when compared with at-height workers, presented a value of p=0.450 for VRA and p<0.001 for LVO. When compared to a Finnish study that researched the prevalence of blocks in 6,315 individuals, the p-value was significant only for LBBB (p=0.020). After a comparison with findings from a population (n=1,067) from the São Paulo region, there was a significant difference for VRA and LVO. (p=0.002 and p=0.047, respectively)[19] (Figure 3).

CONCLUSION

The present study found that the prevalence of LVO and VRA in at-height workers from Serra Gaúcha is higher in comparison to Brazilian population studies. It is possible that the absence of correlation between risk factors and electrocardiographic alterations in the study is due to the fact that the average age of the participant workers is lower than that of the average population. The ECG remains a nec-

essary exam, fundamental for the CVD diagnosis, since the morbidity profile is not linear and the implemented health actions do not have the expected effectiveness. New studies in specific populations are necessary to assess electrocardiographic alterations associated with CDV risks and sudden death.

STUDY LIMITATIONS

The age of the studied population was a limitation, since electrocardiographic alterations and conduction blocks are more prevalent in older populations. Another limiting factor was the interpretation of the interpretation of electrocardiograms, conducted by a single professional. It is recommended that reports be assessed by two independent professionals, thus confirming the diagnosis.

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RESUMO

FUNDAMENTO: *O Programa de Controle Médico e Saúde Ocupacional estabelece a realização de exames complementares de acordo com a atividade exercida pelo trabalhador e os riscos a ela inerentes. A Norma Regulamentadora nº 35, implantada recentemente, estabelece que trabalhadores que exercem funções em altura realizem o eletrocardiograma como um exame complementar de rotina.*

OBJETIVO: *Avaliar o padrão eletrocardiográfico dos trabalhadores em altura por meio da realização do ECG de repouso.*

MÉTODOS: *Estudo transversal, desenvolvido de maio de 2014 a janeiro de 2015 com trabalhadores masculinos que exercem funções em altura. Foram coletados dados clínicos e demográficos e, após, realizado o eletrocardiograma (ECG). Os trabalhadores incluídos eram vinculados a um serviço de medicina do trabalho da Serra Gaúcha, destinado à realização de avaliação médica e exames ocupacionais. Todos foram avaliados pela pesquisadora.*

RESULTADOS: *Participaram 561 trabalhadores em altura. A média de idade foi de 35,9±12,2 anos, e 176 (31%) apresentaram alterações eletrocardiográficas na análise dos ECG de repouso. Das alterações do ECG de repouso, 15,7% foram atribuídas a alterações da repolarização ventricular; 8% como bloqueios de condução e 5,8% como sobrecarga de ventrículo esquerdo. As variáveis demográficas não estavam associadas com alterações no traçado eletrocardiográfico.*

CONCLUSÃO: *Este estudo verificou que a prevalência de sobrecarga de ventrículo esquerdo e alteração da repolarização ventricular, nos trabalhadores em altura, é maior quando comparada a estudos populacionais brasileiros. A associação de fatores de risco e alterações eletrocardiográficas em indivíduos difere de populações específicas.*

PALAVRAS-CHAVE: *Eletrocardiografia. Saúde do trabalhador. Medicina do trabalho. Doenças cardiovasculares.*

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ORIGINAL ARTICLE

Analysis of influencing factors of severity in acute pancreatitis using big data mining

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SUMMARY

OBJECTIVES: *To evaluate the epidemiological characteristics of acute pancreatitis (AP) and explore potential relationships between these factors and severity.*

METHODOLOGY: *Data-sets of 5,659 patients with AP from health statistics and the Information Center of Jiangsu province, between 2014 and 2016, were analyzed. A self-organizing map (SOM) neural network was used for data clustering.*

RESULTS: *Biliary acute pancreatitis (BAP) (86.7%) was the most frequent etiological factor. A total of 804 (14.2%) patients had severe acute pancreatitis (SAP). The mean age of patients was 53.7 ± 17.3 (range 12~94y). Most of the AP patients were married (75.4%); 6% of mild /moderately severe AP (MAP/MASP) patients were unmarried, which was less than SAP patients (P=0.016). AP patients with blood type AB in the general population (8.8%) was significantly lower than that of AP cases (13.9%) (P=0.019) and SAP cases(18.7%) (P=0.007). The number of AP patients in southern Jiangsu was much higher than that in northern Jiangsu province, especially in Nanjing (1229, 21.7%). The proportion of acute alcoholic pancreatitis (AAP) in the north of Jiangsu (Xuzhou 18.4%) was much higher than that in southern Jiangsu (Suzhou 2.6%). The whole sample was divided into five classes by SOM neural network. If BAP patients were male, old, divorced, and blood type AB or B, they were more likely to develop SAP. Middle-age, unmarried or divorced male patients with blood type B/AB who suffered from HAP or AAP were also more likely to develop SAP.*

CONCLUSIONS: *The number of unmarried patients with MAP/MASP was smaller than that of SAP. Blood types AB and B were more frequent in AP, especially in SAP. The differences between southern Jiangsu and northern Jiangsu, in number of AP patients and the proportion of AAP, were significant. In class I and class IV, the ratio of SAP was much higher than in other classes and the whole sample.*

KEY WORDS: *Pancreatitis. Acute Necrotizing Pancreatitis. Data Mining. ABO Blood-Group System.*

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INTRODUCTION

In recent years, acute pancreatitis (AP) has become one of the most severe acute digestive disorders all over the world, including in China.[1-3] The mortality rate of mild AP (MAP) is lower than 1%, however, 20% of all cases may develop into severe acute pancreatitis (SAP). The mortality rate for SAP remains high, from 10% to 30% due to pancreatic necrosis and organ failure. Although many epidemiological studies on etiology and severity in AP have been carried out, most of them used simple statistical correlation analysis or single factor analysis, and their sample size was relatively small.

Big data is defined as information assets characterized by such high velocity, variety, and volume that specific data mining methods and technology are required for its transformation into value.[4] In some studies, big data mining provided useful information for the healthcare area. The number of data sets obtained from routine operations in healthcare has rapidly increased and valuable information can be extracted from large and complex datasets.[5,6] Big data from healthcare may not only provide useful information, enabling the public sector and healthcare providers to assess their healthcare systems and distribution of resources, but also has excellent potential to improve our understanding of the effectiveness of treatments in the real world, as well as of the incidence, management, and prognosis of various medical conditions. Useful information obtained from big data will allow health professionals to provide better medical care.[7]

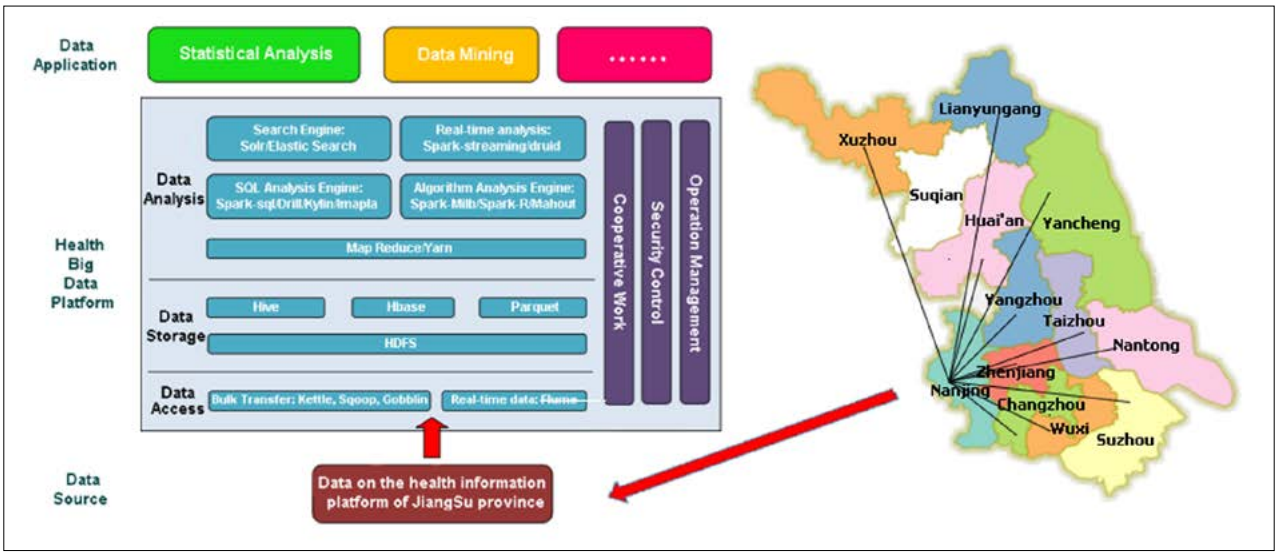
In our study, we chose the Jiangsu province the research target and analyzed data of hospitalized patients with AP in the multicenter of Jiangsu province, between January 2014 and December 2016. This was the first and most extensive series of patients with AP used to investigate its incidence, character and severity in China. The aim of this study was to evaluate the epidemiological characteristics of AP and explore potential relationships between these factors and severity.

METHODOLOGY

The data-set came from the Health Information Platform of the Jiangsu province and was provided by the Health Statistics and Information Center of the Jiangsu province. Twelve prefecture-level cities, including Nanjing, Zhenjiang, Wuxi, Changzhou, Suzhou, Nantong, Yancheng, Xuzhou, Lianyungang, Yangzhou, Taizhou and Huai'an, were connected to the Health Statistics and Information Center of the Jiangsu province and authorized it to store, integrate and process data. The data storage and parallel computing architecture are based on open source big data processing framework, including Hadoop and Spark. The concrete frame can be found in Figure 1.

The data in the current study were structured, highly organized and searchable by a straightforward and simple algorithm. The data-set contained 5,659 consecutive AP patients who were admitted to hospitals from ten prefecture-level cities of the Jiangsu province, between January 2014 and December 2016. Medical history, demographics, severity and mortality, interventions, complications and medical costs of

FIGURE 1



AP patients were extracted from the data-sets. The study was approved by the Ethics Review Committee at the Jinling Hospital and the Health Statistics and Information Center of the Jiangsu province. The research was carried out according to the principles of the Declaration of Helsinki.

Diagnostic standard and severity of AP were also in accordance with the revision of the Atlanta classification consensus of 2012.[8] AP patients were diagnosed based on the presence of at least two of the following three criteria: (1) an initial serum amylase and/or lipase level at least three-fold above the normal upper limit; (2) typical abdominal pain consistent with AP; and (3) suggestive imaging evidence compatible with AP, such as CT, MRI and ultrasonography. SAP was diagnosed according to organ function failure, and/or local complications (abscess, necrosis, or pseudocyst).[9] Organ function failure was defined as a shock (systolic pressure less than 90 mm Hg), renal function failure (serum creatinine more than 2.0 mg/dL after hydration), pulmonary function insufficiency (PaO_2 no more than 60 mm Hg), or gastrointestinal hemorrhage (more than 500ml/24 hr.). The etiologies of AP were distinguished as follows: If gallstones were found by imaging tests in the gallbladder, or in the bile duct, or in both, the case would be diagnosed as acute biliary pancreatitis (ABP);[10] If triglyceride level in blood plasma was more than 11.3mmol/L, the case would be diagnosed as hyperlipidemic acute pancreatitis (HAP);[11] Alcoholic acute pancreatitis (AAP) was considered when daily alcohol consumption was over 80g for more than five years or if there was social or weekend abuse on a regular basis for not less than five years.[12] When AP was induced by traffic accidents, falling injuries, abdominal surgery, and various kinds of injury factors, it was defined as traumatic acute pancreatitis (TAP).[13] In addition to the above etiologies, AP induced by a parathyroid tumor, pancreatic carcinoma, mumps, hypertriglyceridemia, or some drugs (chlorpromazine, phenformin, azathioprine, etc.) was summarized as other types of AP (OTAP). If etiologies could not be found for AP patients in their clinical history, by laboratory or imaging tests, these cases would be defined as idiopathic AP (IAP).

