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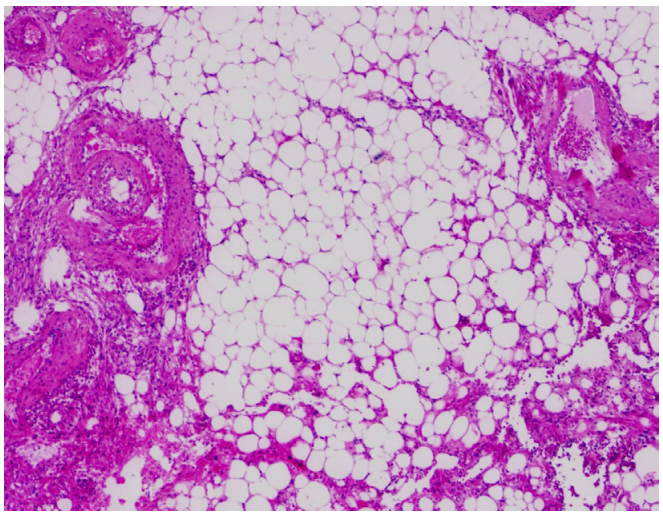

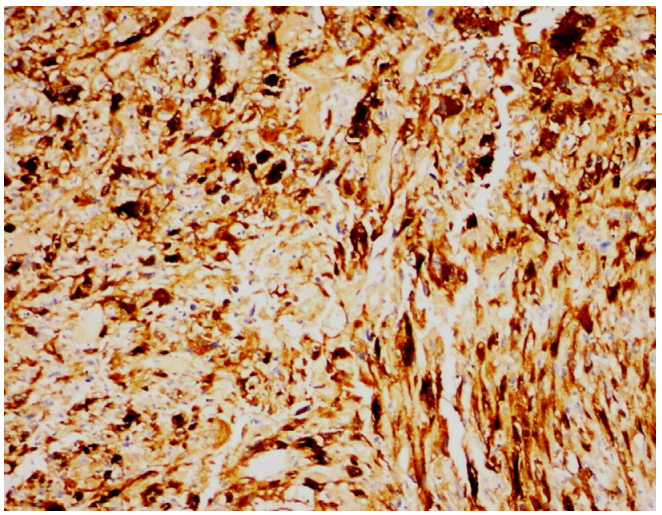

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EDITORIAL

Exposed patients: a reflection on confidentiality, narcissism and bioethics education

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KEYWORDS: *Bioethics. Narcissism. Confidentiality. Physician-Patient Relations. Patients.*

Physicians pose proudly next to their patients online. They expose patients to lay audiences without taking care to hide identifiable data. They comment on medical information on social networks.[1] The duty of secrecy or confidentiality is often neglected in everyday practice. Is that due to narcissism, deficiencies in self-regulation or in education? The goal here is not to pass judgment but to remember the importance of reflecting on these aspects in professional practice, since this can cause embarrassment to the patients, influence colleagues, in addition to leading to ethical and judicial procedures. Beginners or experts, physicians can eventually forget about patient privacy, possibly due to gaps in training. But learning and incorporating ethical and bioethical principles in professional practice require, in addition to information, some maturity. These are linked to the notion of identity, responsibility, and otherness,[2] to the limits between the Self and the Other, to the respect the patient's individuality.

Unfortunately, the importance of psychosocial and emotional development has often been neglected over the course of training, and, not infrequently, during professional life. The maintenance of balance and coping with the crisis inherent to the different stages of life require a combination of capabilities that are developed since childhood, depending on the interaction with the environment to which the child is exposed. The ability to regulate emotions, thoughts, and behaviors is built through a complex process that involves multiple domains and skills.[3] Childhood experiences shape their functioning later in life, influencing learning and communication skills. Using a psychoanalytical referential, narcissism refers to the period of development during which the baby still does not recognize the existence of others (the mother or her substitute). This recognition of the self and others happens gradually, under normal circumstances, throughout childhood and adolescence and continues in a dynamic process throughout life. When people have gaps in early development, in the integration of the *self* or self-image, and on the so-called individuation, the search for "narcissistic" compensation can become, unconsciously, a strategy for psychic

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survival. A self-centered functioning and "satisfaction at any cost" can have harmful consequences. Some people have greater difficulties, such as high intolerance to frustration and diverse interpersonal problems.[4] However, a "dose" of narcissism is also necessary for the well-being. To have one's effort and skills recognized generates joy and enhances self-esteem. "Healthy narcissism" brings satisfaction through learning and developing skills. The social value of the medical profession and work can stimulate growth. But, on the search for professional recognition and admiration, one should avoid the potential pitfalls of narcissistic seduction that the relationship with the patients may present. Healthy narcissism takes into account the needs of others. Maturity makes it possible to understand when the other is in search of narcissistic rewards and assess its adequacy in the relationship. If the patient decides to post a photo with the physician on a social network, provided the physician agrees, there is no problem. It is the physician who is prevented from taking this type of action due to professional confidentiality.

The therapeutic relationship is based on trust and the patient's belief that physicians will do what is best for their patients. From this confidence comes the duty of confidentiality. The duty to safeguard and not disclose, to those who do not need to know, information, images, and data obtained during the exercise of the profession. Even if the patient, or their representative, authorize it. Even if the person is already deceased or no longer a patient. The duty of secrecy has been present from classical antiquity, with the Hippocratic oath, until the present time, with the recently updated Code of Medical Ethics. The moral code that governs medical practice does not exist by accident. It protects the professional and patients of abuse and reinforces fundamental values and rights. In this case, the respect for persons and the right to privacy.[5] Physicians must not forget to respect the privacy of the patient. They cannot publicly expose, or to lay audiences, information, and images of patients without hiding identifiable data. In academic environments and healthcare institutions, all professionals, employees, and students have a duty of confidentiality associated with the clinical information to which they have access. Even though these values appear to be in disuse nowadays, they are required in healthcare professions. And there is no point in whining.

Handling frustration and uncertainty requires effort and maturity. Clinical practice is full of such challenges. Valuing opportunities that promote psychosocial development is fundamental throughout the medical career. The individual search for treatments, psychotherapies, and other forms of personal growth can improve the capacity for reflection and interpersonal relationships within and outside the work environment. Stimulating educational environments can contribute to new learnings in all stages of life. Within healthcare institutions, Clinical Bioethics committees can have an important role in bioethics education. They are recommended in complex hospital environments to create opportunities that stimulate reflection in the face of the challenges and anxiety caused by complex cases.[6] In order for them to effectively operate as an instance with educational and support roles to the clinical body on the search for appropriate decision making, the availability and continuous education of its members is required. In the search for better practices, healthcare institutions and physicians need to change their culture and experiences both in relation to mental health and Bioethics. But it is never too late. As Guimarães Rosa wrote in *Grande Sertão: Veredas*[7]:

"...Look and see: the most important and beautiful thing in the world is this: that people are not always the same, they are still incomplete - but that they are always changing. In and out of tune. The greatest truth.[...]"

PALAVRAS-CHAVE: *Bioética. Narcisismo. Confidencialidade. Relações médico-paciente. Pacientes.*

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Interstitial nephritis associated with nivolumab in a patient with hodgkin lymphoma

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KEYWORDS: *Nephritis, Interstitial. Hodgkin Disease. Immunotherapy.*

Dear editor

A 19-year-old woman who had had advanced mixed cellularity Hodgkin's lymphoma (HL) since she the age of 11 was treated initially with a standard ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) with a complete response at the time; however, HL relapsed four years later, in 2011. We used an ICE regimen (ifosfamide, carboplatin, and etoposide) as salvage chemotherapy. Then, we performed high dose chemotherapy, followed by autologous stem cell infusion. After one year, her condition worsened again. We used brentuximab-vedotin (BV) in order to induce a response so that allogeneic transplantation would be feasible. After six cycles of brentuximab, the patient presented clinical signs of disease progression, such as lymph node enlargement, fever, cutaneous lesions, and weight loss. Anti-PD1 checkpoint inhibitor was administered to treat multi-refractory Hodgkin's lymphoma. After the first dose, symptoms subsided, and the patient was in excellent clinical condition.

After the sixth dose of nivolumab, she presented with generalized edema, respiratory distress, and pleural effusion at the radiological evaluation. The 24h proteinuria was 36.0 g and serum albumin 2.5 mg/dl, configuring nephrotic range proteinuria. A renal biopsy was performed, which was compatible with lymphocytic interstitial nephritis (Fig. 1 and 2). A CT scan was performed, which showed new lymph node enlargement, configuring disease progression despite the checkpoint inhibitor. The anti-PD1 drug was interrupted, and the patient was closely evaluated to determine the response of urinary albumin loss

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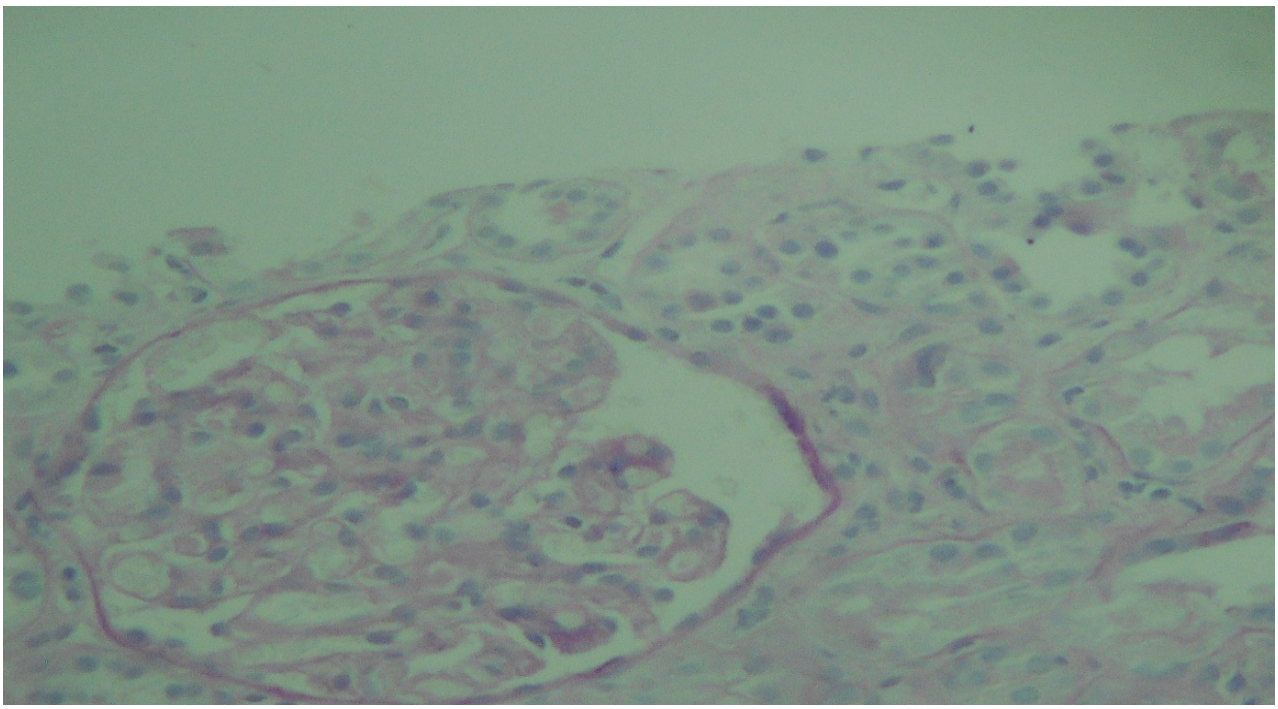

FIGURE 1. INTERSTITIAL NEPHRITIS (HEMATOXYLIN-EOSIN - HE 100X)