A Self-organizing map (SOM) is a clustering tool that focuses on the neighborhood structure between classes. A SOM is a predefined network, it defines a mapping from the input data space R^n onto a 2-d array of nodes. It can convert complex nonlinear statistical relationships between high-dimensional data items into simple geometric relationships on a low-dimensional display.[14-15] Recently, the SOM method has been introduced more extensively in many fields.[16-17] In our study, a batch SOM algorithm was used for training. The training mode was composed of an input layer and a computational layer; six variables were brought into the input layer, including age (eight categories: 0~20y, 21~30y, 31~40y, 41~50y, 51~60y, 61~70y, 71~80y,>80y), gender (two categories: male and female), marital status (four categories: unmarried, married, divorced and widowed), blood type (four categories: A, B, O and AB), etiology (six categories: BAP, HAP, AAP, TAP, IAP and OTAP) and severity (two categories: MAP/moderately severe AP (MSAP) and SAP). First, initialization was performed, each node distributed its parameters randomly and had the same number of parameters as the input dimension. Then, each input data was matched to the most appropriate node, if the input is D dimensional, that was X = {x_i , i= 1,... D}, the discriminant function could be represented by the Euclidean distance: $d_j(x) = \sum_{i=1}^{D}(x_i - w_{ij})^2$. An adjacent neighborhood was set up as $S_k(t)$, The power of the output neuron and its adjacent neurons were modified by the formula: $w_{ij}(t+1) = w_{ij}(t) + \eta(t)[x_i(t) - w_{ij}(t)]$, in which h(t) is a gain term which tended to gradually decreased to zero to facilitate convergence, and $\eta(t) = 0.2(1 - \frac{t}{10000})$. Output (O_k) equals to $f(\min \mathrm{P} X_j - W_j \mathrm{P})$, New normalized learning samples were used to repeat the learning process. The training automatically stopped when the full number of epochs had been reached. The learning rate of the classification phase was 0.8, and the neurons of the computational layer were presented with a 20×20 hexagonal topology. The graphical diagram of the SOM neural network can be found in supplementary figure 1, and the Matlab code of the program in appendix. The Davies-Bouldin index (DBI) was used to access clustering separation. The formula was as the follows: $DBI = \frac{1}{c}\sum_{i=1}^{c}\max_{i \neq j}\left\{\frac{\Delta(X_i) + \Delta(X_j)}{\delta(X_i, X_j)}\right\}$,in which D($X$ k) presented the in-class distance of class k, (Xi, X j) presented the between-class distance from class i to class j, and c was the number of classes. The results were evaluated according to the following rule: the lower the DBI value, the better the clustering effect.

Continuous data were expressed as mean values + standard deviation. Significant differences between groups were determined by chi-squared analysis and unpaired Student t-test. Modeling was developed to cluster the variables related to AP using Matlab2017 software (MathWorks Institute, USA). Statistical

analysis was performed using SPSS 21.0 software (SPSS, Chicago, IL, USA). Dichotomous variables were created out of continuous variables by using clinically-important cut off points. In our study, P values<0.05 were considered statistically significant.

RESULTS

Gender, etiology of AP and severity of AP

Out of all AP patients, 3,152 were male (55.7%) and 2,507 females (44.3%). In the etiological factors of AP, BAP (86.7%) was the most frequent, followed by AAP (7.7%), HAP (3.4%), TAP (1.1%), IAP (0.5%) and OTAP (0.6%). Out of the total number of patients, 804 (14.2%) had SAP and 4,855 (85.8%) had MAP or MSAP;

Age and AP

The mean age of patients was 53.7 + 17.3 (range 12~94y). AP often occurred in three periods, 50-60 years old (29.3%), 40-50 years old (21.8%) and 60~-70 years old (17.2%).

Marital status and AP

Most of AP patients were married (75.4%). Among MAP/MSAP patients, 6% were unmarried. However, 16% of SAP patients were unmarried, thus the difference was significant (*P*=0.016).

ABO blood type and AP

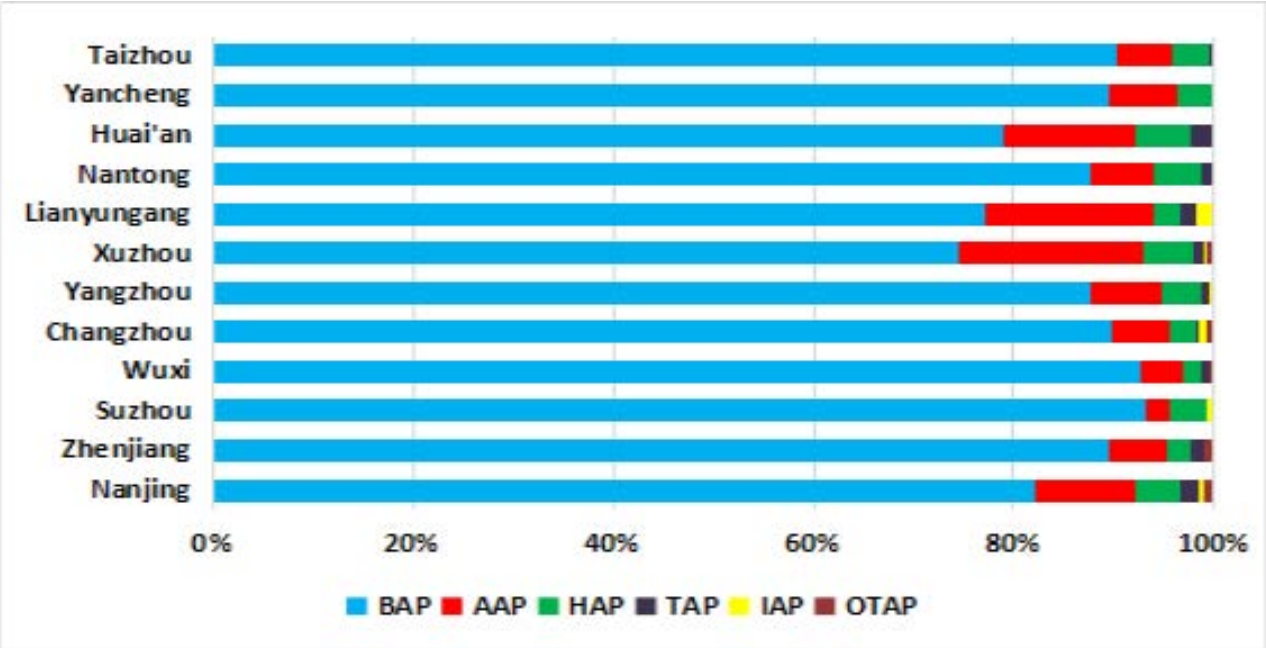
In terms of ABO blood type, AP patients with blood type AB accounted for 8.8% of the general population and was significantly lower than that of AP cases (13.9%)(*P*=0.019). In subgroups of SAP cases, the number of AP patients with AB blood type reached 150 (18.7%)(*P*=0.007). A similar phenomenon was found in AP patients with blood type B (33.4%). However, the difference between AP cases and the general population (30.1%) wasn't significant (*P*=0.094).

Regional distribution of AP

A total of 5,659 patients with AP were included in the data-sets. Based on the heat map of the geographical distribution of AP patients in the Jiangsu province (Supplementary Figure2), there were much more AP patients in the southern Jiangsu province than in the northern Jiangsu province, especially in Nanjing (1,229; 21.7%), Suzhou (764; 13.5%) and Yangzhou (663; 11.7%). The total number of AP patients in the three areas made up approximately 50% of the whole of Jiangsu province.

The relationship between the geographical distribution of AP and etiological factors was analyzed. The proportion of AAP in the northern Jiangsu province (Xuzhou 18.4%, Lianyungang 16.9%, Huai'an 13.2%) was much higher than that in the southern Jiangsu province (Suzhou 2.6%, Wuxi 4.4%, Changzhou 5.8%). The incidence of HAP in all regions was approximately the same, but it was relatively lower in Wuxi (1.8%) and Lianyungang (2.5%) when compared with other places in the Jiangsu province. TAP occurred more frequently in Nanjing and Huai'an (Figure 2).

FIGURE 2



SOM neural network

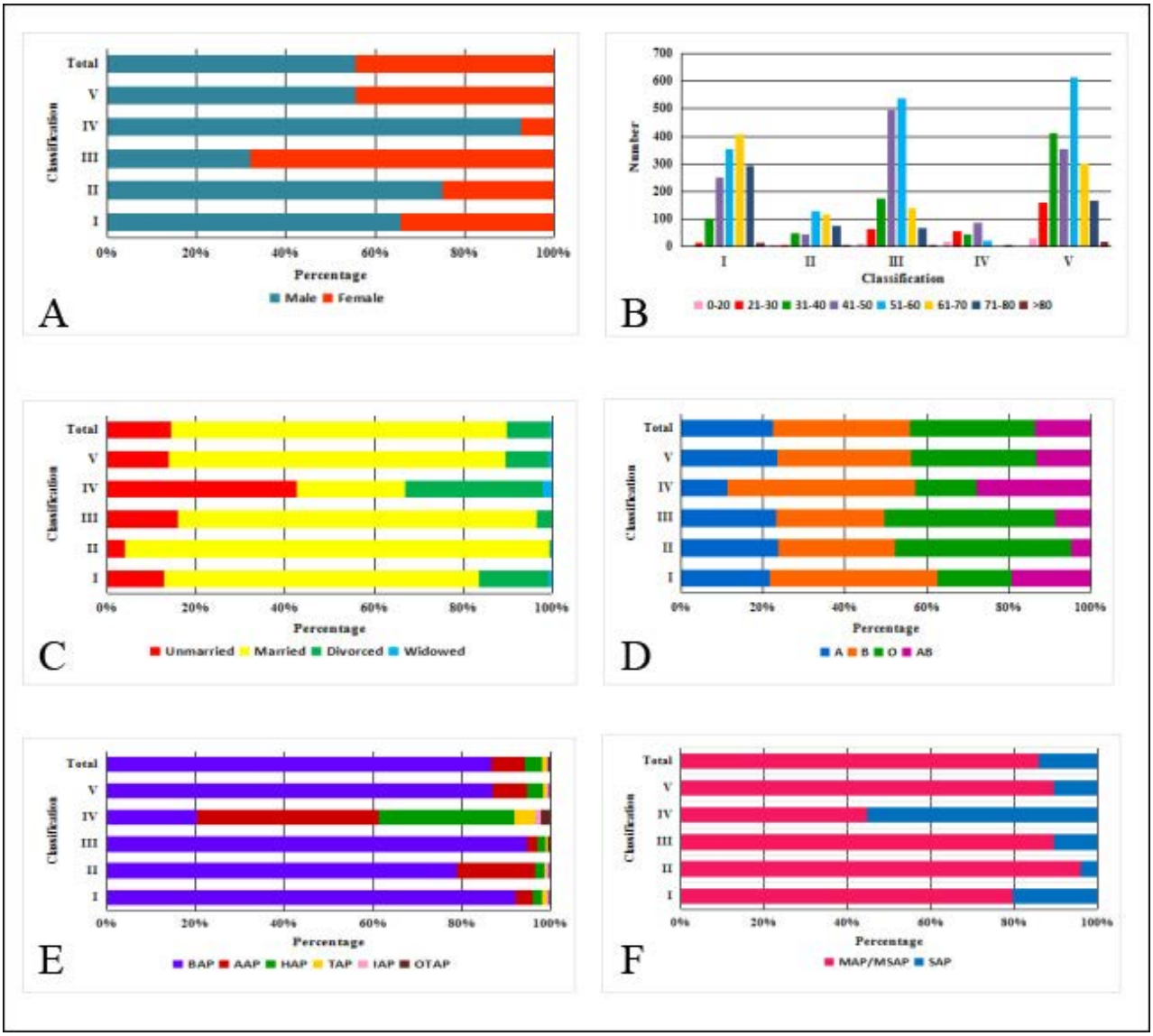
After the training by the SOM network classification algorithm, we found that the DBI index was the smallest (DBI = 0.89) when the number of steps was 200 epochs, so the study was based on 200 epochs. Then the distance matrix and color matrix of the SOM neural network were calculated, and a cluster distribution feature map was drawn (supplementary figure 3). In the picture, each hexagon in the diagram represents a case, the between-classes distance was gradually increasing when the color of the unit changed from black to white, and there was no clear distinction between the cluster results. The class boundary was set by dark, continuous, adjacent nodes. The whole SOM network was divided into five parts, which defined the number of clustering categories as five. The clustering results of the SOM neural network were evaluated by the DBI index. When the number of clustering was five, the DBI index was the smallest value (0.89), which showed the effect of clustering model was the best.