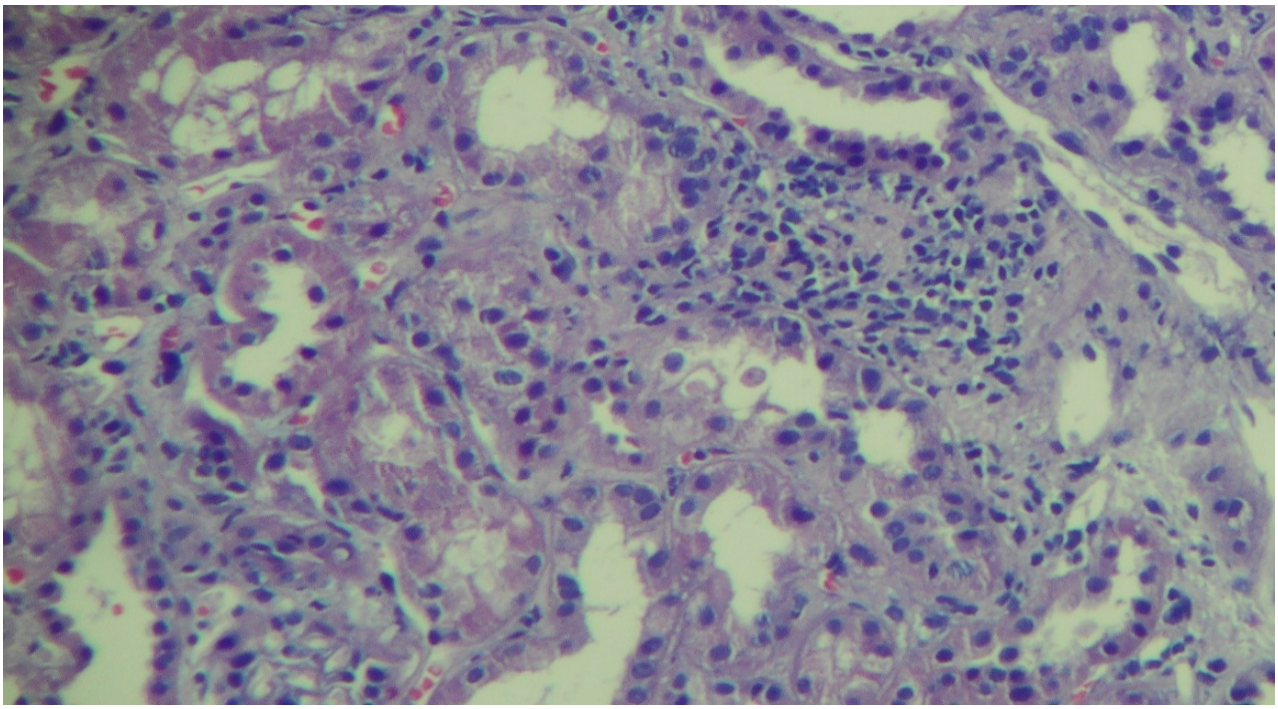

FIGURE 2. INCREASED CELLULARITY AND THE GLOMERULAR MATRIX (NEPHRITIS PERIODIC ACID-SCHIFF - PAS)

to corticotherapy (prednisone 1mg/kg/day). Initially, we used angiotensin-converting enzyme inhibitors (captopril), diuretics (furosemide), and simvastatin to manage the nephrotic syndrome.

Lymph node enlargement decreased over time, proteinuria range fell to 200mg/24h, and serum albumin increased from 2.5 mg/dl to 3.6 mg/dl. There was no more edema, and drugs to control fluid wastage were stopped. We resumed nivolumab administration; currently, the patient has no sign of edema even with no antiproteinuric drugs, such as captopril and furosemide.

This new class of drugs can activate the immune response and facilitate the attack on neoplastic cells,

especially in Hodgkin's lymphoma[1,5]. Unfortunately, this immune attack may be associated with loss of self-tolerance mechanisms. In this sense, there should be constant surveillance of patients using checkpoint inhibitors to detect the appearance of adverse immune reactions.

Kidneys are one of the sites of immune attack, especially in our report. There are many types of immune injury, such as glomerulonephritis, tubulointerstitial damage, and vasculopathy. The evaluation of proteinuria is important to define if the patient needs a biopsy to determine the causative pattern of the lesion. In our report the presence of nephrotic range proteinuria and the biopsy indicating lymphocytic damage allows us to link this presentation with the anti-PD1 drug. There are no standard indications of suspension and reintroduction guidelines in the context of adverse immune reactions.

We presented a successful reintroduction of the anti-PD1 drug after the adverse immune reaction. The pathophysiology background definition was very important to elucidate the pattern of damage and therapeutic options. We recommend that patients in use of anti-PD1 drugs presenting kidney function alteration be evaluated as soon as possible by a kidney biopsy.

Conflict of interest

The authors have no conflict of interest to declare.

PALAVRAS CHAVE: *Nefrite Intersticial. Doença de Hodgkin. Imunoterapia.*

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Elderly patients with glioblastoma: the impact of surgical resection extent on survival

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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.

The impact of the neurosurgery in elderly patients with glioblastoma multiforme (GBM) is still unclear. The objective of this systematic review was to evaluate the overall survival of patients over 65 years old submitted to GBM surgical treatment and analyze the rates of postoperative complications in this population. A search on the Medline, Cochrane e Google Scholar electronic databases between January 2005 and April 2018 identified seven studies that evaluated the neurosurgical treatment of patients older than 65 years with GBM. Surgical procedures included complete or partial resection or tumor biopsy. In elderly GBM patients, total surgical resection of the tumor was associated with longer overall postoperative survival when compared with the partial resection or biopsy. Based on this study, neurosurgery is recommended to increase the overall survival of elderly patients with GBM and a good overall preoperative condition. The high rate of complications in this population should be taken into consideration for the surgical decision.

The details of the methodology of this guideline are set out in Annex I.

INTRODUCTION

Glioblastoma multiforme (GBM), the most common type of primary brain tumor in adults, is associated with a deeply unfavorable prognosis, with an estimated 5-year survival rate of only 10%. Several prognostic factors associated with GBM have been evaluated in the medical literature, among them the patient's age and clinical performance consistently appear as having a negative influence on survival[1]. The estimated average survival of GBM patients older than 75 years is 2.5 months[2].

More than one-third of patients newly diagnosed with GBM have are over 65 years old. As the population ages, neurosurgeons face an increasing probability of having to manage patients with GBM in increasingly advanced ages. However, while studies conducted in populations younger than 65 years favor the degree of resection as one of the main factors of better prognosis[3,4], elderly patients are often excluded from clinical trials[5]; therefore, data assessing

the importance of the neurosurgical resection degree in this age group are still illusory.

Based on these considerations, the aim of this study was to evaluate the effect of surgical treatment in elderly patients with GBM.

RESULTS

Data Collection and Analysis

In the study by Hoffermann et al., the morbidity associated with neurosurgery was 19.3%. Permanent neurological deficits (defined by the authors as focal neurological deficits that interfere significantly in daily living activities) affected 12.1% of the cases in the study, while wound infections and healing problems affected 4% of them. As a whole, 3.2% of elderly patients with GBM treated with neurosurgery presented transitional medical complications (deep vein thrombosis, pulmonary embolism, pneumonia, or myocardial infarction)[6](B).

In the study by Oszvald et al., the disease-free survival in elderly patients was of 7.5 months. There was no statistical difference between total and partial resection. However, in the comparison of surgery (with partial or total resection) versus biopsy, there was a significative difference (p<0.0027)(B).

The performance status of ECOG PS (Eastern Cooperative Oncology Group) (ECOG PS) in the series by Lombardi et al. was between 0-1 in 82% of the elderly patients who underwent neurosurgery, while Harris et al.reported a smaller percentage (64.7%) for the same ECOG PS group[8](B).

In the study by Ewelt et al., the authors speculated that the clinical condition at the presentation was more important to the overall survival of patients of that age (Karnofsky performance score [KPS]> 70, p <0.001; age <75 years, p = 0.224). For the analysis, our study considered only data consistent with the neurosurgical therapy alone. But in the three comparison groups of the study (Group A = surgery alone; Group B = surgery + chemotherapy and Group C = surgery + radiotherapy + chemotherapy), the longest survival was with complete surgery (resection of the tumor uptake area)[2](B).

Gerstein et al.: The authors found that the KPS at the time of surgery in elderly patients with GBM, as well as the degree of surgical resection were the most important factor related to survival time[9] (B).

Pretanvil et al.: The authors reviewed the therapy used in elderly patients with GBM. This publication included at least eight modalities of treatment, including types of neurosurgical resections (partial and total biopsy) and associations with chemotherapy and radiotherapy, evidencing the heterogeneity of therapy in elderly patients. When compared withyounger patients, the biopsy was more prevalent (38.3%) among those aged > 70 years (versus 24.9% in patients aged between 18-70 years). This treatment difference led to significantly lower survival in the group of elderly patients, considering the degree ofresection[10](B).

Analysis of the combined results

The grouped analysis of the seven studies that assessed total and partial surgical resection included 473 and 513 patients, respectively, while the four studies that evaluated biopsy as a neurosurgical treatment included 90 patients.

Overall, the mean age of patients was 71.98 ± 4.40 years. The definition of "elderly patient" varied between the studies, but all reported results for patients over 60 years old. The mean survival (in months) of the group that underwent total resection was higher than that of the group that underwent partial resection, which, in turn, was greater than that of the group who underwent the biopsy (Figures 1, 2, and 3).

Results according to tumor resection extent

The mean combined overall survival time (COS) was 13.13 months (95% CI 12.02-14.23 months) in patients in whom total resection was possible (Figure1), 7.52 months (95% CI 6.94-8.11 months) in those who underwent partial resection (Figure 2), and 2.56 months (95% CI 2.02-3.06 months) in patients who underwent biopsy alone (Figure 3).

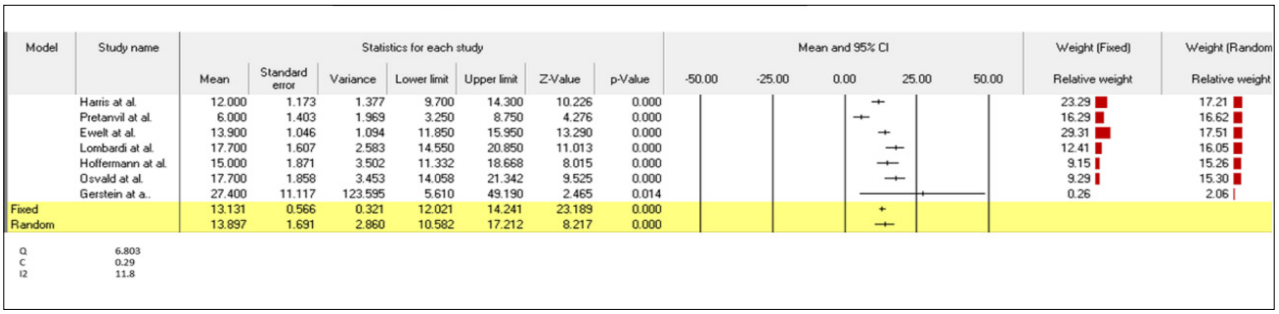
The combined overall calculated survival heterogeneity (I2) of the for total resection, partial resection,and biopsy was 11.8, 84.8, and 78.8, respectively. Forest Plot analysis (Figures 1, 2, and 3) showed that the results for the complete resection were more homogeneous than the other two possible resections.

Complications

Since surgery is not a definitive treatment for GBM, the complications associated with the therapy were often described for the treatment as a whole or as toxicity associated with radiotherapy and chemotherapy combined.

Ewelt et al. observed that almost 25% of the pa-

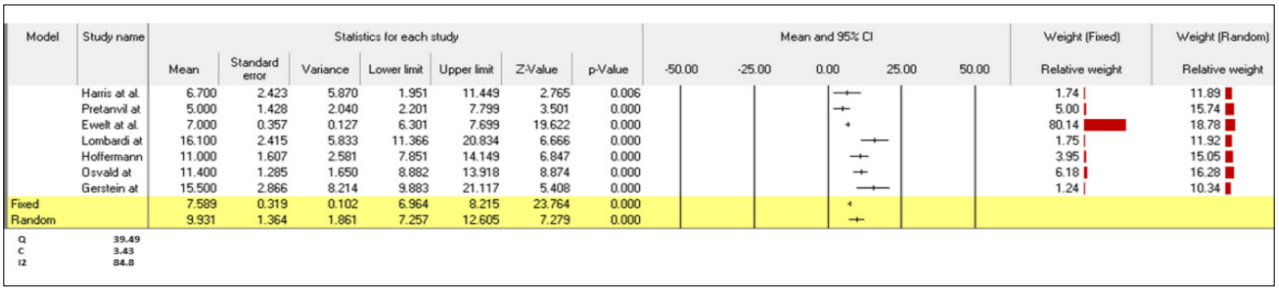
FIGURE 1. FOREST PLOT OF THE OVERALL SURVIVAL RATES FOR TOTAL RESECTION.



Model	Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Harris at al.	12.000	1.173	1.377	9.700	14.300	10.226	0.000	23.29	17.21
	Pretanvil at al.	6.000	1.403	1.969	3.250	8.750	4.276	0.000	16.29	16.62
	Ewelt at al.	13.900	1.046	1.094	11.850	15.950	13.290	0.000	29.31	17.51
	Lombardi at al.	17.700	1.607	2.583	14.550	20.850	11.013	0.000	12.41	16.05
	Hoffermann at al.	15.000	1.871	3.502	11.332	18.668	8.015	0.000	9.15	15.26
	Osvald at al.	17.700	1.858	3.453	14.058	21.342	9.525	0.000	9.29	15.30
	Gerstein at a..	27.400	11.117	123.595	5.610	49.190	2.465	0.014	0.26	2.06
Fixed		13.131	0.566	0.321	12.021	14.241	23.189	0.000		
Random		13.897	1.691	2.860	10.582	17.212	8.217	0.000		

Q	6.803
C	0.29
I2	11.8

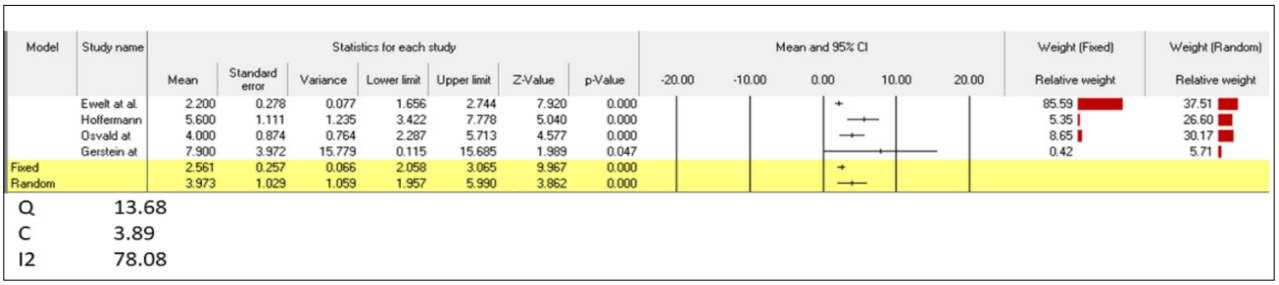
FIGURE 2. FOREST PLOT OF THE OVERALL SURVIVAL RATES FOR PARTIAL RESECTION.