In the data-sets attribute classification feature map (supplementary figure 4), the same neuron represented the same patient. In figure 4, the effect of clustering of etiological factors, severity of AP and ABO blood type was similar to that of the general clustering distribution, which illustrates that the four attributes played critical roles in the process of clustering.

Explanation of clustering results

The variables of age, gender, etiological factors, marital status, severity of AP and ABO blood type were compared in different categories of AP patients by One-way ANOVA. When the difference found was significant ($P<0.05$), it proved the effects of the clus-

FIGURE 3



ter were good (Appendix Table). The whole sample was divided into five classes by the SOM neural network (Figure 3).The characteristics of AP patients in class I could be described as follows: most of the AP patients were male (65.6%); the main range of onset age was 55~65 years; as far as marital status was concerned, the percentage of divorced patients in class I was higher than that of the entire sample (15.8% vs 9.6%); blood type B and blood type AB were more frequent than other types; the main etiology of the class was BAP (92.3%); there were 291 SAP patients in the current class (20.1%), which was more than the whole (14.2%). In class II, the proportion of men accounted for 75.1% of the total and the average age was about 59.5 years; most patients were married (95.5%); the percentage of blood type O patients was higher than that of the whole (42.9% vs 30.7%); in terms of etiology, AAP accounted for 17.5%, which was more than the entire sample (7.7%). Furthermore, few of them were SAP (4.1%). From class III, we found that most of the patients had the following characteristics: female (68.1%), 40~50 years, married (80.7%), blood type O (42.0%), BAP (94.6%) and the number of SAP patients in the class was only 145 (10.4%). However, in class IV, most patients were men (92.7%), the main range of onset age was 25~45 years; unmarried and divorced patients were the primary population (42.5% and 30.9%, respectively); blood type B and blood type AB were more frequent than blood type A or O; most patients suffered from HAP or APP. Furthermore, the proportion of TAP was much higher than in other classes (4.7% vs 1.2%, 0.4%, 0.6%, 0.9%); 55.4% of the patients were diagnosed as SAP, which was much more than in whole sample (14.2%). The characteristics of AP patients in class V were similar to that of the whole sample, including gender, age, marital status, blood type, etiology and severity of AP.

DISCUSSION

To the knowledge of the authors, the study described in the present report was the first and using the most extensive series of patients with AP to investigate characteristics by means of big data mining. The data-sets selected for current the study were nearly representative of the entire JiangSu province population; therefore, selection bias was not a problem.

In the present study, most of the AP patients were married, 40~60 years and BAP. There were relatively more male patients than female. SAP patients accounted for 14.2% of all patients, which was similar to the results of other studies found in the literature.[18,19] As far as blood type was concerned, blood type AB and B were more frequent in AP patients than in the general population of the JiangSu province (AB:13.9% vs 8.8%; B:33.4% vs 30.1%); the phenomenon was more significant in patients with SAP. During the past eight decades, some publications have examined the possible associations between blood type and infection. They reflected uncritical attempts to mathematically link unstratified or random data. The interaction between pathogen and the erythrocyte membrane may reflect antigenic similarity, adhesion through specific receptors, or modulation of antibody response. Epithelial cells express ABH and Lewis antigens, which are effectively cell-surface glycoconjugates used by parasites, bacteria, and viruses as receptors for attachment, resulting in different susceptibilities depending on the antigen profile of an individual.[20] By using the same blood group antigens as their host, certain microbial parasites utilize molecular mimicry as a defense against the host's immune system. The chemical signatures of the membranes of many gram-negative organisms, such as Escherichia coli, resemble A and B blood group antigens. In vitro experiments have shown that anti-B antibodies kill E. coli, and anti-A and anti-B antibodies may therefore play a similar role in destroying gram-negative bacteria in vivo.[21] B and AB blood groups were associated with increased incidence of E. coli, streptococcus pneumoniae, and salmonella infections, which are important pathogens for pancreatic infection, necrosis or sepsis.[22]

Regional distribution of AP was also analyzed. The number of AP patients in the northern Jiangsu province was much lower than that of the southern Jiangsu province. The reasons for that include several aspects: in addition to having a larger population, the economy and medical technology in the southern Jiangsu region is more developed than that of the northern Jiangsu region, which refers patients from surrounding areas to southern the Jiangsu region, especially to Nanjing. In terms of etiology, APP occurred more frequently in the northern Jiangsu region, especially in Xuzhou and Lianyungang. The reasons for geographic differences in the incidence of AAP were related to alcohol consumption. Men in these regions have a habit of alcohol abuse, especially on holidays. Many studies had confirmed that excessive alcohol consumption was a significant risk factor for AP.[23-26]

The strong support of a close link between alcohol and pancreatitis comes from individual-level studies and large samples. TAP occurred more frequently in Nanjing and Huai'an and was associated with the frequent occurrence of fatal traffic accidents in both areas and a higher number of pancreatic injuries from abdominal surgery in the Nanjing region.

The SOM neural network is one of the most suitable networks for segmentation. This is an unsupervised network based on the competitive learning and discovering of topological structures hidden in the input data for visual display in one or two-dimensional spaces.[27] Two huge advantages of the SOM-based segmentation methods are unsupervised training and fast learning. In our study, data-sets of AP patients were clustered by a SOM neural network.

Class I showed that the severity of old divorced male patients with blood type AB or B who suffered from BAP was usually serious. That is because older patients are not sensitive to pain due to the atrophy of the abdominal muscles and the degeneration of the peripheral nerves, meaning the peritonitis symptoms were not obvious, which led to misdiagnosis. The organ function of old patients is often poor, which can easily cause organ failure due to stress. Furthermore, blood type AB proved to be associated with gram-negative bacteria, which is an important type of pathogenic factor for infectious pancreatitis. All of the above would exacerbate AP.

Class II showed that if an AAP patient was old, male, married and had blood type O, he would not be severe. That may be because older men tend to consume less alcohol than the younger man, and the living habits of married men are bound to their families. Furthermore, it has been reported in the literature that alcohol as a cause of AP is not associated with the development of infected pancreatic necrosis.[28-30] These factors contributed to a relatively limited amount of alcohol consumption and didn't cause the necrosis of the pancreas, which reduced the likelihood of SAP.

In class III, middle-aged unmarried female BAP patients with blood type O often belonged to MAP or MSAP. These women may be more concerned with their career and have a more regular life.

Class IV disclosed that middle-age, unmarried or divorced male patients with blood type B/AB who suffered from HAP or AAP were likely to be SAP. Due to social factors, unmarried or divorced middle-aged men often have no good living habits, with excessive alcohol consumption. Crapulent phenomenon and alcohol abuse were much more evident than in other groups. Some studies have shown that blood type is related to infectious diseases. Moreover, the frequency of SAP and organ dysfunction of HAP was significantly higher than BAP. The combination of these factors significantly increased the severity of AP.[31]

There are a few limitations to our study. Firstly, although the data of the present study contains most of the basic information of AP patients from hospitals in the Jiangsu province, there were still a few hospitals that were not connected to the Health Information Platform of the Jiangsu province, and the Suqian district hadn't established medical networks yet, all of which resulted in incomplete data. Secondly, There are some disadvantages to clustering methods that use SOM neural network: increasing the number of neurons in this network does not usually result in a better segmentation performance; they need high-dimensional input space with empirical features for optimal performance;[32] and images with heavy noise cannot be segmented successfully.

In the future, more variables or parameters of AP patients will be dug to acquire more valuable information, and the data in consecutive years will be contrasted to explore the tendencies in AP characteristics and build a guideline for future interventions.

CONCLUSIONS

The number of unmarried patients in MAP/MASP was lower than that of SAP. Blood types AB and B were more frequent in AP, especially in SAP. The differences between southern Jiangsu and northern Jiangsu in number of AP patients and the proportion of AAP were significant. If BAP patients were male, old, divorced, and had blood type AB or B, they were more likely to develop into SAP; Middle-age, unmarried or divorced male patients with blood type B/AB who suffered from HAP or AAP were also likely to be SAP.

DISCLOSURE OF CONFLICT OF INTERESTS

The authors state that they have no conflicts of interest.

PALAVRAS-CHAVE: *Pancreatite. Pancreatite necrosante aguda. Mineração de dados. Sistema do grupo sanguíneo ABO*

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REVIEW ARTICLE

The use of drugs and medical students: a literature review

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SUMMARY

INTRODUCTION: *The consumption and abuse of alcohol and other drugs are increasingly present in the lives of university students and may already be considered a public health problem because of the direct impacts on the physical and mental health of these individuals. The requirements of the medical program play a vital role in the increasing rate of drug users.*

OBJECTIVES: *To carry out a systematic review of the literature on the use of drugs, licit or not, in Brazilian medical students.*

METHODS: *A descriptive-exploratory study, in which the SciELO and MEDLINE databases were used. A total of 99 articles were found, of which 16 were selected for this review.*

RESULTS: *Alcohol and tobacco were the most frequently used licit drugs among medical students. The most consumed illicit drugs were marijuana, solvents, "lança-perfume" (ether spray), and anxiolytics. The male genre presented a tendency of consuming more significant amounts of all kinds of drugs, with the exception of tranquilizers. It was found an increasing prevalence of drug consumption in medical students, as the program progressed, which may result from the intrinsic stress from medical school activities. Students who do not use psychoactive drugs are more likely to live with their parents, to disapprove drugs consumption, to practice religious beliefs and to be employed. Conclusion: The prevalence of licit and illicit drug use among medical students is high, even though they understand the injuries it may cause.*

KEYWORDS: *Substance-related disorders. Students, medical. Street drugs. Alcoholism.*

INTRODUCTION

The beginning of medical school is marked by a drastic change in lifestyle[1]. The student is subjected to enormous stress levels during the course of their academic training, which triggers deleterious consequences in both social and psychological levels[2]. Among them, is substance abuse, which is used by some students as a means of escape and relief to the problems faced during the program[3]. These substances activate the neural circuitry of reward and pleasure, allowing for better control of stress and, therefore, used by students in search of a feeling of well-being[4].

In fact, several studies have demonstrated there is a high prevalence of alcohol, tobacco, and illicit drug consumption among medical students[5]. The consequences of the excessive use of these substances go far beyond the organic damage already thoroughly described in the literature. Alcohol abuse, for instance, is correlated to an increase in crime, traffic violence, and absenteeism statistics[6]. In addition, the population in general expect medical students to be

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role models of healthy behavior. Upon seeing them making use of such substances, people can be falsely led to believe that drug consumption is a harmless practice and may take it up in daily life.

Hence, substance abuse by medical students may be considered a serious public health matter. Despite that, the situation is often underdiagnosed, since students do not seek expert help and tend to hide the problem[7]. Thus, it is essential to acknowledge the actual prevalence of substance abuse in medical schools. Moreover, it is necessary that the causes for this consumption and the possible measures to mitigate it be clarified and assessed.

The purpose of this paper is to carry out a systematic review of the literature on the use of drugs, both licit and illicit, among Brazilian medical students, seeking to identify what are the most commonly used substances, the main reasons that led to this consumption and the most widely reported risk and protective factors.

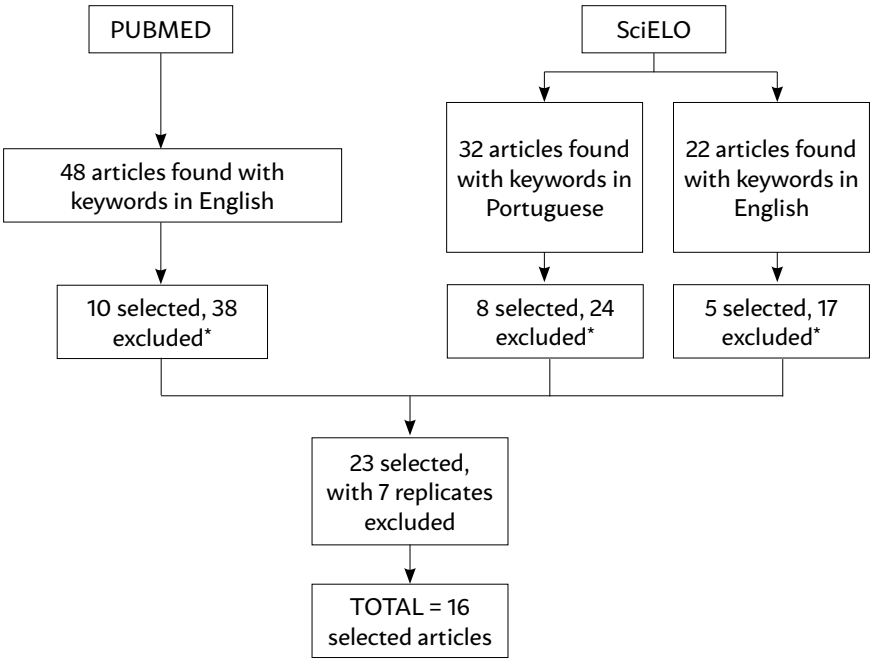
METHODOLOGY

This is a literature review study on the use of licit and illicit drugs by medical students in Brazil. The bibliographical reference used was the Scientific Electronic Library Online (Scielo) and the Medical Literature Analysis and Retrieval System Online (Medline).

On June 28 of 2017, these portals were accessed and the following combinations of keywords in English were used: "medical students, drugs and Brazil". A search for references in Portuguese was also carried out using the following combinations of keywords: "*estudantes de medicina e drogas*". No time limit was set for the studies selected for this review.

The search conducted on Medline with the keywords in English returned 48 references. On SciELO, the search returned 54 references, being 22 with keywords in English and 32 in Portuguese. Out of the total of 102 references found, were excluded all literature reviews, all studies that did not include Brazilian medical students in their samples, and all studies that did not specifically assess drug use. This process led to the exclusion of 79 papers. Out of the remaining 23 references, seven were repetitions and were therefore disregarded as well. Finally, a total of 16 articles were included in this literature review, all of which subsequently read in its entirety. Figure 1 represents the stages for the selection of papers.

FIGURE 1: FLOWCHART FOR ARTICLE SELECTION



*Articles were excluded because they did not evaluate the use of drugs, or Brazilian medical students, or they were review articles.

TABELA 1 – DESCRIPTION OF PUBLICATIONS ANALYZED ON THE USE OF LICIT AND ILLICIT DRUGS BY BRAZILIAN MEDICAL STUDENTS

Year of publication	Sample and type of study	Objectives	Data collection methods	Main achievements
Mesquita et al., 19988	796 of 1,080 students of the Faculty of Medicine of the University of São Paulo (retrospective)	Seek the association between marijuana use and ether sprays (lança perfume).	World Health Organization multiple choice questionnaire.	Male students use ether sprays 1.9x more than female students. Medical students with a history of marijuana use were estimated to use ether sprays 6-7 times more than students who did not use marijuana.
Kerr-Correa et al., 19999	3,725 of 5,225 students enrolled in nine medical programs in the state of São Paulo (retrospective)	Evaluate the use of alcohol and drugs among students from nine different medical programs in the state of São Paulo find the profile of the drugs that are used most often.	Self-administered questionnaire proposed by the World Health Organization.	Alcoholism was considered a health problem by 90% of the students. In descending order, the most commonly used drugs were alcohol, tobacco, solvents, marijuana, tranquilizers, and cocaine, with consumption increasing in the last years of the program. Greater tendency of benzodiazepine use in the final years of the program, due to the ease of access to prescriptions and medication in the hospital, stress at the end of the program and residency exams.
Passos et al., 200610	1,054 medical students from four medical programs in Rio de Janeiro (retrospective)	To estimate the prevalence of psychoactive drug use in four medical programs in Rio de Janeiro and its associated sociodemographic conditions.	Questionnaire used by the World Health Organization.	Alcohol was the most widely used drug (96.4%), followed by tobacco (54.3%), tranquilizers (24.2%), marijuana (20.9%), inhalants (18.4), cocaine (3.4%), LSD (3.3%), amphetamines (1.1%), weight loss drugs (0.9%), and ecstasy (0.4%). A total of 45% of the students know where to get drugs and 62% believe that it is easy to get them.
Boniatti et al., 200711	183 of 318 medical students from the University of Caxias do Sul (retrospective)	Investigate the patterns of psychoactive substance use in medical students.	Questionnaires sent by email. Upon return to class, the questionnaires were returned in an urn.	The most commonly used drugs were alcohol (97.3%), tobacco (54.6%), and marijuana (31.1%). There was no increase in the use of illicit drugs during the course of the program. Living with parents, a harmonious home, disapproval of drug use, and religious practices are variables related to lower drug use.
Di Pietro et al., 200712	456 of 650 students of the medical program of the Faculty of Medicine of the Federal University of São Paulo (retrospective)	Evaluate the use of drugs among medical students and look for associated factors.	A self-administered questionnaire was distributed in classrooms, individually.	The most commonly used drugs were alcohol (76.9%), tobacco (20.4%), and marijuana (16.2%). The consumption of all drugs - with the exception of tranquilizers - was more prevalent in men.
Lemos et al., 200713	404 of 432 students from two medical programs in Salvador (retrospective)	To analyze the local pattern of psychoactive substance use in the academic medical population and contribute to the creation of prevention activities.	Standard self-administered questionnaire proposed by the World Health Organization.	Alcohol (92.8%) and ether spray (46.2%) were the most commonly used drugs. The use of tobacco, ether spray, and tranquilizers increased significantly from the first to the sixth year of the program. The main reason found for drug use was entertainment (57.8%).
Carvalho et al., 200814	465 of 600 medical students of the Faculty of Medical Sciences of Santa Casa de São Paulo (prospective)	To identify risk factors related to sexuality and psychoactive substance use by medical students, in order to organize preventive strategies.	An anonymous, semi-structured questionnaire was used.	The most commonly used drug was alcohol (76.2%), with 46.5% using it at least once a week, 33.5% once a month and 2% daily; 11.1% used tobacco, with an average of 6.4 cigarettes a day. Ether spray was used by 22.6%, 98% at least once a month. Greater use of illicit drugs by men. Increased use of alcohol and tobacco throughout the program. Alcohol consumption is greater to alleviate tension, to share a behavior with colleagues and due to ease of access.
Mesquita et al., 200815	557 of 1,080 students of the Faculty of Medicine of the University of São Paulo (prospective)	To analyze medical students' behavior when faced with drug abuse by colleagues from the academic universe.	Three self-administered questionnaires, focusing on licit and illicit drugs and alcohol, separately.	Faced with cases of alcohol abuse, students tend to intervene in some way. The same is not true for illicit drug cases. Information about the risks of alcohol remains under sociocultural acceptability and this explains why it is the most commonly used drug.
Panduani et al., 200816	303 of 400 students from the Federal University of Uberlândia from the first to the fifth year (retrospective)	To determine the prevalence of alcoholic beverages and cigarettes among medical students.	A self-administered individual questionnaire was distributed in classrooms.	A total of 66.34% of the students interviewed consumed alcoholic beverages. The prevalence increases over the course of the program. Of the interviewed students, 65.17% occasionally drank, 27.86% one to two times a week, 5.97% three to four times a week, and 1% daily. Only 10 students smoked, out of which only 2 smoked from 11 to 20 cigarettes a day.
Tockus e Gonçalves, 200817	88 students of the medical program of the Positivo University (retrospective)	To establish the drugs most commonly used by medical students and the problems related to its use.	Adapted World Health Organization questionnaire, through the university portal.	Alcohol use was more prevalent (70.45%), followed by cigarette (27.3%) and marijuana (10.2%), in the last 3 months. Regarding the use throughout life, prevalence was 78.4% for alcohol, 38.6% for tobacco, 26.1% for marijuana, 21.6% for inhalants, 11.4% for stimulants, and 3.4% for cocaine/crack.
Da Silveira et al., 200818	456 medical students from the Federal University of São Paulo (retrospective)	To identify patterns of drug use among university students in years 1 through 6 of the program to chart prevention strategies.	Anonymous questionnaire, which gathered data on drug use in the past 30 days.	Frequency of drug use by men: alcohol (80.5%), marijuana (25.3%), solvents (25.2%), tobacco (25.2%), amphetamines (3.8%) and tranquillizers (2.9%).

Year of publication	Sample and type of study	Objectives	Data collection methods	Main achievements
Oliveira et al., 201019	457 students of the Faculty of Medicine of the University of São Paulo (retrospective)	To characterize drug use by medical students at different times.	To compare the pattern of drug use in 1996 and 2001.	Alcohol and tobacco consumption remained stable between 1996 and 2001, but the consumption of illicit drugs increased from 36.1% to 43.8%. Alcohol, tobacco, marijuana, and inhalants were the most commonly used drugs in both periods.
Petroianu et al., 201020	332 of 360 medical students of the Federal University of Minas Gerais (retrospective)	To estimate the prevalence of alcohol, tobacco and narcotic use among medical students.	World Health Organization self-administered multiple choice questionnaire, followed by an interview.	Alcohol use by 85.2% of the students, being 37.7% at least once a week and 0.6% daily, with no difference between genders. Tobacco consumption by 16.3% of students, with 1.5% at least once a week and 3.3% daily.
Rodriguez et al., 201221	2876 students from universities in Brazil and other Latin American countries (retrospective)	To observe patterns of drug consumption and multiple drug use and their associated factors.	We interviewed students of the 1st and 2nd years, using 58 questions with the possibility of clarifying doubts.	The use of psychoactive substances during the last year, according to the country: Colombia (66.5%); Brazil (65.1%); Chile (51.1%); Nicaragua (42.6%); Jamaica (29.2%) and El Salvador (18.8%). The most frequent drug associations were alcohol and tobacco, except in Jamaica where they were alcohol and marijuana.
Ribeiro et al., 201422	289 of 608 students. (retrospective)	To identify the use of antidepressants, adhesion and guidance on the medication.	Structured self-report technique. Objective questionnaire.	Of the total, 11.4% stated that they use or have used antidepressants, 72.7% of which reported having had medical follow-up. Anxiety and depression were the most commonly reported reasons.
Silveira et al., 201423	152 of 156 students from the Pontifical Catholic University of Rio Grande do Sul (retrospective)	To evaluate the prevalence of methylphenidate use in medical students.	Cross-sectional survey through a questionnaire.	Of the total, 34.2% of the students had already used methylphenidate, and 23.02% had used without medical indication. The majority (68.57%) of the students who used it without medical indication did so to improve focus and performance in the program.

RESULTS

Table 1 presents the main data found in the papers analyzed.

After the analysis of all 16 papers, we noticed, in relation to the numbers referring to the last century, an increase in scientific studies conducted on the subject. Regarding where these studies were conducted, most of them (75.0%) were carried out in Southeast cities, with an emphasis in São Paulo where nine studies were performed (56.2%); there were only three studies (18.7% in the South region and only one (6.2%) in the Northeast[1]. No publications on the subject were found from the North and Central-West regions.

As for the methodology used, all selected papers were cross-sectional, with 14 (87.5%) being retrospective and only two (12.5%) prospective. Out of that total, 12 studies (75.0%) sought to identify the prevalence of licit and illicit drug use by medical students, as well as the likely predisposing factors and conditions associated with it. The other studies had more specific purposes, such as to assess the link between marijuana and ether sprays (*lança-perfume* in Portuguese) and identify how medical students faced with substance abuse by their peers reacted[15]. All data were obtained through questionnaires adapted and validated in Portuguese.