Model	Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Harris at al.	6.700	2.423	5.870	1.951	11.449	2.765	0.006	1.74	11.89
	Pretanvil at	5.000	1.428	2.040	2.201	7.799	3.501	0.000	5.00	15.74
	Ewelt at al.	7.000	0.357	0.127	6.301	7.699	19.622	0.000	80.14	18.78
	Lombardi at	16.100	2.415	5.833	11.366	20.834	6.666	0.000	1.75	11.92
	Hoffermann	11.000	1.607	2.581	7.851	14.149	6.847	0.000	3.95	15.05
	Osvald at	11.400	1.285	1.650	8.882	13.918	8.874	0.000	6.18	16.28
	Gerstein at	15.500	2.866	8.214	9.883	21.117	5.408	0.000	1.24	10.34
Fixed		7.589	0.319	0.102	6.964	8.215	23.764	0.000		
Random		9.931	1.364	1.861	7.257	12.605	7.279	0.000		

Q	39.49
C	3.43
I2	84.8

FIGURE 3. FOREST PLOT OF THE OVERALL SURVIVAL RATES FOR BIOPSY.



Model	Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight
	Ewelt at al.	2.200	0.278	0.077	1.656	2.744	7.920	0.000	85.59	37.51
	Hoffermann	5.600	1.111	1.235	3.422	7.778	5.040	0.000	5.35	26.60
	Osvald at	4.000	0.874	0.764	2.287	5.713	4.577	0.000	8.65	30.17
	Gerstein at	7.900	3.972	15.779	0.115	15.685	1.989	0.047	0.42	5.71
Fixed		2.561	0.257	0.066	2.058	3.065	9.967	0.000		
Random		3.973	1.029	1.059	1.957	5.990	3.862	0.000		

Q	13.68
C	3.89
I2	78.08

tients had complications after surgery: 21 infections, ten leakages of cerebrospinal fluid (CSF), and seven complications associated with CFS circulation defects. The authors did not consider the adverse events to have significantly affected the survival or the postoperative KPS in the population as a whole, although these observations did show a tendency toward significance[2](B). The same result was demonstrated in a single-center study by Bohman et al. including 382 patients; the authors found no significant differences in survival in patients with GBM and postoperative infections[11](B).

Harris et al. described the results of 108 patients; 35 were treated with the best supportive care, one received temozolomide (TMZ) alone, 40 received only radiotherapy, and 32 received radiotherapy and TMZ combined. Regarding the patients who received active treatment, 29 were hospitalized during the radiotherapy (38%), 22 were hospitalized due to declining functional status related to the disease and seven were hospitalized due to other active medical problems (including infection and comorbidities). None of the patients was admitted to the hospital due to toxicities related to the treatment[12](B).

Lombardi et al. describe only toxicities associated with treatment. In relation to non-hematological toxicities, the authors observed six patients (2%) with grade 3-4 toxicity (two with asthenia, two with increased transaminases, one with nausea, and one with intestinal perforation). A total of 53 patients (22%) received reduced or delayed TMZ during the treatment due to toxicities related to the treatment; among them, 28% and 20% were patients who received radiotherapy with 40 Gy and 60 Gy, respectively, but no fatal toxicity associated with the therapy was observed[8](B). The authors did not consider the neurolo-

gical side effects and the dexamethasone dose during radiotherapy and observed grade 3-4 risk factors in 7% of all patients.

Hofferman et al. briefly described their resultsin relation to complications, pointing that the surgical mortality was 4.0% and the global morbidity was 19.3%[6](B).

Oszvald et al.[7](B) did not describe complications, while Gerstein et al.[9](B) described toxicities related to therapy. Radiotherapy could be completed in just 59% of the patients. Hematological toxicity was found in 7% of the patients and non-hematologic toxicities in 14%. During radiotherapy, one patient had pneumonia, and four others had a progression of the disease and were not able to continue the treatment. Other nine patients presented cytopenia, two had pneumonia, three had rashes, and two showed high levels of transaminases. These were not surgical complications, but complications presented during the global treatment for GBM.

DISCUSSION

In general, the population is aging and the number of elderly patients with GBM is increasing. Studies show that up to 40% of patients with GBM are over 65 years old[7,8,10].

For patients over 65 years old and with high-grade gliomas, the negative outcomes associated with surgery have been regarded as a direct consequence of advanced age. The hypotheses proposed to explain these negative results include increased perioperative and postoperative comorbidities, due to age and comorbidities, and reduced tolerance to the therapeutic procedures. In addition, neurodegeneration, resistance to radiotherapy and chemotherapy, different histological types, and genetic mutations are also possible factors that could explain the reduced survival in this population. In several trials on cancer therapy, age is one of the exclusion criteria.

A question that remains is whether age, as an isolated factor, could have such a strong influence on the surgical outcome. The plethora of different treatments offered to patients with GBM makes it difficult to have an a priori analysis of the effect of the treatment in elderly patients. In addition, experience suggests that elderly patients with GBM are less tolerant of parallel treatments in comparison with younger patients. However, some authors suggest that elderly patients in good clinical conditions should receive treatment similar to that of younger patients[10,12,13].

The existing need to clarify the effect of surgical treatment in elderly patients with GBM was the reason for this analysis.

This review found seven studies that included 1,076 elderly patients with GBM. Of these, 473 were submitted to total resection, 513 underwent partial resection, and 90 were submitted to biopsy. Logically, the possibility and extent of the resection do not depend exclusively on the surgical technique, but also on the degree of tumor involvement and invasion of the cerebral parenchyma. Thus, the presentation of patients is essential to define their prognosis.

Our review suggests that the total resection of the tumor is beneficial to the overall postoperative survival of the patient when compared to the partial resection or biopsy. The life expectancy of patients who underwent partial resection and biopsy was relatively short (7.52 months and 2.56 months, respectively).

Other potentially desirable results for analysis in this review could not be evaluated since they often were not been described in the primary studies. It is worth noting that it would be interesting to assess the neurological status before and after the interventions. These could be related to survival and, very likely, to the quality of life of the patients treated. In patients with severe impairment of cognitive functions, life expectancy is not the best element to be assessed. Even so, these data were not reported in many studies, which makes it difficult to interpret them.

Another limitation of this study is the fact that patients undergoing neurosurgical therapy are subjected to different treatment plans with various regimens of chemotherapy and radiotherapy during the follow-up, making it impossible to compare the therapies.

The complication rates of the studies assessed ranged from 19% to 25%[2,6]. These data should be taken into consideration when surgery is recommended for elderly patients with GBM.

Other models for global analysis that compare the risk rates and the survival curves per treatment regimen have been used as a model for combined analyzes. All studies identified were non-comparative, missing, therefore, comparisons between the

treatments. In addition to these limitations, the wide variation of chemotherapy and radiotherapy regimens associated to surgery that have been described in the literature may have a potential bias in the evaluation of the effect of surgery GBM treatment in elderly patients.

Practical aspects of management perhaps are more important in elderly patients as pre-morbid capabilities, such as mobility, communication, memory, and other intellectual functions. Tumor resection would be beneficial for survival if these functions could be improved with the resection of the tumor. However, these data are not described in the literature.

A total and safe surgical resection is suggested as the ideal treatment for the GBM. The value of this recommendation for the elderly population was not clear until the present moment. Now, our study has shown a benefit in overall survival (OS) associated with the total resection of the tumor in older individuals, even though the rate of postoperative complications was substantial in some series.

Research implications

New prospective studies should be performed to confirm the results found in this review. Specific evaluations in eloquent areas and deep tumors should be performed.

Practical implications

Similarly to the current recommendation for adults younger than 60-year-old with GBM, the total resection of the tumor should be the therapeutic goal in patients over 60 years olwwd in whom the resection is feasible, provided the clinical conditions allow.

RECOMMENDATION

Considering that (1) all the studies included in this review were case series (very low quality evidence), (2) GBM is a fatal disease with a poor prognosis, (3) the total macroscopic removal of the tumor has been associated with greater longevity than its partial removal or biopsy, (4) no alternative treatment other than surgery is available at the moment, and (5) the morbidity associated with surgery is relatively high, surgery is recommended to increase the overall survival in elderly patients with GBM and a condition compatible with low pre-operative morbidity (low to moderate strength of recommendation).

ANNEX I

Clinical question

What is the impact of the surgical resection extent in the survival of elderly patients with glioblastoma?

Eligibility criteria

- Types of study: According to the hierarchy of evidence, our initial goal was to include randomized studies and, in their absence, comparative controlled studies or cohort studies describing the outcome of surgery in the target population (elderly patients with GBM).
- Types of participants/patients: Elderly individuals aged over 65 years. The review included only studies with that treated new GBM, while studies on recurrent GBM were excluded.
- Types of intervention: Our objective was to evaluate the (neuro)surgical treatment outcome. The results were described and compared according to the degree of resection, as total or partial resection or biopsy.
- Types of outcome measures: We evaluated the clinical outcome, neurological status, quality of life, survival, and disease-free survival.

The evaluation also included the complications reported.

Search for papers

Database

Electronic searches were conducted in the Medline, Cochrane Controlled Trials Register,, and Google Scholar databases using the following key terms:

("glioblastoma"[MeSH Terms] OR "glioblastoma"[All Fields] OR ("glioblastoma"[All Fields] AND "multiforme"[All Fields]) OR ("glioblastoma multiforme"[All Fields]) AND (older[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) AND ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]) OR ("surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgical"[All Fields]) OR resection [All Fields]) AND "humans"[MeSH Terms].

Identification of descriptors

P – glioblastoma
I – surgery, surgical procedure
C - not determined
O – impact, quality of life, survival, neurological status

Data collection

We determined the year 2005 as the initial year of publication of articles for this study since this was the year when the Protocol Stupp, which is currently used as a guide for high-grade glioma therapy, was established. We identified a total of 1,960 titles between January 2005 and April 2018.

The search strategy was outlined by five authors, and the selection of the articles was performed by two independent authors. Disagreements were resolved by discussion between the authors.

Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information in medicine to standardize approaches and assist in decision-making.

Methodological Analysis

The methodological quality of the studies included in the analysis was assessed using a validated and revised version of the Minors tool (Methodological Index for Non-Randomized Studies). The items assessed were the following:

1. A clear of the study, established *a priori*. The objective of the research should be relevant and accurate in light of the literature available.

2. Consecutive inclusion of patients in the study. All patients who met the inclusion criteria should be included in the study during the period of evaluation (without exclusions, or the reasons for exclusions of patients recruited must be detailed in the article).

3. Prospective data collection: implies that data must be collected in accordance with a protocol established before the beginning of the study.

4. Appropriate endpoints to the objective of the study. Clear explanation (without ambiguity) of the criteria used to assess the main outcome, in accordance with the objective of the study. The results should be assessed on an intention-to-treat analysis.

5. Unbiased assessment of the study endpoints: Independent assessment (blind) of the endpoints or double-blind assessment of subjective results. The reasons for unblinded assessments must be declared.

6. Appropriate follow-up period to the objectives of the study. The studies should have a sufficient period of follow-up for the proper evaluation of the outcomes and adverse events.

7. Loss of follow-up not exceeding 5% of the sample treated. All patients must be included in the assessment.

8. Prospective calculation of sample size included in the study. Difference information to detect and calculate the 95% confidence intervals(ICs), in accordance with the expected incidence of endpoints and information on the level of statistical significance and power estimation in the comparison of outcomes.

The evaluation of the methodological quality of the studies is described in Table 1. The quality of the evidence was evaluated according to the Grading of Recommendations, Assessment, Development, and Evaluations (Grade)[14].

TABLE 1. EVALUATION OF THE METHODOLOGICAL QUALITY OF THE STUDIES INCLUDED IN THE ANALYSIS.

AUTHORS & YEAR	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	<5% lost to follow-up	Prospective calculation of study size	Total
HARRIS (2017)	2	2	2	2	2	2	2	1	15
PRETANVIL (2017)	2	2	2	2	2	2	2	1	15
EWELT (2011)	2	2	2	2	2	2	2	1	15
LOMBARDI (2015)	2	2	2	2	2	2	2	1	15
HOFFERMANN (2015)	2	2	2	2	2	2	2	1	15
OSZVALD (2012)	2	2	2	2	2	2	2	1	15
GERSTEIN (2010)	2	2	2	2	2	2	2	1	15

Statistical analysis

Data are presented as descriptive statistics using summary measures (mean, standard deviation, median, minimum, and maximum). The standard deviations were calculated using the confidence intervals (CI). All tests were performed with a significance level of 5%. The analyses were carried out using a 2006 version of the Comprehensive Meta-Analysis (CMA) software (Statplus, Englewood, NJ, USA).

RESULTS

From the titles retrieved in the search, 75 articles were identified that addressed the treatment of GBM specifically in elderly patients. After an individual analysis of 75 Abstracts, 26 articles were selected on the neurosurgical treatment of elderly patients with GBM. In seven of these studies, we obtained results of the surgical treatment of GBM in elderly patients with total and partial resection and only four studies with biopsy, all of them with a retrospective cohort design.

The data were tabulated and analyzed (Table 2).

The results obtained from the search strategy are described in the Prisma flowchart (Figure 4).

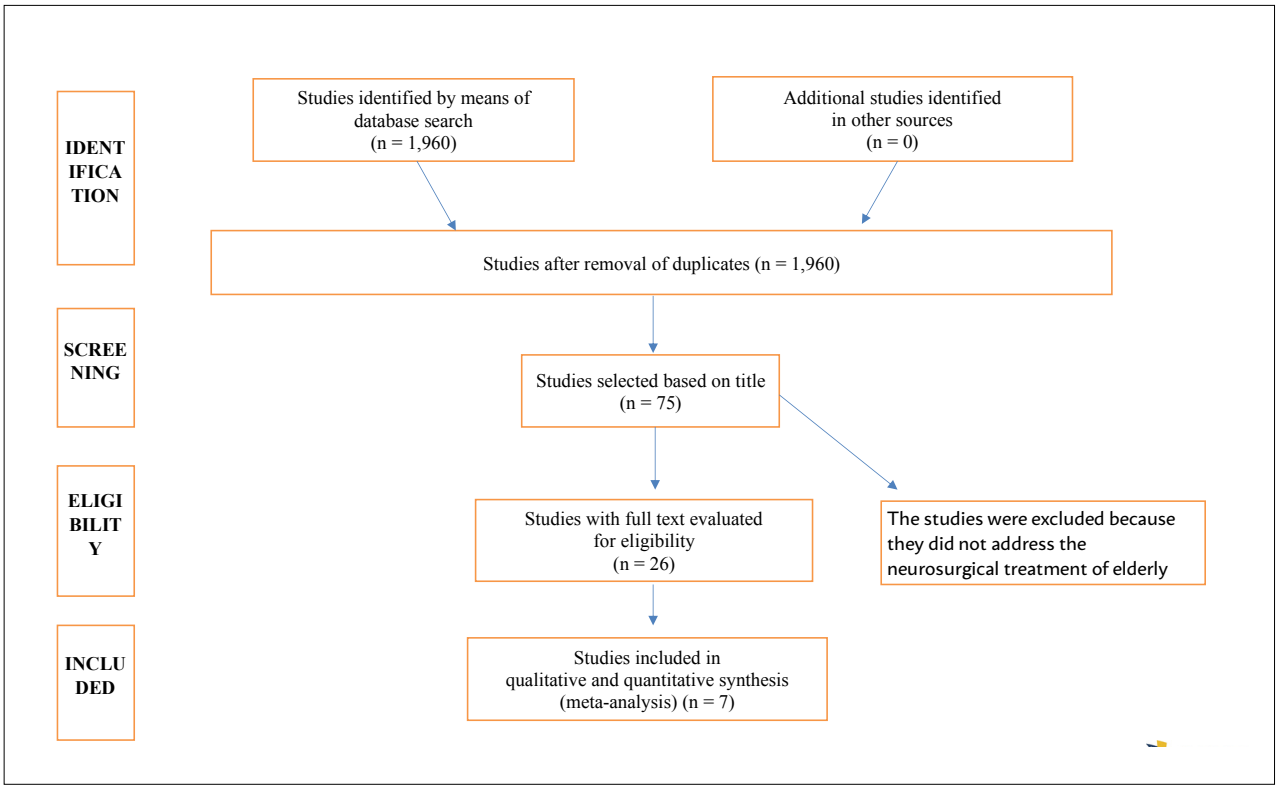
The seven studies included in the analysis had a retrospective design and included elderly patients who underwent surgery due to GBM. The objective of each

TABLE 2. PREFERRED REPORT ITEMS FOR SYSTEMATIC REVIEW AND META-ANALYSIS CHECKLIST (PRISMA).

Section/Topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable to this study
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow_up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving a rationale.	4-8 and Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4-8 and Table 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in the systematic review, and, if applicable, included in the meta_analysis).	4-5
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable to this study
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta_analysis.	Not applicable to this study
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies	Not applicable to this study
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre_specified	Not applicable to this study

Section/Topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6 and flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable to this study
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	Not applicable to this study
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable to this study
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15).	Not applicable to this study
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable to this study
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); the role of funders for the systematic review.	14

FIGURE 4. PREFERRED REPORT ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSIS FLOWCHART (PRISMA).



study was clearly established *a priori*. All studies included convenience samples, evaluated the entire sample treated as defined in the protocol and followed-up all patients until the outcome. All studies have had small losses of follow-up and followed-up the patients for sufficient time for the primary evaluated outcome (time of survival), which was the same in all studies. Therefore, the final analysis was not distorted. Since there was no variable for comparison, with the exception of different chemotherapy or radiotherapy regimens (which was not the objective of our study), all studies were considered non-comparative series of cases, with no variables for comparison. Considering the quality limit established by the Minors scale, which assigns 12 points to studies of good quality (non-comparative), we considered that the designs of all the studies had a good methodological quality.

Application of evidence - Recommendation

The recommendations were designed by the review authors with the initial characteristic of the synthesis of evidence and were submitted to validation by all authors who participated in the creation of the guidelines.

Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician, responsible for the conduct to be followed, given the reality and clinical condition of each patient.

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Pulmonary hypertension could be a risk for deep vein thrombosis in lower extremities after joint replacement surgery

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SUMMARY

A background of Pulmonary Hypertension (PH) indicates a progressive elevation of pulmonary vascular resistance, leading to overfilling, elevation of venous pressure, congestion in various organs, and edema in the venous system. This study aimed to investigate whether PH is a risk factor for deep vein thrombosis (DVT) of the lower extremities after hip and knee replacement surgery.

METHODS: *A total of 238 patients who received joint replacement of lower extremities in our department of orthopedics from January 2009 to January 2012 were examined by echocardiography and Color Doppler flow imaging (CDFI) of the lower extremities. Based on pulmonary artery pressure (PAP), the patients were divided into a normal PAP group (n=214) and PH group (n=24). All the patients were re-examined by CDFI during post-operative care.*

RESULTS: *Among the 238 patients, 18 had DVT in the lower extremities after the operation. DVT total incidence rate was 7.56% (18/238). In the PH group, 11 patients had DVT (45.83%, 11/24), but in the normal PAP group, only 7 had DVT (3.27%, 7/214). The incidence of DVT was significantly lower in the normal PAP group than in the PH group (P<0.01). In addition, there was a positive correlation between PAP and the incidence of DVT.*

CONCLUSION: *PH could be a high-risk factor for the occurrence of DVT in patient's lower extremities after joint replacement surgeries.*

KEYWORDS: *Hypertension, Pulmonary. Arthroplasty, Replacement. Venous Thrombosis. Risk factors.*

INTRODUCTION

Deep venous thrombosis (DVT) is one of the major complications after joint replacement[1]. DVT affects the patient's postoperative rehabilitation, and it may even lead to fatal pulmonary embolism (PE)[2]. Effective preventive measures could lower the risk of venous thromboembolism (VTE), alleviate pain, and reduce health care costs[3]. The Chinese Orthopedic Association (COA) specially formulated guidelines for the prevention of VTE in major orthopedic surgeries in order to guide clinical thrombosis prevention in orthopedic surgery. However, it remains unclear whether pulmonary hypertension (PH) is a risk factor of DVT.

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In this retrospective study, we enrolled patients who underwent hip and/or joint replacement surgeries in the First Affiliation Hospital of Xinjiang Medical University from January 2009 to January 2012 and examined the correlation of PH with DVT after hip or knee replacement surgeries.

METHODS

Patients

This study was approved by the Institute of Ethics Committee of the First Affiliation Hospital of Xinjiang Medical University (No. 20130325-01), and all patients signed the consent form. Among all the patients who underwent joint replacement at our orthopedic center from January 2009 to January 2012, 238 received preoperative echocardiography, venous CDFI and postoperative CDFI examinations of the lower extremities. The patients included 89 males and 149 females, aged 54 to 92 (average age 65.9 years). There were 149 cases of total knee replacement surgery in knee joint osteoarthritis, 74 cases of total joint replacement in hip joint osteoarthritis, and 15 cases of hip replacement surgeries after hip fracture (10 total joint replacements, and 5 semi-joint replacements). The 238 patients were divided into two groups: the normal PAP group and PH group, according to their preoperative pulmonary artery pressure (PAP).

Diagnostic methods

Normal mean pulmonary artery pressure (mPAP) under quiescent conditions detected by Doppler echocardiography is 20-35 mmHg. A mPAP of 36-50 mmHg indicates mild PH, 51-80 mmHg indicates moderate PH, and > 81 mmHg is diagnosed as severe PH.

The main diagnostic criteria of lower extremity DVT by Doppler echocardiography are as follows: (1) thrombus in the Lumen of vein, the fact that the form of vascular cavities (especially the anterior and posterior diameter) shows little or no change after the probe is pressurized, which is the most reliable sign for diagnosing DVT; (2) disappearance of normal Lumen of vein and emergence of solid echoes of low or ranging intensity; (3) completely obstructed Lumen of vein, no signals of blood flow detected by color and pulse Doppler at the diseased region. Zero increase of blood flow after pressurization of distal limb indicates that the thrombus is located at the spot under examination or at the distal end[4].

Statistical analysis

Data were analyzed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). The data were expressed as the mean±SD and the comparison between the two groups was performed using the $\chi 2$ test. A $P<0.05$ was considered statistically significant.

RESULTS

Amongst the 238 patients, 214 were in the normal PAP group (84 males, 130 females, average age 65.63 years), and 24 patients were in the PH group (5 males, 19 females, average age 68.3 years). A total of 18 cases of lower extremity DVT occurred in both groups; the total occurrence of DVT was 7.56% (18/238). There were 11 cases of postoperative DVT in lower extremities in the PH group (5 males and 6 females, average age 68.7 years, 7 knee replacements, 3 hip replacements, 1 semi-hip joint replacement after hip fracture), which is equivalent to 45.83% (11/24). There were 7 postoperative DVT cases in the normal PAP group (3 males and 4 females, average age 62.4 years, 4 knee replacements and 3 hip replacements), equivalent to 3.27% (7/214).

Statistical analysis showed that the incidence of DVT in the PH group was significantly higher than that in the normal PAP group ($\chi 2=65.776$, $P<0.01$, Table 1). According to the mPAP values shown in the echocardiography, the incidence of DVT in the normal, mild, moderate, and severe PH patients was calculated with the application of the Cochran Armitage trend test. The results showed that the incidence of postoperative DVT was inclined to increase with the elevation of preoperative mPAP in patients ($\chi 2=49.996$, $P<0.01$, Table 2).

DISCUSSION

The current diagnostic standard of PH is mPAP>25 mmHg at sea level and under a quiescent

TABLE 1. COMPARISON OF THE CASES OF POSTOPERATIVE LOWER EXTREMITIES DVT IN TWO GROUPS

	PH (percentage)	Non-PH (percentage)
DVT	11 (45.83%)	7 (3.27%)
Non-DVT	13 (54.17%)	207 (96.73)
Total	24	214

TABLE 2. THE RELATIONSHIP BETWEEN MPAP AND THE INCIDENCE OF DVT

			mPAP (mmHg)		Total
	≤35 (normal)	36~50 (mild PH)	50~80 (moderate PH)	≥81(severe PH)	
DVT	7	7	3	1	18
Non-DVT	207	12	1	0	220
Total	214	19	4	1	238
Incidence (%)	3.27	36.84	75	100	7.56

condition[5]. According to "Guidelines for the diagnosis and treatment of pulmonary hypertension" published by the European Respiratory Society and the European Society of Cardiology in 2009[6], PH is classified into five categories: (1) Pulmonary arterial hypertension (PAH); (2) PH due to left heart disease; (3) PH due to lung diseases and/or hypoxia; (4) Chronic thromboembolic PH; and (5) PH with unclear and/or miscellaneous. Among different types of PH, the typical clinical manifestation is the constant elevation of PAP along with the continuous rise of venous pressure of the right ventricular, which would lead to overfilling, elevation of venous pressure, congestion in various organs as well as edema in the systemic venous system, or even right heart failure[5,7]. Meanwhile, hypoxia could be aggravated due to the lack of effective circulating blood in the systemic circulation. Chronic hypoxia could also cause secondary polycythemia, increased blood viscosity, and elevated circulation resistance. Any cause leading to vein injury, stagnant or slow venous blood flow or hypercoagulative state of blood could potentially be a risk factor of venous thromboembolism (VTE)[8]. Additionally, total knee replacement (TKR) or total hip replacement (THR) is a strong stimulating factor for DVT[9]. Therefore, for patients with PH who also have the aforementioned risk factors for thrombosis, surgeons should be highly sensitive to the incidence of DVT in the perioperative period. A previous report compared patients with PH after THR or TKA and patients without PH and undergoing these surgeries and found that the preoperative mortality among patients with PH was 3.7 and 4.6 times higher for those undergoing THA or TKA, respectively[10].