Finally, regarding the use of drugs, the studies found were unanimous in pointing out alcohol as the substance most often consumed by medical students[8-23]. Even though the prevalence of smoking has decreased over the past years, several studies still indicate that tobacco is the second most used drug[10, 11]. Among the illicit drugs, the most often consumed were marijuana, solvents, ether sprays and anxiolytics.

DISCUSSION

Several studies on substance abuse by medical students were published in the first half of this century[10-20]. When that number is compared to the number of studies from the last century[8,9], it can be noted that the academic community has been giving greater emphasis to this matter over the years. This information indicates the social importance of the subject. The study of drug consumption by medical students, and well as of the reasons that lead to that consumption, allow us to infer relevant information around the psychological stress of the academic environment and the interpersonal relationships that arise from it. This information can be used to improve the curricular approach of medical programs, reducing the number of students who turn to drugs.

Despite the importance of the subject, a shortage of studies was found in some regions of Brazil. While almost all of the articles found were produced in medical schools from the Southeast region[8-10,12,14-16,18-21], few data were located from the South and Northeast. Worst still, no data for the Central-West and North regions was observed. That is a worrying scenario, since the small number of studies from these regions makes it impossible for the differences between Brazilian regions to adequately assessed, thus limiting the comparisons between the results found.

In regard to the methodology employed, the fact that all papers[10-23] found were cross-sectional also prevents the actual consequences of substance abuse by medical students to be known, since this model does not allow us to assess the long-term situations of the scenario. In addition, almost all authors, to this moment, investigated mostly the prevalence of drug use in this population[8,10,12-14,16-18,20-23]. In this context, it is vital that longitudinal studies are carried out to thoroughly investigate the relationship between the students and these substances, seeking to identify what are the actual situations that lead to the use of drugs, the adequate way of handling the problem, and which measures can be adopted to mitigate the use of these substances.

All studies reported that alcohol was the substance most widely consumed by medical students. The prevalence of alcohol consumption in this population ranged from 66.34% to 97.3%. These differences can be explained by the variation in the sample size of each study, as well by the particular differences between the populations assessed - such as in which year of medical school the students were and their social class. Despite that, it is important to report that, even though there is a high prevalence of alcohol consumption, it remained stable between 1996 and 2001[19].

In 1999, Kerr-Corrêa et al.[9] assessed, in retrospect, the use of drugs in 3,725 medical students and showed that, even though 90% of them understood that alcoholism was a public health issue, 80% of the students in the sixth year classified their link to alcoholism patients as week or bad. That data shows that medical programs are effective in teaching the deleterious consequences caused by alcohol abuse. However, they fail to supply practical and theoretical foundations so that the students can handle these situations appropriately.

Considering that most medical undergraduate students seem to understand the harmful effects of alcohol consumption, the high prevalence of the habit is contradictory. The situation seems to stem from the fact that alcohol is the most socially accepted drug[9] and, therefore, its consumption is not seen as something that should be discouraged nor assessed by expert health professionals.

For example, even though some students declared that when faced with friends abusing alcohol they felt compelled to personally intervene in the situation, when there was an abuse of any other type of drug these same students judged it was necessary the intervention of an expert health professional[14]. Ergo, the assessed students do not see alcoholism as a problem as dangerous as the consumption of other types of drugs. Thus, they tend to be more permissive with alcohol ingestion.

Despite all that, it is important to note that even though the studies identified a high prevalence of alcohol consumption, the frequency of ingestion was not equally high. Petroianu et al.[20], for example, reported that 46.9% of students assessed by him consumed alcohol in rare occasions over the previous year and only 0.6% of them declared to intake it on a daily basis. This data is corroborated by a study by Paduani et al.[16], that affirms that 27.86% of students consumed alcohol once or twice a week, whereas only 1% did so daily.

Even though alcohol intake is not frequent, it is noteworthy that the habit is often associated with the concomitant use of other psychoactive substances, leading to risk behaviors[20]. The association of alcohol and tobacco, another licit drug, was the most often reported in the literature[22].

In fact, tobacco was the second most used drug by Brazilian medical students, but its prevalence also varied considerably among the studies. Passos et al.[10] and Boniatti et al.[11], for example, observed that around 54% of the students had used tobacco at some point of their lives, while other authors[12,17,23] reported lower prevalence of about 20%. Like with alcohol consumption, the difference between the results may be explained by the different number used as a sample in the studies, as well as the socioeconomic level of each participant student. Among the students who smoked, only 3.3% reported to do it daily; the rest claimed to smoke on rare casual occasions over the year[20].

It is possible that this low rate of student smokers, when compared to the vast number of drinkers, is due to the several anti-smoking measures employed by the Ministry of Health in recent years. Among them is the creation of laws that forbid smoking in enclosed spaces, that vetoed commercial advertisement of cigarettes and that disclose, as a warning, the harmful effects of smoking.

With respect to illicit drugs, 48.6% of students reported to have used some illicit drug at least once in their life[11]. In most studies, marijuana was the most commonly used, with a consumption prevalence estimated in 10% to 31%[11,14,17,20]. This is particularly worrying, since the prior use of marijuana was asso-

ciated with a higher probability of using other illicit drugs. For example, students who made use of marijuana are seven times more likely to become ether-spray users than the general population[8].

Despite this, the consumption of other substances also showed a significant prevalence. In 2006, Passos et al.[10] assessed 1,054 students and reported that 24.2% had already made use of tranquilizers, 18.4% of inhalants, and 3.4% of cocaine. These results were similar to those found in several other studies[11,12,23]. Even though the consumption of illicit drugs is lower than that of socially acceptable substances, 45% of the students reported knowing where to buy it and 62% believe it would be easy to buy it, if they so desired[10].

Some studies[9,11,13-15] sought to understand the reasons that led the students to the consumption of drugs. In the study by Kerr-Correa et al.[9], out of a total of 3,725 students, 60% were not able to explain the reason for using drugs, whereas 17% did so out of curiosity, and 9.0% for fun. These data differ in the literature. Boniatti et al.[11], for example, observed that 39.1% of the 183 students in the study made use of these substances out of curiosity and 31.5% for fun. It is possible that this divergence is due to the different number of participants in each study, since the first one assessed a larger sample than the second. Finally, some studies[13-15] mentioned the stressful nature of the medical program as an initial cause and motivator for drug consumption. Regardless of the initial reason, friends were most often named as the person who first introduced students to the experimental use of these substances[9].

Regarding gender, most studies observed that men had a higher tendency to consume all types of drugs, with the exception of anxiolytics and antidepressants, which were most often consumed by females[9,12-14,21]. Moreover, the use of psychoactive substances tends to begin at an early age, alcohol being the most prematurely used with an average starting age of 14.4 (SD=2.5)[10]. According to Passos et al.[10], the average starting age for other drugs are: tobacco (15.6), marijuana (17.4), inhalants (17.7), tranquilizers (18.1) and cocaine (18.5).

Several studies demonstrated that the use of licit drugs, tranquilizers and ether sprays increases over the course of the medical program[9,13,14,16]. Based on that, it can be deduced that students make use of these drugs as an escape mechanism, suggesting there are stressful factors or triggers within the program. Among these factors are: the pressure to which the student is subjected, the huge workload, significant amount of work and responsibility, social and family deprivation, the need to handle situations of human suffering and death, tiredness and the search for good academic results[24]. Nevertheless, it is worth pointing out that all studies analyzed were cross-sectional and, therefore, are not capable of establishing cause and effect relationships between these variables.

Regarding the use of prescription drugs, the prevalence of antidepressant use was of 11.4%[22], whereas 23% of students reported having taken methylphenidate without a prescription[23]. It is possible that these drugs are used as a way to relieve the stress of upcoming residency tests at the end of the program, as well as a way of handling the extreme work shifts and changes in the sleep/wake cycle.

Finally, the factors related to an increase in the consumption of alcohol and other drugs included: being a male, having a favorable attitude towards the use of alcohol and other substances, and missing classes for no good reason[9]. The factors related to the protection against this type of attitude were: living with parents, not having close links with drug users, disapproving of drug consumption, religious practices and being employed.

CONCLUSION

After analyzing the selected papers, we observed a high consumption of psychoactive substances, despite the medical students' understanding of its harmful effects. Several reasons may contribute to this type of attitude, especially the stress to which they are subjected to during the medical program. However, the absence of longitudinal studies in the literature makes it difficult to comprehend the actual causes of this reality.

Considering the vast number of medical schools in Brazil, it is evident the need to conduct more studies in different regions of the country, especially in the North and Central-West. In addition, we recommend that comparative studies are carried out to follow the students over time so that specific preventive measures and treatments can be made available to them.

STATEMENT OF CONFLICT OF INTERESTS

The authors declare there are no conflicts of interest.

RESUMO

INTRODUÇÃO: *O consumo e o abuso de álcool e outras drogas estão cada vez mais presentes na vida dos estudantes universitários, e podem ser considerados problemas de saúde pública pelos potenciais prejuízos acarretados na saúde física e mental. No curso de medicina, as exigências acadêmicas e o estresse têm papel fundamental no aumento do uso de drogas entre os estudantes.*

OBJETIVO: *Realizar uma revisão sistemática da literatura sobre o uso de drogas, lícitas e ilícitas, em estudantes de medicina brasileiros.*

MÉTODOS: *Estudo de revisão de literatura, cuja fonte bibliográfica foram os portais de periódicos SciELO e Medline. No total, 99 artigos foram encontrados, dos quais 16 foram selecionados para esta revisão.*

RESULTADOS: *O álcool e o tabaco foram as drogas mais consumidas por estudantes de medicina. Dentre as drogas ilícitas, as mais frequentemente utilizadas incluem maconha, solventes, lança-perfume e ansiolíticos. O sexo masculino apresentou maior proporção de consumo de todos os tipos de drogas, com exceção de tranquilizantes. Foi encontrado um aumento da prevalência de consumo de drogas ao longo do curso de medicina, o que pode ser resultante do estresse próprio das atividades do curso. Estudantes que fazem menos uso de substâncias psicoativas tendem a viver com os pais, não possuir vínculos próximos com usuários de drogas, desaprovar o consumo de drogas, possuir e praticar crenças religiosas e trabalhar.*

CONCLUSÃO: *A prevalência de consumo de drogas lícitas e ilícitas entre estudantes de medicina é alta, mesmo eles tendo conhecimento sobre os malefícios que o uso pode causar.*

PALAVRAS-CHAVE: *Transtornos relacionados ao uso de substâncias. Estudantes de medicina. Drogas ilícitas. Alcoolismo.*

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REVIEW ARTICLE

Are women living with HIV prone to osteoporosis in postmenopause? A systematic review

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SUMMARY

BACKGROUND: *Some researchers have suggested that HIV infections can increase the cytokines, which might interfere with the bone metabolism and increase the risk of bone mass loss. However, this issue has yet to be consolidated in postmenopausal women.*

OBJECTIVE: *To analyze studies that evaluated the loss of bone mass through DEXA in women living with HIV.*

MATERIALS AND METHODS: *A systematic review was conducted following the PRISMA guideline. The MEDLINE, EMBASE and Cochrane databases were consulted from January 1987 to March 2017. Studies assessing bone mineral density (BMD) in postmenopausal women living with HIV were included. The secondary outcome was to evaluate the impact of antiretroviral on BMD.*

RESULTS: *Sixty percent of the manuscripts suggested that women living with HIV had more bone loss than women in the control group, mainly in the lumbar spine. Forty percent did not observe any difference between groups. One study reported the influence of antiretroviral drugs on bone mass but did not find any difference between groups.*

CONCLUSION: *Our data suggest that HIV infections may have a negative influence on bone mass loss in women. Further studies on the mechanism of this HIV consequence are necessary to clarify the connection as well as the impact of the antiretroviral action on BMD in postmenopausal women.*

KEYWORDS: *Climacteric. Osteoporosis. HIV. Bone Density.*

INTRODUCTION

HIV infections are related to systemic inflammatory processes, which may increase some mediators and cytokines that play a role in the regulation of several endocrine and metabolic processes. In fact, HIV infections can increase the TNF-alpha e IL-6, thus increasing bone resorption.[1,2] Therefore, information on the bone metabolism of patients infected with the human immunodeficiency virus (HIV) is of real interest due to the regularly recurring changes of physiologic states during the course of disease.[3,4]

A clinical trial with 112 HIV-infected men reported that users of protease inhibitors presented a 2.2-fold enhanced relative risk of bone loss (osteopenia or osteoporosis) on the whole-body measurement[4]. Notwithstanding, the majority of studies focused only on a male young-adult population around peak bone mass, for which osteoporosis prevalence is not high[5]. However, it is not clear if the loss of body mass in female patients is only related to HIV infections or the used drugs.[5-8] Therefore, the aim of this research was to analyze studies and evaluate the influence of HIV on the women bone mass as a first outcome.