In 2009, the Chinese Orthopedic Association published a guideline for VTE prevention to guide the clinical practice, which confirmed that major orthopedic surgery is a very high-risk factor of VTE[11], especially of THR and TKR. The guidelines also summarized other common secondary risk factors including age, trauma, history of VTE, obesity, paralysis, immobility, application of tourniquet in surgery, general anesthesia, malignant neoplasm, central vein catheterization, chronic venous valvular incompetence. However, there is no report on PH as a risk factor of DVT.

During many years of clinical work, we examined clinical data of DVT patients after joint replacement and found abnormalities in the preoperative cardiac echocardiography of most DVT patients. Notably, PAP values increased to different extents, which led us to explore whether postoperative DVT was correlated to the changes in hemodynamics and hypercoagulative state that caused by elevated PAP. In this study, we analyzed the clinical data of 238 patients during three years. By comparing the incidence of postoperative DVT between the normal PAP group and PH group, we found that patients with PH had a significantly higher occurrence of DVT in the lower extremities compared with the normal PAP group. We believe that orthopedic surgeons should pay close attention to patients diagnosed with PH in preoperative echocardiography.

Among different means of clinical examination, right heart catheterization is a golden diagnostic criterion of PH[12]. However, this cannot be applied as a routine test because of its invasiveness. Doppler echocardiography is the most commonly used non-invasive, convenient, accurate, and reproducible method of examination. Many studies showed that PH diagnosis by echocardiography maintained a good correlation with the measured PAP from the right heart catheter[13]. In this study, we found that the risk of postoperative DVT was likely to increase with the rise of mPAP values in preoperative echocardiography, which indicated the correlation between postoperative DVT and preoperative mPAP value in PH patients. In fact, mPAP value is an exclusive risk factor for COPD[14].

In the intermediate or late stage of heart diseases, the prognosis could be deteriorated if the diseases were accompanied by PH [15]. Among the 11 postoperative DVT patients in PH group, 4 cases had problems in the left heart function, three of them suffered from aortic valve insufficiency and one suffered from mitral insufficiency. Orthopedic surgeons should pay particular attention to such patients with PH in the perioperative stage to prevent the occurrence of DVT. In addition, the average age of the 238 patients in this study was relatively high, and the operation procedures were difficult to perform. So preoperative echocardiography could not only assess general heart function but also enable the physician to know the patient's PAP value. Therefore, we believe that echocardiography should be considered as one of the routine tests of preoperative examination.

Currently, the literature reports that postoperative DVT mostly occurs in the vena cava. However, among the 18 postoperative DVT patients, the thrombus appeared in the venous plexus of calf muscles in 4 patients, with 2 patients in each group. There are fewer venous valves in the venous plexus of calf muscles, slow blood flow, absence of hard tissues as deep fascia, and vulnerability of the lumen to dilation, which makes it a likely area of thrombosis. Thrombus in the plexus of calf muscles accounts for 40% of peripheral deep venous thrombosis in the lower extremities. 20% of undiscovered thrombus in the plexus of calf muscles develops towards the proximal end in the following two weeks[16]. Among those who died of unknown causes within two weeks after hip and knee replacement, most died from pulmonary embolism caused by shedding of emboli of DVT in lower extremities[17,18]. Therefore, for PH patients with thrombosis in the plexus of calf muscles, surgeons should review the ultrasound test and reinforce follow-up anticoagulation therapy to avoid the development to real DVT or even fatal pulmonary embolism (PE) after discharge from hospital.

CONCLUSION

PH is a high-risk factor for DVT in the lower extremities post-joint replacement. The pre-existing slow blood flow in the vein and highly coagulative state of patients with PH are risk factors of thrombosis and likely to persist for a long time after the operation. Patients with PH should be informed of thrombosis prevention after discharge from hospital in order to reduce DVT and mortality rate.

Financial Disclosure

No financial disclosure was declared.

Conflict of Interest

No conflict of interest was declared.

Authors Contributions

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RESUMO

OBJETIVO: *A hipertensão pulmonar (HP) indica elevação progressiva da resistência vascular pulmonar, levando ao excesso de enchimento, elevação da pressão venosa, congestão em vários órgãos e edema no sistema venoso. Este estudo teve como objetivo investigar se a HP é um fator de risco para trombose venosa profunda (TVP) das extremidades inferiores após cirurgia de prótese de quadril e joelho.*

MÉTODOS: *Um total de 238 pacientes que receberam a substituição da articulação das extremidades inferiores em nosso departamento de ortopedia de janeiro de 2009 a junho de 2012 foi examinado por ecocardiograma e fluxo de imagem Doppler colorido (CDFI) dos membros inferiores. De acordo com a pressão arterial pulmonar (PAP), os pacientes foram divididos em grupo PAP normal (n=214) e grupo PH (n=24). Todos os pacientes foram reexaminados por CDFI durante os cuidados pós-operatórios.*

RESULTADOS: *Entre os 238 pacientes, 18 pacientes tiveram TVP nas extremidades inferiores após a operação. A taxa de incidência total de TVP foi de 7,56% (18/238). No grupo PH, 11 pacientes tiveram TVP (45,83%, 11/24), mas no grupo PAP normal, apenas sete pacientes tiveram TVP (3,27%, 7/214). A incidência de TVP foi significativamente menor no grupo PAP normal do que no grupo PH (P<0,01). Além disso, houve uma correlação positiva entre a PAP e a incidência de TVP.*

CONCLUSÃO: *A HP poderia ser um fator de alto risco para a ocorrência de TVP nas extremidades inferiores do paciente após cirurgias de substituição articular.*

PALAVRAS-CHAVE: *Hipertensão pulmonar. Artroplastia de substituição. Trombose venosa. Fatores de risco.*

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COMMENTARY

Comments on 'Pulmonary hypertension could be a risk for deep vein thrombus in lower extremities after joint replacement surgery'

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Pulmonary hypertension identified the progressive elevation of pulmonary vascular resistance, which would lead to many negative effects on the venous system and relevant organs. In Rexiti et al.[1] study, the authors showed that pulmonary hypertension could be a risk for deep vein thrombus of lower extremities after hip and knee replacement surgery.

In sum, 238 patients who underwent joint replacement at the First Affiliation Hospital of Xinjiang Medical University were recruited and studied. The good sample size in this study made the results therein convincing. Among the interesting results was that the incidence of deep venous thrombosis was found to be significantly lower in the normal pulmonary artery pressure group than in the pulmonary hypertension group. Also, a positive correlation was found between pulmonary artery pressure and the incidence of deep venous thrombosis. Afterward, the authors concluded that pulmonary hypertension could be a risk factor for deep venous thrombosis in the patient's lower extremities after joint replacement surgeries. From this perspective, patients with pulmonary hypertension should be informed of thrombosis prevention after discharge from hospital in order to reduce deep venous thrombosis and the mortality rate, which provides significant prognostic values in a real clinical scenario.

This study systematically investigated the association of pulmonary hypertension regarding deep venous thrombosis, which provided insights into the field. The results are based on many years of clinical work and the related clinical data generated, which have reasonably good reference merits. The work conducted is fundamental and, therefore, highly recommended to readers.

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ORIGINAL ARTICLE

The role of maximum compressed thickness of the quadriceps femoris muscle measured by ultrasonography in assessing nutritional risk in critically-ill patients with different volume statuses

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SUMMARY

PURPOSE: *In this prospective observational study, we aimed to investigate the role of the maximum compressed (MC) and uncompressed (UC) thickness of the quadriceps femoris muscle (QFMT) measured by ultrasonography (USG) in the detection of nutritional risk in intensive care patients (ICPs) with different volume status.*

METHODS: *55 patients were included. Right, left, and total ucQFMT and mcQFMT measurements were obtained by a standard USG device within the first 48 hours after ICU admission. Clinical examination and the USG device were used to determine the volume status of the patients. SOFA, APACHE II, modified NUTRIC scores, and demographic data were collected.*

RESULTS: *There was a significant difference between the nutritional risk of patients in terms of left, right, and total mcQFMT measurements (p=0.025, p=0.039; p=0.028, respectively), mechanical ventilation requirement (p=0.014), presence of infection (p=0.019), and sepsis (p=0.006). There was no significant difference between different volume statuses in terms of mcQFMT measurements. In the multi-variance analysis, mcQFMT measurements were found to be independently associated with high nutritional risk (p=0.019, Exp(B)=0.256, 95%CI=0.082-0.800 for modified NUTRIC score ≥ 5), and higher nutritional risk (p=0.009, Exp(B)=0.144, 95%CI=0.033-0.620 for modified NUTRIC score ≥ 6). a Total mcQFMT value below 1.36 cm was a predictor for higher nutritional risk with 79% sensitivity and 70% specificity (AUC=0.749, p=0.002, likelihood ratio=2.04).*

CONCLUSION: *Ultrasonographic measurement of total mcQFMT can be used as a novel nutritional risk assessment parameter in medical ICPs with different volume statuses. Thus, patients who could benefit from aggressive nutritional therapy can be easily identified in these patient groups.*

KEYWORDS: *Ultrasonography. Quadriceps Muscle. Malnutrition. Intensive Care Units.*

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INTRODUCTION

Malnutrition occurs in 20-50% of the patients admitted to hospitals[1]. Early nutritional screening and detection of malnutrition and its treatment can reduce the requirement of mechanical ventilation, duration of hospitalization, and mortality in critically-ill patients[2,3]. However, there is no gold standard method to detect malnutrition in intensive care unit (ICU) patients. Therefore, we can use the "modified Nutrition Risk in the Critically ill" (mNUTRIC) score to assess nutritional risk in intensive care units (ICU)[4]. The mNUTRIC score can determine which patients can benefit from increased nutritional intake in ICU. Thus, early and more aggressive nutritional support in ICU patients with a high mNUTRIC score may improve their nutritional status and outcome. Another important aspect of the mNUTRIC score is that it is correlated with skeletal muscle loss of ICU patients[5]. This is an expected condition as skeletal muscle tissue is adversely affected by systemic inflammation and sepsis[6]. However, skeletal muscle tissue is also affected by different factors such as immobilization, hypervolemia, advanced age, length of ICU stay, and duration of mechanical ventilation in ICU patients[7]. Furthermore, skeletal muscle mass measurements are affected by fluid changes such as overhydration or dehydration[8]. Therefore, it is a research topic to examine how muscle mass measurements change in ICU patients with different nutritional status (mNUTRIC), volume status, and other clinical settings. The muscle mass of ICU patients can be quantified by using ultrasonography (USG). Furthermore, quadriceps femoris muscle thickness (QFMT) can be measured by using USG as an indicator of lean body mass as it has been found to correlate with CT measurements[9,10]. In addition, the swelling effect of hypervolemia on muscle mass may be corrected by maximum compression during USG measurement. Therefore, it is not known how uncompressed (UC) and maximal compressed (MC) QFMT measurements will change in ICU patients with different nutritional status, volume status, and other clinical settings. For this purpose, we aimed to determine the effect of different volume, nutritional risk, and other clinical settings of critically-ill patients on QFMT measurements by USG. Furthermore, we hypothesized that measurement of QFMT can help determine nutritional risks of ICU patients, like the mNUTRIC score.

METHODS

Patient population

All patients who were older than 18 years and hospitalized in the medical ICU of Gazi University Hospital between August 01, 2017 and March 01, 2018 were included in this study. The first admissions of the patients were evaluated. Patients who had muscular atrophy in lower extremities due to cerebrovascular accident, neuromuscular disease, or trauma were excluded from the study. Patients who stayed in the ICU for less than 48 hours were not included in this study. Approval was obtained from the local ethics committee on December 25, 2017, under number 616. Written informed consent was obtained from the patients and/or their relatives.