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METHODOLOGY

This systematic review of the literature followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines[9]. The databases used for consultation were MEDLINE and Cochrane. Articles published in English, Spanish, Portuguese, Italian and French from 1987 (the first study of HIV) to September 2016 were selected using the search strategies reported in Fig. 1. Systematic reviews, meta-analyses, and references cited in the papers were consulted, but only original work was included in this review. The study selection, as well as the evaluation of titles and abstracts, was carried out by two researchers (P.Y.A.C. and R.S.S.), skilled in conducting blind systematic reviews independently, who closely followed the inclusion and exclusion criteria. After this stage, the original articles were critically assessed before being included or not in the study. When selection became a source of discord, a third reviewer was consulted (J.M.S.).

In the inclusion of studies, preference was shown for prospective observational studies or clinical trials. Furthermore, they should include postmenopausal women living with HIV who were undergoing antiretroviral therapy and were informed about bone mineral density. The latter was measured using dual-energy X-ray absorptiometry (DEXA). Also, based on the WHO criteria for the osteoporosis diagnosis, a T-score below or equal to -2.5 SD (standard deviation) for lumbar spine, femoral neck, and/or total femur was adopted.[10]

The eligibility criteria for the studies in this review consisted of women between 45 and 65 years of age, who were in postmenopause, and who had received antiretroviral therapy for more than five years. Studies of populations with characteristics different from those just mentioned were excluded.

When the evidence selected after applying the inclusion criteria was defined as a randomized controlled clinical trial, it was run through an appropriate checklist for critical evaluation (JADAD). Studies were considered for inclusion if the JADAD score was equal to or higher than 3.[11] When the evidence was defined as a comparative study (observational studies or nonrandomized clinical trials), it was also run through an appropriate checklist for critical evaluation (NEWCASTLE OTTAWA), and only those studies with a score over 6 were included.[12].

The information gleaned from the selected studies was displayed in a table comprising the following variables: authors' names, publication year, study design, number of patients, CD4 count, age, form and duration of antiretroviral therapy, duration of HIV infection, and expected outcome (Table 1). To date,

TABLE 1 – THE CHARACTERISTICS AND PRIMARY OUTCOME OF SELECTED STUDIES.

Authors and publication year	Study design	Number of patients	Age	CD4 + count	Type of ARV	ARV Treatment length	Length of HIV infection	Outcome
Grund et al., 2009 (13)	RCT	Total n=275 TARV-i (n=142) TARV-c (n=133)	44 years ± 2.5 years	>350 cel./mm^3	PI: 36% Tenofovir: 3% NRTI: 52% RTINNA : 35%	2.4 years (± 1.2 years)	9 years (± 5.5 years)	No negative impact on the BMD
Dolan et al., 2004 (7)	Transversal	HIV+: n=84 HIV-: n=63	41 years (± 0.9 year)	385 (± 25 cel./mm^3)	PI: 42% NRTI: 80% RTINNA : 27%	IP: 18.3 (± 2.1 months) RTIN : 41.2 (± 4.2 months) NNRTI: 8.1 (± 1.0 month)	8 years (± 2.5 years)	No negative impact on the BMD
Yin et al., 2005 (14)	Transversal	HIV+: n=31 HIV-: n=186	56 years (± 1.1 year)	458 (± 72 cel./mm^3)	PI: 34% NRTI: 11% RTINNA : 7% PI + NNRTI: 48%	IP: 35.1 (± 6 months) RTIN : 63.4 (± 10.1 months) NNRTI: 12.5 (± 4.1 months)	7 years (±1.5 years)	HIV+ patients with low BMD in the lumbar spine
Calmy et al., 2013 (15)	Transversal	HIV+: n=22 HIV-: n=44	44.3 years (± 1.8 year)	626 (± 220 cel./mm^3)	PI: 41% Tenofovir: 14% NNRTI: 45%	11.4 years (8.9 a 13.5 years)	16.5 years (± 1.4 years)	HIV+ patients with low BMD in the lumbar spine
Teichmann et al., 2003 (6)	Transversal	HIV+: n=50 HIV-: n=50	39.4 years (± 2.2 years)	339,5 (±46,2 cel./mm^3)	-	51.7 years (± 4.5 years)	-	HIV+ patients with low BMD in the lumbar spine and femur

RCT = randomized clinical trial; N = number; ARV: antiretroviral; IP: protease inhibitor; RTIN = reverse transcriptase inhibitor nucleoside analogue; RTINNA = reverse transcriptase inhibitors, non-nucleoside analogues; BMD = Bone Mass Density

Medline: (Highly Active Antiretroviral Therapy OR HAART OR Antiretroviral Therapy, Highly Active OR Anti-HIV Agents OR Agents, Anti-HIV OR Anti HIV Agents OR Anti-AIDS Agents OR Agents, Anti-AIDS OR Anti AIDS Agents OR Anti-HIV Drugs OR Anti HIV Drugs OR Drugs, Anti-HIV OR AIDS Drugs OR Drugs, AIDS OR Anti-AIDS Drugs OR Anti AIDS Drugs OR Drugs, Anti-AIDS OR CCR5 Receptor Antagonists OR HIV Fusion Inhibitors OR HIV Integrase Inhibitors OR HIV Protease Inhibitors) AND (Osteoporosis OR Osteoporosis, Post-Traumatic OR Osteoporosis, Post Traumatic OR Post-Traumatic OR Osteoporosis OR Post-Traumatic Osteoporosis OR Osteoporosis, Senile or Osteoporosis, Senile OR Senile Osteoporosis OR Senile Osteoporosis OR Osteoporosis, Involutional OR Osteoporosis, Age-Related OR Osteoporosis, Age Related and Bone Loss, Age-Related and OR Age-Related Bone Loss OR Age-Related Bone Losses OR Bone Loss, Age Related OR Bone Losses, Age-Related OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Osteoporosis OR Osteoporosis, Age-Related)

Cochrane: Highly Active Antiretroviral Therapy AND Osteoporosis

FIG. 1 – Databases and search strategies.

there is not a sufficient number of randomized clinical trials to perform a meta-analysis, which would provide a more robust analysis.

RESULTS

A total of 347 articles were identified in the primary database. After titles and abstracts were carefully read and the inclusion criteria were applied, five studies were selected for critical evaluation (Fig. 2). Table 1 presents their main characteristics. There were altogether 462 women who were living with HIV and whose median age was 44 years ± 6.5 years. The mean length of HIV infection was 8.1 ± 3.2 years and the CD4 cell count varied from 339 to 626 (482.5 ± 71.5 cells). The mean length for ART treatment was 6.3 ± 1.2 years; only the randomized clinical trial conducted by Grund et al[13] was included. Also, there is not a sufficient number of randomized clinical trials to perform a meta-analysis.

Sixty percent of manuscripts suggested that women living with HIV had more bone loss than women in the control group, especially for lumbar spine (n= 409 patients with HIV)[13-15]. Forty percent did not observe any difference between groups. One study reported the influence of antiretroviral drugs on bone mass but did not find any difference between groups (Table 1). In fact, the study using continuous ART or with CD4 count inferior to 250 cells/mm3 was not related to osteoporosis at the lumbar spine (RRA=-0,012 com 95% CI: -0.053 a 0.042)[13].

DISCUSSION

Retroviral therapy has brought a new perspective to women living with HIV and prolongs the longevity, thus increasing the number of women entering the menopause stage, when there is a reduction in the production of steroids.[16-20] However, there are questions on whether women have a higher propensity to osteoporosis due to HIV infection and the effect of ARVs hypoestrogenism during this period. Our study suggests that HIV negatively influences bone mass density in postmenopausal women.[6,14,16] However, we found no evidence that ARVs could increase this risk, because of a low number of studies.

Women infected by HIV may be asymptomatic for 10 years, as the reduction in lymphocytes is slow.[21] However, the infection can determine a loss of bone mass due to a decrease in the health of the patient and changes in the immune system[21]. Indeed, increased levels of cytokines such as TNF present in chronic HIV infection can increase bone turnover by stimulation of osteoclasts[17,18] and enhancement in bone resorption. In more severe forms of infection by HIV, low levels of CD4 are also related to reduced bone mineral density, as demonstrated in the study cohort.[19] In these cases, opportunistic infections, a decrease in nutrition, reduced bone mass and general condition could be the factors that negatively influence bone mass.[16-19]

Three studies evaluated the risk of osteoporosis in HIV+ population.[6,14,16] However, only the study of Teichmann et al.[6] found an increase in osteoporosis risk for HAART users. The authors did not report the time of HIV infection, previous use of antiretroviral therapy prior to the study, or the ART composition used. That is a concern regarding this study. Another limitation of the studies was the absence of factor makers, which can make data interpretation more difficult. Also, It is known that type of drug used in HAART is essential, because it may be responsible for a higher or lower impact in the bone microenvironment. For example, reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PI) act in blocking RANKL decreased calcitriol and inhibition in osteoblasts. In turn, Zidovudine accelerates the genesis of osteoclasts and Tenofovir impairs bone