Clinical information of patients

Demographic data, ICU admission diagnostics, comorbidities, APACHE II (Acute Physiology and Chronic Health Evaluation) scores, SOFA (Sequential Organ Failure Assessment) scores, mNUTRIC (modified Nutrition Risk in the Critically Ill) scores[4], mechanical ventilation requirements and total fluid balances of the patients were recorded. The mNUTRIC score was calculated at ICU admission to determine the nutritional risk of patients and to identify which patients would benefit from aggressive nutritional support therapy. Interleukin 6 levels were not used when calculating mNUTRIC scores. The presence of mNUTRIC score ≥ 5 was considered evidence of high nutritional risk. mNUTRIC score ≥ 6 was considered evidence of higher nutritional risk. Total fluid balances of the patients were obtained from daily patient follow-up sheets noted by nurses. Maximal compressed QFMT (mcQFMT) and uncompressed QFMT (ucQFMT) measurements of both legs of the patients were recorded within 48 hours of ICU admission. The maximum (VCImax) and minimum (VCImin) diameters of the vena cava inferior (VCI), collapsibility of the VCI (VCIcol), pleural, hepatorenal, splenorenal and intraabdominal free fluid presence, and total fluid balances of the patients were recorded to evaluate their volume status. In patients who were not mechanically ventilated, the presence of two or more criteria was accepted as hypervolemia. These criteria were VCImax > 2.1 cm, VCIcol < 50%, presence of free fluid in the third space (pleural or intra-abdominal) or total fluid balance above 2000 cc in the last 48 hours of ICU stay. In mechanically ventilated patients, the VCIcol criteria changed to <20%. These criteria were obtained from

the results of previous studies and used in this study to distinguish the volume statuses of the patients[11-14].

USG device and probe

GE brand S7 model ultrasonography device (GE Healthcare, General Electric Company, USA) and 5 megahertz (MHz) convex probe were used to measure mcQFMT and ucQFMT.

Measurement methods

Measurements were performed by an intensive care physician with adequate practical and theoretical training about ultrasonography and 2 years of experience. It was known that mcQFMT and ucQFMT measurements by USG were a reproducible technique with high Intraclass correlation coefficient[10,15]. Patients were placed in the supine position before measurement. During the measurement, the physician ensured the patella could move freely and that the quadriceps femoris muscle was relaxed. QFMT measurements were obtained at the midpoint of the line between the anterior superior iliac spine and the upper point of the patella by using USG[15]. At this point, measurements were carried out in transverse section by not applying compression at first and by applying maximal compression the second time (Figure 1). Maximum compression is an amount of pressure applied with the probe, which can minimize the muscle thickness observed during ultrasound B mode imaging, and it is a limit of pressure that cannot achieve a thinner muscle thickness with more pressure. QFMT measurements were obtained from the upper margin of the femur bone to the lower margin of the deep fascia of the quadriceps femoris muscle perpendicularly to the femur surface. Both mcQFMT and ucQFMT measurements were calculated as the average of three separate measurements in each leg. Especially in some obese and edematous patients, a convex probe was used for QFMT measurements due to the insufficiency of depth of the linear probe. VCI measurements were performed in accordance with the definition in the literature[16]. The presence of pleural or intra-abdominal free fluid was investigated by using a convex probe.

STATISTICAL ANALYSIS

Statistical analysis was performed using the IBM SPSS statistics program version 22 (IBM, NY, USA). The distributions of continuous variables were examined using the Kolmogorov-Smirnov normality test. Continuous variables without normal distribution were described as median (interquartile range). Categorical variables were described as frequencies and percentages. Comparison between survivors and non-survivors, hypervolemic and normovolemic patients and high nutritional risk and low nutritional risk patients were made by using the Mann-Whitney U test for continuous variables and the χ^2 test for qualitative data. The correlation between the data was investigated using Spearman's correlation test. The parameters which had a significant difference in terms of nutritional risk in the univariate analysis were subjected to logistic regression analysis as multivariate analysis. Logistic regression analysis was performed to determine independent risk factors related to nutritional risk. After the determination of independent risk factors for mortality and nutritional status, ROC (Receiver Operating Characteristic) curve analyses were performed. P values lower than 0.05 were considered statistically significant.

RESULTS

55 patients were included in the study. The demographic data of the patients are presented in Table 1. Nutritional risk was high in 37 patients (mNUTRIC

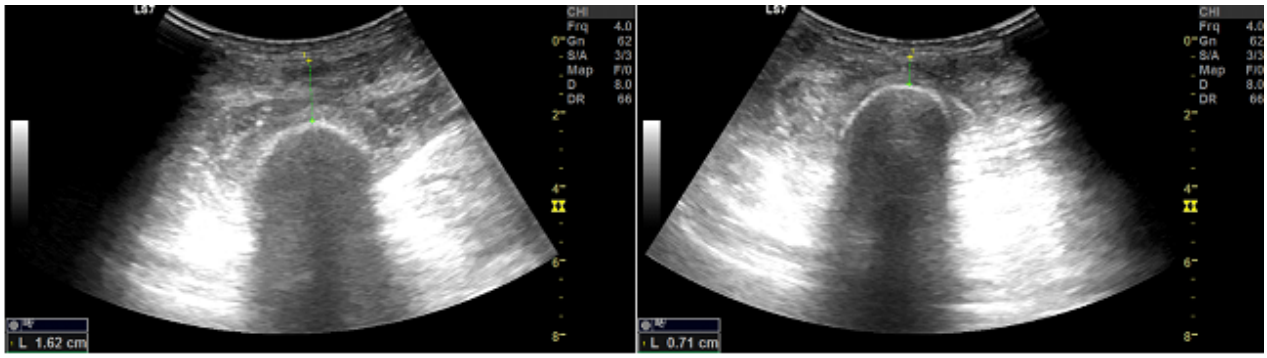

FIGURE 1

FIGURE 2

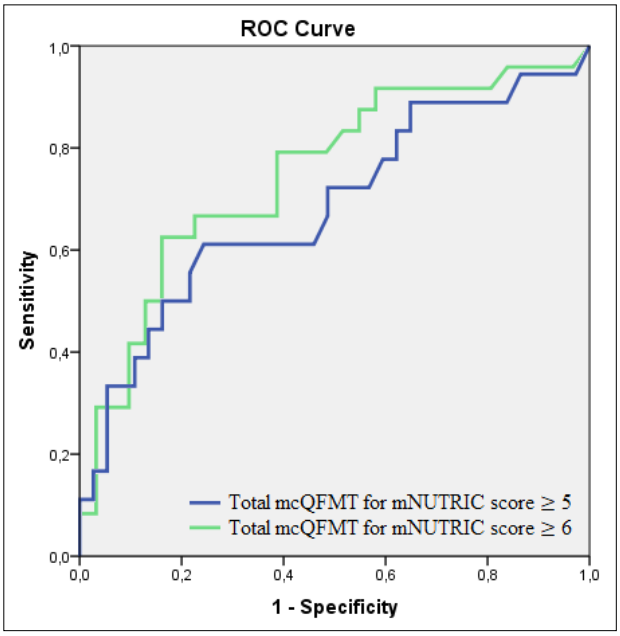

TABLE 1. DEMOGRAPHIC DATA AND ADMISSION DIAGNOSIS OF THE PATIENTS INCLUDED IN THE STUDY

Parameters	All patients (n=55)
Age (Years)*	72 [57-83]
Gender, F/M, n	25 / 30
APACHE II score*	24 [18-30]
SOFA score*	6 [4-9]
mNUTRIC score*	6 [4-7]
High Nutritional risk (mNUTRIC ≥ 5), n (%)	37 (67)
Total fluid balance for all days (mL)*	425 [(-460) – (2370)]
Total fluid balance for last 48 hours (mL)*	660 [(-433) – (3419)]
Hypervolemic volume status, n (%)	27 (49)
Invasive mechanical ventilation, n (%)	22 (40)
Mortality, n (%)	22 (40)
Length of ICU stay (day)*	5 [3-11]
Admission diagnosis	
Infection, n (%)	48 (87.3)
Sepsis, n (%)	38 (69.1)
Pulmonary, n (%)	31 (56.4)
Renal, n (%)	20 (36.4)
Neurological, n (%)	18 (32.7)
Cardiovascular, n (%)	13 (23.6)
Shock, n (%)	13 (23.6)
Malignancy, n (%)	11 (20.0)

*Data are presented as median and [interquartile range]. N, n: number; F: female; M: male; APACHE-II: Acute Physiology and Chronic Health Evaluation Score; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; mNUTRIC: modified Nutrition Risk in the Critically Ill

score ≥ 5); 27 patients were hypervolemic. All data with statistically significant differences in terms of volume and nutrition risk are presented in Table 2. There was a moderate correlation between total mcQFMT measurements and mNUTRIC score (p = 0.001, r = -0.425), APACHE II score (p = 0.007, r = -0.359), SOFA score (p = 0.005, r = -0.371), mortality (p=0.012, r=-0.338), duration of ICU stay (p=0.018, r=-0.319), invasive mechanical ventilation requirement (p = 0.006, r = -0.367), and sepsis (p=0.008, r=-0.356). When logistic regression analysis was performed, it was revealed that total mcQFMT was independently associated with high nutritional risk (mNUTRIC score ≥ 5) (Table 3). When the effect of mcQFMT on high nutritional risk (mNUTRIC score ≥ 5) was investigated by ROC analysis, AUC was calculated as 0.684 (p = 0.028) (Figure 2). It was determined that a total mcQFMT value below 1.69 cm was a predictor for high nutritional risk (mNUTRIC score ≥ 5) with 61% sensitivity and 71% specificity (Likelihood ratio = 2.05).

The mNUTRIC score was also ≥ 6 in 31 patients, as the majority of these 37 patients with high nutritional risk. In addition to this higher nutritional risk defined by the mNUTRIC ≥ 6, there was also a statistically significant difference in right mcQFMT (p=0.015), left mcQFMT (p=0.0001), total mcQFMT (p=0.002), APACHE II score (p = 0.0001), SOFA score (p=0.0001), presence of infection (p = 0.017), sepsis (p = 0.001), shock (p = 0.003) at ICU admission, invasive mechanical ventilation requirement (p=0.002), and mortality (p=0.0001). It was also revealed that the total mcQFMT was independently associated with higher nutritional risk (mNUTRIC score ≥ 6) (Table 3). When the effect of mcQFMT on higher nutritional risk (mNUTRIC score ≥ 6) was investigated by ROC analysis, AUC was calculated as 0.749 (p = 0.002) (Figure 2). It was determined that a total mcQFMT value below 1.36 cm was a predictor for higher nutritional risk (mNUTRIC score ≥ 6) with 79% sensitivity and 70% specificity (Likelihood ratio = 2.04).

DISCUSSION

Hypervolemia is a condition frequently observed in critically-ill patients[17]. In one study, one-third of patients who were followed-up in ICU for sepsis had hypervolemia, and almost all of them had positive fluid balance[18]. Similarly, hypervolemia was detected in half of the patients in our study. Hypervolemia adversely affects nutritional status detection methods. For example, the presence of hypervolemia during

TABLE 2. CLINICAL PARAMETERS ACCORDING TO VOLUME STATUS AND NUTRITIONAL RISK OF THE PATIENTS INCLUDED IN THE STUDY

Parameters	All patients n=55	Normovolemia n=28	Hypervolemia n=27	P-value
APACHE II score	24 [18-30]	22 [16-26]	28 [21-33]	0.010**
Mortality, n (%)	22 (40)	8 (28.5)	14 (51.8)	0.078
High nutritional risk, n (%)	37 (67.3)	16 (29)	21 (38)	0.103
TFB for all days*, (mL)	425 [(-460)-(2370)]	-150 [(-524)-(965)]	2285 [(150)-(3545)]	0.001**
TFB for last 2 days*, (mL)	660 [(-433)-(3419)]	-300 [(-935)-(749)]	3419 [300-5700]	0.001**
VCImax* (cm)	1.47 [1.28-1.75]	1.41 [1.19-1.73]	1.51 [1.31-1.97]	0.186
VCIcol* (%)	37 [16-61]	51 [35-63]	18.7 [11-39]	0.0001**
Right ucQFMT* (cm)	2.06 [1.34-2.80]	2.28 [1.55-3.20]	1.93 [0.95-2.47]	0.038**
Left ucQFMT* (cm)	2.10 [1.49-2.75]	2.40 [1.60-2.88]	1.80 [1.07-2.46]	0.037**
Total ucQFMT* (cm)	4.39 [2.66-5.60]	4.82 [3.20-5.67]	4.02 [2.27-4.68]	0.016**
Right mcQFMT* (cm)	0.70 [0.47-1.15]	0.85 [0.54-1.14]	0.55 [0.43-1.15]	0.150
Left mcQFMT* (cm)	0.71 [0.54-1.09]	0.80 [0.59-1.09]	0.65 [0.41-1.00]	0.080
Total mcQFMT* (cm)	1.50 [0.99-2.12]	1.69 [1.24-2.15]	1.28 [0.86-2.12]	0.070
	All patients N=55	Low nutritional risk n=18	High nutritional risk n=37	P-value
IMV, n (%)	22 (40)	3 (16.6)	19 (51.3)	0.014**
mNUTRIC score	6 [4-7]	3.5 [2.0-4.0]	6 [6-8]	0.0001**
Mortality, n (%)	22 (40)	2 (11.1)	20 (54.0)	0.002**
Hypervolemic patients, n (%)	27 (49)	6 (33.3)	21 (56.7)	0.103
VCIcol* (%)	37 [16-61]	51.0 [38.0-62.5]	29 [13-50]	0.012**
Right ucQFMT* (cm)	2.06 [1.34-2.80]	2.41 [1.72-3.20]	1.80 [1.26-2.58]	0.094
Left ucQFMT* (cm)	2.10 [1.49-2.75]	2.42 [1.56-3.49]	1.96 [1.48-2.64]	0.123
Total ucQFMT* (cm)	4.39 [2.66-5.60]	4.80 [3.47-6.57]	4.08 [2.55-5.34]	0.097
Right mcQFMT* (cm)	0.70 [0.47-1.15]	1.00 [0.58-1.31]	0.63 [0.45-0.95]	0.039**
Left mcQFMT* (cm)	0.71 [0.54-1.09]	0.95 [0.63-1.33]	0.65 [0.47-0.97]	0.025**
Total mcQFMT* (cm)	1.50 [0.99-2.12]	2.00 [1.21-2.59]	1.34 [0.91-1.76]	0.028**