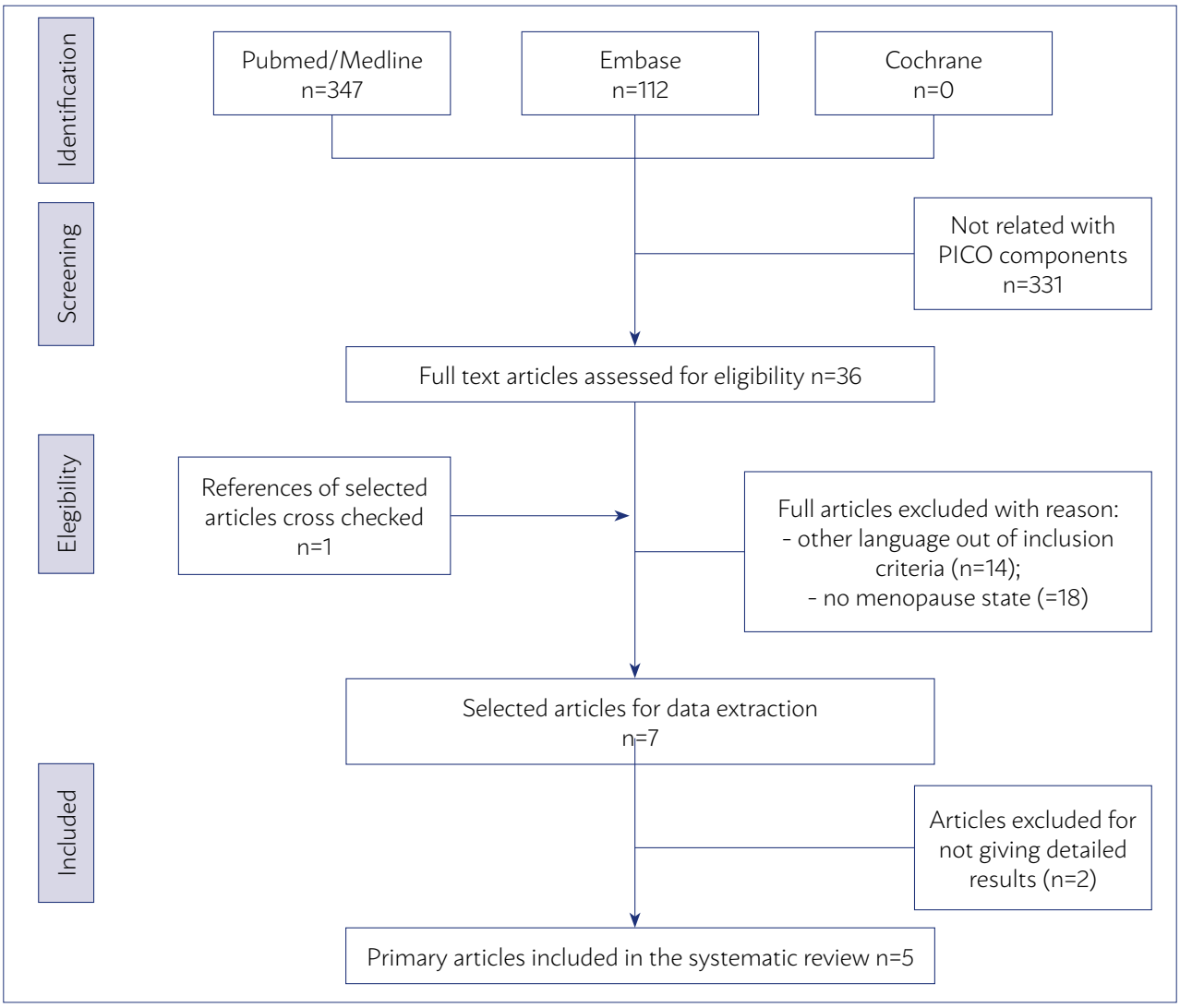

FIG. 2 – Systematic review algorithm.

mineralization. Thus, the composition is essential to evaluate the use of HAART in bone mass and risk of osteoporosis, which can be a limitation of the studies analyzed.

Dolan et al.[7] reported the type of ART used and time of HIV infection but failed to inform HAART use time before inclusion in the study. Additionally, there was heterogeneity in the population, including women who were still menstruating and with higher levels of estrogen, which complicates the assessment of osteoporosis related to low estrogen levels. Furthermore, there is a selection bias in study type, primary outcome, and population in the selected randomized studies,[13] which may hinder the risk analysis of osteoporosis in women with HIV during the climacteric. Also, another limitation of our study was the lack of a sufficient number of randomized clinical trials to perform a meta-analysis, which would provide a more robust analysis. Another bias was the study of Teichmann et al.[6] related to the inclusion of young patients.

The survival of women living with HIV has dramatically increased because of retroviral drugs[15]. However, there is concern that these substances have an adverse impact on bone mass, mainly in climacteric women, who experience the effects of hypoestrogenism on the bone density.[11] Therefore, there is great concern about the bone mass loss in the HIV population.

CONCLUSION

Finally, our data suggest that HIV infections may have a negative influence on the bone mass loss in postmenopausal women. Further studies on the mechanism of this HIV consequence are necessary to clarify this connection as well as the impact of the antiretroviral action on BMD in postmenopausal women.

PALAVRAS-CHAVE: *Climatério. Osteoporose. HIV. Densidade Óssea.*

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REVIEW ARTICLE

Traditional and ultrasound physical examinations: a hybrid approach to improve clinical care

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SUMMARY

Point-of-care ultrasonography, which is performed at the bedside by physicians who are not specialists in imaging, has become possible thanks to recent technological advances that have allowed for a device with greater portability while maintaining image quality. The increasing use of point-of-care ultrasonography in different specialties has made it possible to expand physical examinations, make timely decisions about the patients and allows the performance of safer medical procedures. In this review, three cases from our experience are presented that highlight the use of point-of-care ultrasonography by clinicians. Bedside ultrasonography is a convenient modality used in a clinical setting to aid in early diagnosis of several common conditions. It is suggested that a hybrid approach of physical examination and point-of-care ultrasonography in the everyday clinical practice is an inevitable change of paradigm that is improving quality of care in a variety of clinical settings.

KEYWORDS: *Ultrasonography. Physical Examination. Nephrotic Syndrome. Aortic Aneurysm, Abdominal. Pneumothorax.*

INTRODUCTION

Traditional physical examinations, which have been performed practically unchanged over the past 200 years,[1] contribute only 10-20% to the final diagnostic process;[2,3] in addition, clinical signs are not always reliable.[4] In turn, particularly over the past 25 years, the increasing use of point-of-care ultrasonography (POCUS) has been observed. POCUS means the ultrasonography (US) performed at the bedside by physicians who are not specialists in imaging, aiming to answer simple 'yes' or 'no' binomial questions that allow the physical examination to be enhanced by new clinical information, and guiding several medical procedures to be performed in a safer way.[5] The increasing use of POCUS in various medical specialties is due to the growing need for immediate information that cannot be obtained using a traditional physical examination and the greater portability (currently, palmtop devices and applications that allow the use of smartphones to generate the image are available) and affordability of ultrasound devices.[6]

Although there are recommendations based on published evidence for the use of POCUS,[7,8] and its use is already recognized by foreign societies

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(such as the Society of Critical Care Medicine and the American College of Emergency Physicians), in Brazil, its use is still restricted to a few physicians, particularly those who work in Intensive and/or Emergency Treatment Units. However, it is important to note that a careful clinical history analysis and thorough physical examination will remain the cornerstones of the diagnostic process; as with the stethoscope, reflex hammer and penlight, ultrasound is a tool that, by allowing a "look inside" the patient, should be used not to replace the physical examination but as an extension of it.[5] Three cases from our experience will be presented and discussed below that highlight how POCUS allows for safer clinical practice of better quality.

CASE REPORT 1:

A 46-year-old white female patient sought medical care due to lower limb edema, followed by edema around the eyes, which had started approximately two weeks prior. The patient also reported foamy urine and weight gain. Her previous pathological history was unremarkable and she denied the use of continued medication. In the "conventional" physical exam, periorbital edema and edema in the lower limbs up to the root of the thighs (with godet sign) were observed. Her weight was 75 kg (according to the patient, her "normal" weight is 61 kg), and she had a blood pressure of 146/84 mmHg, non-palpable kidneys and negative bilateral costovertebral angle tenderness. Cardiac-pulmonary auscultation was inexpressive. Abdominal distention, shifting dullness, and bulging flanks were absent. Proteinuria, which was checked with a urine dipstick test, was positive (4+).

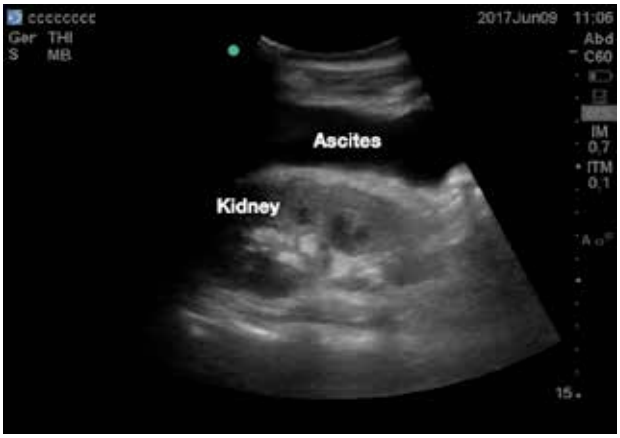
Based on the clinical history and findings of the physical examination, particularly for the presence of proteinuria in the urine dipstick test, the diagnosis of nephrotic syndrome was made, and percutaneous renal biopsy was considered for etiological confirmation. However, while discussing the case, the following questions were raised, and POCUS was performed to answer them: 1. Given the considerable weight gain of the patient, is there fluid in the peritoneal cavity, pleural or pericardial space? 2. Do the kidneys have typical anatomical characteristics that could allow the histologic diagnosis of the underline glomerular disease?

Case Discussion

Regarding the first question, it is important to note that the use of POCUS in the identification of free intraperitoneal fluid (FIPF) has been recognized since the mid-1980s.[9] A study using cadavers as a model showed that US allows the physician to visualize up to 100 mL of FIPF.[10] However, the use of the US in the evaluation of FIPF gained considerable momentum from research performed on patients with abdominal trauma, leading to the Focused Assessment with Sonography in Trauma (FAST) protocol. In the upper right quadrant window of the FAST (which encompasses Morison pouch, the lower pole of the kidney and the space between the diaphragm and the liver), US can identify volumes of liquid on the order of 500-600 mL.[11] In the upper left quadrant and suprapubic windows, US has also been used by clinicians in the identification of ascites. The use of POCUS in the diagnosis of ascites was consolidated by the fact that the diagnosis based on the physical examination shows a sensitivity of only 70-80% in the presence of large volumes of FIPF.[12,13]

Technically, the search for ascites by POCUS is relatively easy and rapid using a low-frequency, high-wavelength probe (convex and/or cardiac). After adjusting for image gain and depth, the FIPF search can be initiated in the upper right quadrant window, followed by the upper left quadrant and suprapubic regions, with the patient in the supine position. In the patient presented above, free liquid (appearing as an anechoic image) was observed in the Morison (Figure 1) and Douglas pouches, confirming the diagnosis of ascites, which was not identified in the physical examination.

FIGURE 1. Ascites, an abnormal collection of fluid that appears as an anechoic image, observed in Morison's pouch (posterior subhepatic space).

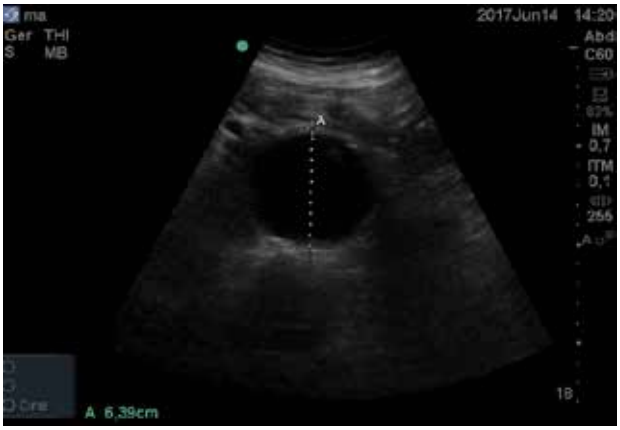


Marcus

In the thoracic cavity, there are two "enemies" of US: the air inside the lungs and the ribs. Both generate acoustic shadows, which would make it difficult to perform lung ultrasound. Thus, for several years, it was believed that US could not be used to assess pulmonary pathologies. However, in the past two and half decades, US of the lung has gained credibility and is currently one of the primary indications for POCUS, particularly in emergency and intensive care units. An important recommendation of lung US is in the diagnosis of pleural effusion, which is established by the replacement of the mirror image of the liver, an artifact generally observed above the diaphragm, by an anechoic image generated by pleural fluid accumulation. Additionally, pleural effusion can also be identified by the observation of vertebral bodies above the diaphragm, a finding usually not seen due to pulmonary interference, which results from the replacement of lung air by a liquid medium, which is a good conductor of sound. In the present case, pleural effusion was diagnosed examining the pulmonary base between the anterior and posterior axillary lines using a low-frequency convex probe.

Pericardial effusion is a noninflammatory complication of nephrotic syndrome;[14] its diagnosis based on a physical examination in mild and moderate cases is challenging. However, transthoracic echocardiography provides a rapid and reliable diagnosis of pericardial effusion and cardiac tamponade.[15] The diagnosis can be made through the four cardiac windows frequently used in POCUS, that is parasternal long and short axes, apical and subcostal, using low-frequency probes with small footprints. In the present case, a small pericardial effusion was diagnosed, with no hemodynamic repercussion.

FIGURE 2. Abdominal aortic aneurysm (6.39 cm) diagnosed during ultrasonography done by the assistant physician during a physical examination of the hypertensive patient.