*Data are presented as median and [interquartile range]; ** There was statistically significant difference; n: number; IMV: Invasive mechanical ventilation; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; TFB: Total Fluid Balance; SOFA score: Sequential Organ Failure Assessment score; mNUTRIC: modified Nutrition Risk in the Critically Ill; VCImax: Maximum vena cava inferior diamater; VCIcol: Vena cava inferior collapsibility index; QFMT: quadriceps femoris muscle thickness; ucQFMT: Uncompressed QFMT; mcQFMT: Maximum compressed QFMT;

TABLE 3. LOGISTIC REGRESSION ANALYSIS FOR DETERMINING INDEPENDENT RISK FACTORS FOR HIGH NUTRITIONAL RISK IN THE STUDY POPULATION

Logistic regression analysis for high nutritional risk (mNUTRIC score ≥ 5)			
Parameters	P-value	Exp (B)	CI 95% (Confidence Interval)
Total mcQFMT	0.019	0.256	0.082-0.800
VCIcol	0.177	0.972	0.932-1.013
Requirement of IMV	0.214	3.143	0.516-19.160
Volume status	0.902	0.904	0.183-4.462
Length of ICU stay	0.136	0.939	0.865-1.020
Logistic regression analysis for higher nutritional risk (mNUTRIC score ≥ 6)			
Parameters	P-value	Exp (B)	CI 95% (Confidence Interval)
Total mcQFMT	0.009	0.144	0.033-0.620
VCIcol	0.029	0.947	0.901-0.994
Requirement of IMV	0.158	3.770	0.598-23.779
Volume status	0.266	0.389	0.074-2.052
Length of ICU stay	0.075	0.911	0.823-1.009

QFMT: quadriceps femoris muscle thickness; mcQFMT: Maximum compressed QFMT; IMV: Invasive mechanical ventilation; mNUTRIC: modified Nutrition Risk in the Critically Ill; VCIcol: Vena cava inferior collapsibility index;

DEXA measurements causes errors in the detection of lean body mass[19]. Body mass index, which is a simple measurement method, cannot predict malnutrition, especially in patients with volume overload[20]. The presence of edema, especially in ICU patients, is a serious problem for the use of anthropometric measurements for evaluation of malnutrition[21]. Serum levels of biochemical markers used to detect malnutrition such as prealbumin, albumin, and transferrin vary with the intravascular volume excess and infection or inflammation[22]. For these reasons, it may be helpful to use nutritional risk assessment tools to assess nutritional status in ICU patients. In fact, the mNUTRIC score is a nutritional risk assessment tool developed specifically for ICU. However, a significant limitation of usage of the mNUTRIC score is that it does not include anthropometric or body composition parameters. Therefore, as the results of this study suggest, the use of total QFMT measurements may be more useful in assessing the nutritional risk of ICU patients. However, QFMT measurements with the use of USG may be false since the capacity of the skeletal muscles to contain fluids is quite high[8]. In our study, ucQFMT values measured by USG had a statistically significant difference when compared to hypervolemic patients and normovolemic patients. However, the effects of excess fluid volume on maximal compressed muscle thickness are unknown. In our study, there was no statistically significant difference between hypervolemic and normovolemic patients in terms of mcQMFT. Therefore, it can be thought that excess fluid volume has less effect on the mcQFMT measurement when compared to the ucQFMT measurement in ICU patients.

In a previous study, QFMT measurements by USG and without compression were found to be negatively correlated with malnutrition[23]. In addition, in this study, thinner QFMT measurements were obtained in malnourished dialysis patients compared to healthy and well-nourished individuals. In another study, it was found that uncompressed QFMT measurements by USG could be high in ICU patients with better nutritional support[24]. In one study, it was found that maximal compressed QFMT measurements obtained by USG showed moderate correlation with abdominal wall muscle section in abdominal CT images of ICU patients[10]. Therefore, we can conclude that QFMT measurements are directly related to nutritional status because they contain data related to body composition. Thus, this feature of QFMT measurement can provide an advantage in evaluating nutritional status compared to the mNUTRIC score. We noticed that the relationship between the maximum compressed QFMT measurements and nutritional status has not been previously investigated in ICU patients. Therefore, this study is very important for nutrition literature. Also in our study, when uncompressed and maximal compressed QFMT measurements were evaluated in terms of their ability to detect nutritional risk, mcQFMT measurements were found to be very precious for determining nutritional risk in ICU patients. We also understood that the total mcQFMT measurements (total mcQFMT measurements of right and left legs) can be used to detect the nutritional risk in ICU patients with different volume statuses.

CONCLUSION

The total maximum compressed QFMT measurements obtained by the sum of the maximum compressed QFMT measurements of left and right legs can be used as a novel ultrasonographic nutritional risk assessment parameter in medical ICU patients with different volume statuses. Thus, patients who have nutritional risk or who can benefit from aggressive nutritional therapy can be easily identified in these patient groups.

Conflicts of Interest:

The authors declare no conflict of interest.

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Author's Contributions

1. Uğur Özdemir, Contribution: Obtaining clinical data from patients, detecting appropriate patients, collecting ultrasonography measurement data and images, analyzing data, researching literature, writing the article.

2. Merve Özdemir, Contribution: Researching literature, writing the article.

3. Gulbin Aygencel Contribution: Analyzing the data, researching literature, writing the article.

4. Burcu Kaya, Contribution: Obtaining clinical data from patients, detecting appropriate patients, researching literature

5. Melda Türkoğlu, Contribution: Obtaining clinical data from patients, detecting appropriate patients, researching literature

RESUMO

OBJETIVO: *Neste estudo observacional prospectivo, objetivamos investigar o papel da espessura do músculo quadríceps femoral (QFMT) comprimido (mc) e não comprimido (uc) medida pela ultrassonografia (USG) na detecção do risco nutricional em pacientes de terapia intensiva (ICPs) com status de volume diferente.*

MÉTODOS: *Cinquenta e cinco pacientes foram incluídos. As medidas direita, esquerda e total de ucQFMT e mcQFMT foram obtidas por um dispositivo USG padrão nas primeiras 48 horas após a admissão na UTI. O exame clínico e o dispositivo USG foram usados para determinar o status volumétrico dos pacientes. Sofa, Apache II, escores Nutric modificados e dados demográficos foram coletados.*

RESULTADOS: *Houve diferença significativa entre o risco nutricional dos pacientes em termos de medidas da QTFMT esquerda, direita e total (p=0,025, p=0,039; p=0,028, respectivamente), necessidade de ventilação mecânica (p=0,014), presença de infecção (p=0,019) e sepse (p=0,006). Não houve diferença significativa entre os diferentes status de volume em termos de medidas de mcQFMT. Na análise de variância múltipla, verificou-se que as medidas da FCFMT estavam independentemente associadas a alto risco nutricional (p=0,019, Exp (B)=0,256, 95%CI=0,082-0,800 para escore Nutric modificado ≥ 5) e maior risco nutricional (p=0,009, Exp (B)=0,144, 95%CI=0,033-0,620 para o escore Nutric modificado ≥ 6). O valor total de mcQFMT abaixo de 1,36 cm foi um preditor de maior risco nutricional com sensibilidade de 79% e especificidade de 70% (ASC=0,749, p=0,002, razão de verossimilhança = 2,04).*

CONCLUSÃO: *A medida ultrassonográfica do mcQFMT total pode ser usada como um novo parâmetro de avaliação de risco nutricional em ICPs médicas com diferentes status de volume. Assim, pacientes que podem se beneficiar de uma terapia nutricional agressiva podem ser facilmente identificados nesses grupos de pacientes.*

PALAVRAS-CHAVE: *Ultrassonografia. Músculo quadríceps. Desnutrição. Unidades de Terapia Intensiva.*

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ORIGINAL ARTICLE

Combination of GI-RADS and 3D-CEUS for differential diagnosis of ovarian masses

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SUMMARY

OBJECTIVE: *The purpose of this study is to evaluate the efficacy of the combination of gynecologic imaging reporting and data system (GI-RADS) ultrasonographic stratification and three-dimensional contrast-enhanced ultrasonography (3D-CEUS) in order to distinguish malignant from benign ovarian masses.*

METHODS: *In this study, 102 patients with ovarian masses were examined by both two-dimensional ultrasound(2D-US) and 3D-CEUS. Sonographic features of ovarian masses obtained from 3D-CEUS were analyzed and compared with 2D-US. All patients with ovarian masses were confirmed by operational pathology or long-term follow-up results.*

RESULTS:*(1)The Chi-square test and multiple Logistic regression analysis confirmed that there were only eight independent predictors of malignant masses, including thick septa (≥3mm), thick papillary projections(≥7mm), solid areas, presence of ascites, central vascularization, contrast enhancement, distribution of contrast agent, and vascular characteristics of the solid part and their odds ratios which were 5.52, 5.39, 4.94, 4.34, 5.92, 7.44, 6.09, and 7.67, respectively (P<0.05). (2)These eight signs were used to combine the GI-RADS with 3D-CEUS scoring system in which the corresponding value of the area under the curve (AUC) was 0.969, which was superior to using GI-RADS lonely (Z-value=1.64, P<0.025). Using 4 points as the cut-off, the scoring system showed the performance was clearly better than using GI-RADS alone (P<0.05). (3) The Kappa value was 0.872 for two different clinicians with equal experience.*

CONCLUSIONS: *The combination of GI-RADS and 3D-CEUS scoring system would be a more effective method to distinguish malignant from benign ovarian masses.*

KEYWORDS: *Neoplasias ovarianas. Doenças ovarianas. Ultrasonography. Imaging, three-dimensional/methods.*

INTRODUCTION

Ovarian cancer is the fifth most common type of cancer and the most aggressive. Despite advances in surgery, chemotherapy, and intensive ongoing researches, 5-year survival has not significantly increased.[1] Thus, the early detection of ovarian tumors and accurate assessment of their properties are still the major issues attracting attention in the medical community.[2] Currently, ultrasonic determination of

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benign or malignant ovarian tumors primarily involves subjective and qualitative diagnosis. There is a lack of quantitative information and a strong dependence on the physicians' experience and operative techniques.[3] Therefore, semi-quantitative sonographic scoring system (SSS) has been proposed, with sensitivity, specificity, and diagnostic accuracy significantly higher than using a conventional two-dimensional ultrasound (2D-US) method.[4] The SSS can be utilized to score a tumor based on its 2D-US sonographic characteristics, including size, shape, border, wall thickness, internal echo characteristics, septa, posterior shadowing, presence of ascites, color flow distribution, and other factors. In addition, SSS would be appropriate to incorporate a multi-mode diagnostic ultrasound system including power Doppler sonography, three-dimensional power Doppler (3D-PD) sonography, contrast-enhanced ultrasonography (CEUS), and 3D contrast-enhanced power Doppler ultrasonography (3D-CE-PDU) into the scoring system.[5-7] However, the sonographic characteristics of the selected SSS were baseless and unjustified.

In 2009, Amor et al.[8] proposed a gynecologic imaging reporting and data system (GI-RADS) for reporting results in adnexal masses based on six characteristics including thick septa (≥3mm), thick papillary projections(≥7mm), solid areas, presence of ascites, central vascularization and resistance index (RI)<0.5, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), which were 92%, 97%, 85%, and 99%, respectively. A new transvaginal ultrasonographic technique called 3D contrast-enhanced ultrasonography (3D-CEUS) added more information by incorporating 3D imaging with CEUS and has been confirmed as superior to 2Dcontrast-enhanced ultrasonography (2D-CEUS) in differentiating benign and malignant ovarian tumors.[9] In this study, we describe and propose a new scoring system including six factors from GI-RADS and four factors from 3D-CEUS, which is, in fact, a combination of GI-RADS and the 3D-CEUS scoring system for conducting a semi-quantitative evaluation of the nature of ovarian tumors as well as comparing the diagnostic accuracy of this new SSS method with that of GI-RADS.