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Regarding the second question, if the kidneys presented common anatomical characteristics, POCUS may be fundamental, considering the great difficulty of obtaining renal access through a traditional physical examination. First, because of the decision to perform a renal biopsy, knowledge of whether the patient had both native kidneys was important. Second, since the patient did not present any documentation of previous renal function, it was essential to determine whether her kidneys had normal echotexture and size, as well as corticomedullary differentiation, characteristics that suggest kidneys with proper functionality.[16] These are important information and indicate that the renal tissue to be obtained is preserved enough to allow the histological diagnosis of the glomerular lesion causing the nephrotic syndrome. The POCUS allowed us to determine that the patient had two kidneys with characteristics of functional preservation, indicating that a renal biopsy was fundamental for characterizing the underlying glomerulonephritis.

CASE REPORT 2:

A 73-year-old black male patient was seen in the outpatient clinic for blood pressure control. He reported being hypertensive for approximately 26 years and was completely asymptomatic. He had a smoking history that began at 15 years of age (roughly a pack of cigarettes/day), denied having had any previous surgeries, and mentioned that the laboratory evaluation (blood and urine) performed about six months prior was normal. He reported being in regular use of the prescribed antihypertensive medication. During the physical examination, the patient was well oriented, in good general condition, afebrile and with blood pressure of 150/88 mmHg. Pulmonary examination revealed no abnormalities. In the cardiovascular evaluation, cardiac auscultation was interpreted as usual; however, the ankle-brachial index (ABI) showed values lower than 0.9 bilaterally. In the abdomen, inspection, palpation and percussion were inexpressive. The prostate examination was also normal.

However, because he was an elderly male patient with a long-standing history of smoking, hypertensive and with evidence of cardiovascular impairment

(ABI <0.9), the following question was raised: "Is the patient's abdominal aorta normal?"

Abdominal US is the screening examination of choice for abdominal aortic aneurysm (AAA) because it is innocuous, can be done expeditiously and at the bedside, with the additional advantage of having high sensitivity of 95 to 100% and a specificity of nearly 100%.[17,18] With the patient in the supine position, the abdominal aorta is scanned at the level of the iliac artery bifurcation with a convex or cardiac transducer (both low-frequency), since approximately 90% of AAAs occur inferiorly to the renal arteries.[19,20] For the identification of the aorta, the vertebral bodies, which are hyperechoic and generate the artifact acoustic shadow, are the anatomical landmark. The aorta is identified to the left of the midline, anterior to the vertebral bodies, whereas the inferior vena cava is seen to the right side. The diameter of the abdominal aorta should preferably be measured on the transverse axis from the outer anterior and posterior walls of the vessel. AAA is considered in adults when the aortic diameter is larger than 1.5 times its normal diameter or if the distal aorta exceeds 3 cm. It is always prudent to scan the aorta transversely and longitudinally and over its entire abdominal length.

Case Discussion

In patients such as the one presented, examination of the abdominal aorta should always be performed. A segmental dilatation of the aortic wall responsible for considerable morbidity and health care costs.[21,22] AAAs are relatively common and potentially fatal,[23] and constitute the 14th leading cause of death in the United States.[24] AAAs are usually asymptomatic until they expand or rupture. During the period of its expansion, the AAA can cause sudden, severe, and constant back, flank, abdominal, or groin pain. Eventually, these symptoms may be accompanied by episodes of syncope. Large aneurysms in thin people are easy to detect, however, the accuracy of the clinical examination is tremendously reduced by obese body habitus and small aneurysm size.[25] The occurrence of shock suggests parietal rupture of the AAA, a clinical condition with a high percentage of mortality.

In the patient under discussion, the POCUS allowed the assistant physician to identify an AAA of 6.39 cm in diameter (Figure 2). Considering that aneurysm size is one of the strongest predictors of the risk of rupture, that such risk increases markedly at aneurysm diameters greater than 5.5 cm, and that the diameter of the AAA diagnosed in our patient has an estimated annual rupture risk of 10% to 20%,[26] the patient was referred for follow-up with a vascular surgeon.

CASE REPORT 3:

A 25-year-old woman was admitted to the Emergency Unit with nausea and vomiting for 48 hours. The patient said she had had chronic kidney disease diagnosed for approximately 10 years. In the laboratory evaluation, a glomerular filtration rate of 7 mL/min/1.73 m ^{2}, a urea level of 310 mg/dL and a potassium level of 6.8 mg/L were observed. The attending physician requested a nephrological evaluation, and immediate hemodialysis treatment was indicated by the nephrologist. As the patient did not have an arteriovenous access previously placed for hemodialysis, the nephrologist decided on central venous access through the right internal jugular vein (IJV). The procedure was based on traditional landmark-based approach as routinely used, but was difficult to perform. After venipuncture, the patient began with dyspnea, and the diagnosis of pneumothorax was raised.

Case Discussion

Central venous access is a commonly performed procedure with multiple indications in clinical practice, especially in intensive care units. The traditional technique, based on anatomical landmark, is associated with a high risk of failure rates and complications rates as high as 30% and 18%, respectively, particularly in the needle insertion stage.[27] Some factors related to the operator's experience and others related to the patient (i.e., obese body habitus, coagulopathies and urgency of the procedure) justify this rate.[28-30]

The use of US for venous access was first described in 1978, but only for the purpose of marking the skin overlying the IJV.[31] However, only in the mid-eighties the use of real-time US guidance for IJV cannulation was first described.[32] Therefore, since 2001, American and European societies have included bedside ultrasonography during vascular access as one of 11 practices with "strength of evidence for supporting more widespread implementation",[33,34] and in 2008 ultrasonographic guidance for venous

access was listed as a "core or primary emergency ultrasound application" by the American College of Emergency Physicians.[8]

US-guided central vascular access is performed with the patient in the dorsal decubitus position and, in the case presented, the IJV (vessel preferably chosen in clinical situations similar to that of the patient described) is punctured with the head in a neutral position and the operator manipulates the high-frequency transducer ipsilateral next to the patient, from the head of the bed. The anatomical differentiation of the IJV and the carotid artery occurs through compression maneuvers, since the venous system is more compressible than the arterial system, and/or through the Valsalva maneuver when the venous system becomes engorged. It is worth noting that before performing the vessel puncture, it is important to verify its patency, i.e., the absence of venous thrombosis, an absolute contraindication to the procedure that might be present in patients who have had previous accesses in the same vessel.[35]

An IJV access, in general, carries multiple potential complications, being pneumothorax one of the most serious and frequent. The initial diagnosis of pneumothorax is classically based on the chest X-ray, but this imaging modality exhibits a low sensitivity of 36% to 48% in some studies.[36] The sensitivity of lung POCUS in detecting pneumothorax dramatically exceeds that of an X-ray,[37] with a sensitivity close to that of computed tomography.[38-40] With the advantage that it can be carried out repeatedly, US also allows the follow-up of the expansion of the pneumothorax by monitoring the point at which the lung touches the thoracic wall (lung point) and, thus, assists in the decision-making process of thoracic drainage before complete pulmonary collapse occurs. An additional advantage is the unnecessary transfer of the patient to the imaging department, which sometimes is impossible.

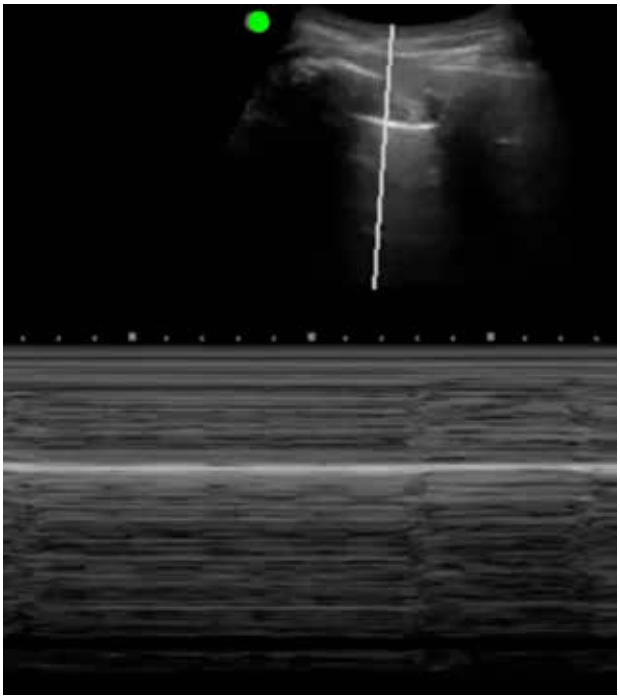
In the search for pneumothorax using bedside ultrasonography, low-frequency and high-wavelength probes (convex or cardiac) can be used, although the high-frequency linear transducer is most suitable because it provides images of higher-resolution of the more superficial structures.

The examination should begin with the patient in a supine position, with the transducer' marker facing the patient's head and positioned longitudinally over the third or fourth intercostal space in the mid-clavicular line. The parietal and visceral pleura are identified as a hyperechoic line found at the inferior border of the space between the two ribs, sliding one under the other, a sign called lung (or pleural) sliding. The pleural interface should be scanned in at least three different intercostal spaces, concentrating the examination at the most superior and anterior portion of the chest.

The presence of lung sliding excludes the diagnosis of pneumothorax. However, its absence, although sensitive, is not specific for pneumothorax. Since lung sliding represents movement between the two pleurae, other clinical conditions, such as contralateral selective endobronchial intubation, previous pleurodesis, severe pneumonia and acute respiratory distress syndrome, may be associated with its absence.[41,42]

In situations where lung sliding is difficult to discern, the M-mode (movement mode) of US can be used. In M-mode, data referring to a single vertical slice (appears as a vertical line at the first press of the M-mode button) are displayed as a function of time. In M-mode, structures that are typically "still" (from the skin to the pleura) appear as parallel horizontal lines (or "barcode") above the pleura, and the moving lung is viewed as a granular appearance below the

FIGURE 3. Lung ultrasonography in M-mode showing a barcode image above and below the pleural line, compatible with the diagnosis of pneumothorax.



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pleura (or "beach sand"), as shown in Figure 4. In the occurrence of pneumothorax, as the lung is "still", the M-mode image appears as a barcode above and below the pleural line (Figure 3).[41,43]

It is important to note that lung US also allows the diagnosis of hemothorax, another complication associated with central venous catheterization, which, unlike pneumothorax, should be investigated at the base of the lung. In addition, POCUS allows the determination of whether the tip of the catheter (particularly double-lumen rigid catheters frequently used in hemodialysis accesses) is correctly positioned at any point in the superior vena cava instead of the right atrium, where it can cause perforation of the cardiac chamber. For this purpose, an injection of saline *bolus* or previously formed micro-bubbles (by mixing 10 mL of serum with 1 mL of air) can be used to determine the position of the tip of the catheter.[40]

In the case under discussion, POCUS of the lung was performed. The absence of pleural (lung) sliding and "barcode" patterns above and below the pleural line in the M-mode observed allowed the diagnosis of pneumothorax due to accidental catheterization of the right IJV.

FINAL COMMENTS

The practice of medicine is based on the diagnosis and treatment of medical conditions. The three clinical scenarios presented exemplify the importance of incorporating disruptive technologies such as POCUS into medical practice, which can enable the clinician to extend his physical examination, obtain immediate answers to simple questions at the bedside and perform medical procedures that are safer for both the patient and the physician. The current trend is for POCUS to be definitively incorporated into all medical specialties. As is already the case in several medical schools in North America and Europe, and a few in Brazil (ours included), the teaching of US is being incorporated in undergraduate medical education. However, for POCUS to be definitively utilized in everyday medical practice, barriers to its implementation must be supplanted and medical education has to be changed, as proposed by Solomon and Saldana: [44] "A generation of physicians will need to be trained to view this technology as an extension of their senses, just as many generations have viewed the stethoscope. That development will require the medical education community to embrace and incorporate the technology throughout the curriculum."

PALAVRAS-CHAVE: *Ultrassonografia. Exame físico. Síndrome nefrótica. Aneurisma da aorta abdominal. Pneumotórax.*

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