METHODS

In this study, 102 women (age range 16–68 years; mean age 32.8 ± 12.2years) with diagnoses of ovarian masses participated with cystic-solid, solid, thick separation, or thick papillary projections on B-mode between July 2015 and July 2016. Exclusion criteria were pregnancy, breastfeeding, severe heart failure based on the New York Heart Association (NYHA) classes (class IV was adopted), and ultrasound contrast agents (UCAs) contraindicated in patients. The patients or their legally authorized representatives consented to the treatment by signing and dating the informed consent documents. This study was approved by the institutional review board (IRB) and followed the Helsinki Declaration for human studies.[10]

2D-US

All 2D-US examinations were performed using the Voluson E8 Expert (GE Medical Systems, MA, USA) ultrasound machine with dedicated 3D imaging software. The vaginal probe model was RIC5-9-D, with a frequency range of 5.0-9.0 MHz, and a mechanical index (MI) of 0.08. The 2D-US examinations were undertaken at our department by experienced sonographers (>10,000 pelvic sonographies). After the examinations, the GI-RADS was used with the following classifications. GI-RADS 1, definitively benign; normal ovaries were identified, and no adnexal mass was seen. GI-RADS 2, very probably benign; this category included adnexal lesions thought to be of functional origin, such as follicles, corpora lutea, and hemorrhagic cysts. GI-RADS 3, probably benign; this category included neoplastic adnexal lesions thought to be benign, such as endometrioma, teratoma, simple cyst, hydrosalpinx, paraovarian cyst, peritoneal pseudocyst, pedunculated myoma, and findings suggestive of pelvic inflammatory disease. GI-RADS 4, probably malignant; this category included adnexal lesions that could not be included in the other groups, with 1 or 2 findings suggestive of malignancy (i.e., thick papillary projections, thick septations, solid areas, central vascularization, ascites, and a lowest RI<0.5). GI-RADS 5, very probably malignant; this category included adnexal masses with 3 or more of the findings suggestive of malignancy listed for GI-RADS 4.[8]

3D-CEUS

In this study, a SonoVue contrast agent (Bracco, Milan, Italy) was used. A bolus of 2.4 mL was injected into the median cubital vein and was immediately followed by injections of 5-10 mL saline. As a contrast agent, 59 mg SonoVue was added to 5 mL saline and mixed well. The scanning was carried out by steadily

moving the probe from top to bottom using freehand static 3D-CEUS mode, and the sampling was repeated every 10 seconds until 90 seconds. All 3D-CEUS images were stored.

The analysis was made through rotation and tomographic ultrasound imaging (TUI). The four following criteria were observed: enhanced time, contrast enhancement, distribution of contrast agent in enhanced solid part, vascular characteristics of solid part, quickly enhanced time, significant enhancement, inhomogeneous distribution of contrast agent in enhanced solid part, and abnormally vascular characteristics of solid part were detected as malignancy signs.

The reference standard for the final diagnosis of a benign or malignant tumor was the histological examination of the operative specimen or long-term follow-up findings.

STATISTICAL ANALYSIS

In order to do the statistical analysis, data were analyzed using SPSS software(Version 22.0) for Windows (SPSS, Chicago, IL, USA). The Chi-square test and multiple Logistic regression analysis were performed to investigate whether the independent risk predictors in the differential diagnosis of benign and malignant ovarian could be confirmed. In addition, using a combination of GI-RADS and 3D-CEUS scoring system, the receiver operating characteristic (ROC) curve was drawn to determine the cut-off value. The cut-off value was then applied as an original score to calculate sensitivity, specificity, diagnostic accuracy, PPV, and NPV. A Two-tailed $P<0.05$ was considered statistically significant.

Two blinded examiners evaluated 20 consecutive cases. Interobserver reproducibility was assessed using the Kappa index.

RESULTS

Histological follow-up results

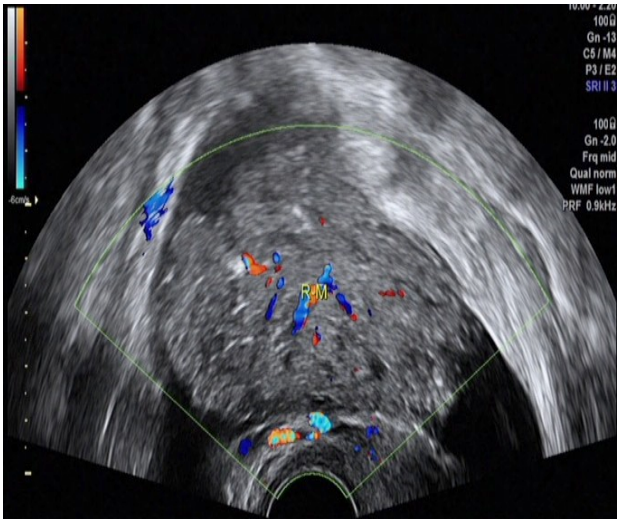
Among 102 ovarian masses, 67 were benign, which was confirmed by surgical pathology (63 masses) or long-term follow-up (4 masses); the remaining 35 were malignant masses, all pathologically confirmed.

Ten characteristics of ovarian masses

The Chi-square test showed ten characteristics that can be used to differentiate benign and malignant ovarian masses. However, multiple Logistic regression analysis confirmed that there were only eight independent predictors of malignant masses, including thick papillary projections, thick septa, central vascularization, ascites, solid lesions, contrast-enhanced, distribution of contrast agent, and vascular characteristics of solid tumors ($P<0.05$= as displayed in Figure1).

Combination of GI-RADS with 3D-CEUS scoring system and comparison of the diagnostic efficiency with GI-RADS

The combination of GI-RADS with 3D-CEUS scoring system based on the mentioned eight independent



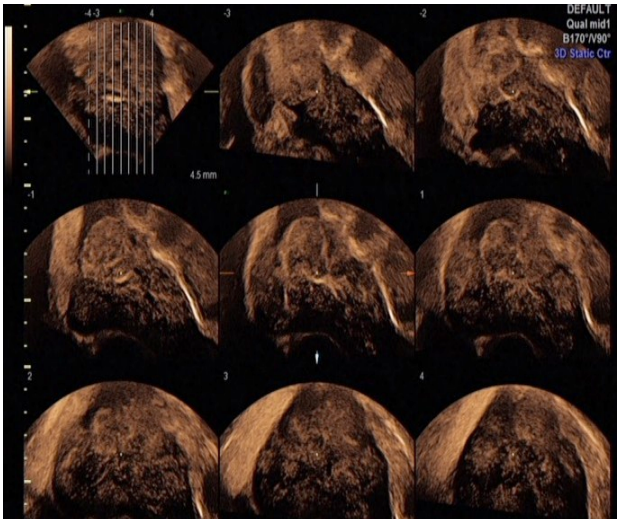


FIGURE 1. A serious adenocarcinoma (stage Ia). A) Transvaginal sonogram showing a solid area with irregular contours and blood flow within it and ascites (thick arrow). B) 3D-CEUS shows a significant, inhomogeneous enhanced region in the parenchyma. Stereoscopic vascularity and clear courses of blood vessels (thin arrow) can be seen in every layer of the 3D TUI-CEUS. The GI-RADS combination with 3D-CEUS system score was 6.

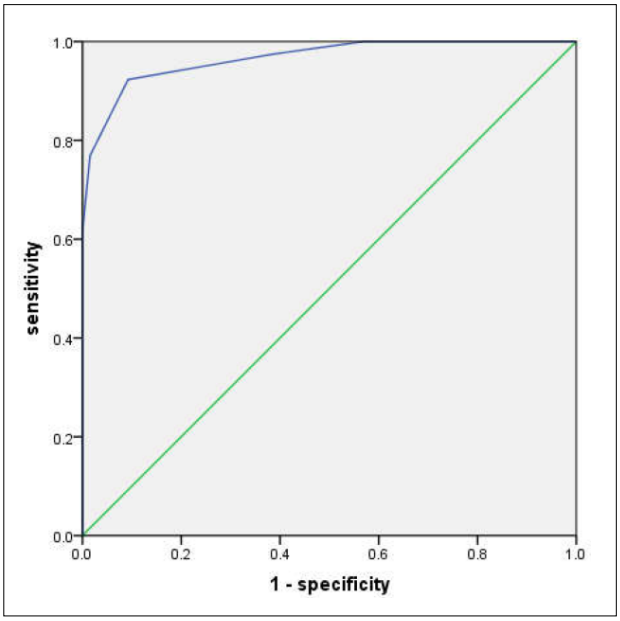


FIGURE 2. ROC curves of the combination of GI-RADS with 3D-CEUS scoring system in distinguishing benign from malignant small adnexal masses.

predictors and the area under the curve (AUC) was 0.969, as depicted in Figure 2, which was superior to the 0.837 of GI-RADS (Z-value =1.64, $P<0.05$=, as illustrated in Figure 3). It is noteworthy that a score of 4 was chosen as the cut-off, and the sensitivity, specificity, diagnostic accuracy, PPV, and NPV of the new scoring system are all superior to those of GI-RADS. Furthermore, the same Kappa value of 0.872 was reached by between two different clinicians with equal experience.

DISCUSSION

Currently, the transvaginal scan (TVS) is the most commonly used and effective approach for detecting and diagnosing ovarian tumors. However, the subjective nature of ultrasound interpretation makes its clinical application somewhat unreliable.[11] In 2012, a scoring system based on surface, wall thickness, inner wall structures, septa, contrast enhancement of the masses, relationship with surrounding tissues and ascites called the 3D-CEUS scoring system was developed by Xiang et al.[12] with high sensitivity and specificity, 100% and 98%, respectively. Nevertheless, the selection of factors lacked statistical basis and may be appropriate only for those with a largest diameter smaller than 4cm. In this study, we attempted to use Chi-square test as primary screening and then multiple Logistic regression analysis to exclude the factors containing collinearity and eventually verified its sensitivity, specificity, and accuracy values for detecting ovarian malignant masses, which were 94.2%, 95.5%, and 95.0%, respectively. Furthermore, by covering the signs of GI-RADS containing ovarian mass when the lesions are >5cm, an applicable field of combination of GI-RADS and 3D-CEUS scoring system was herein expanded.

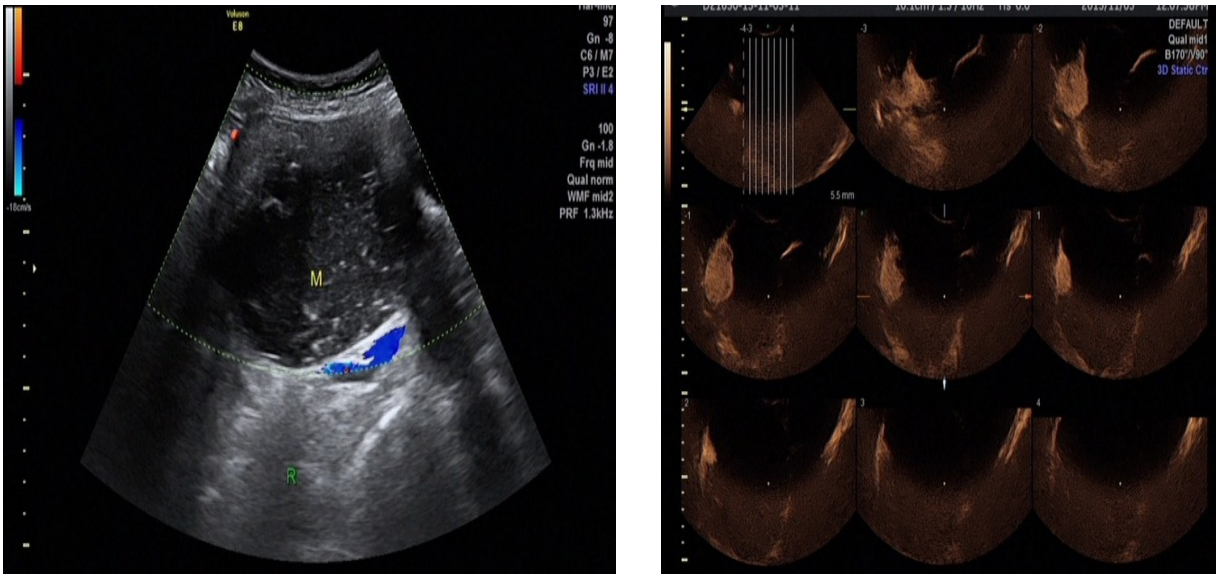


FIGURE3. Comparative analysis of an ovarian mucinous cystadenoma with focal carcinogenesis using TVS (A) and 3D-CEUS(B). In this case, TVS only shows that the solid area is more than 50% without blood flow within or around it, 3D-CEUS presents more information by clearly showing a significant enhanced, inhomogeneously solid area with disorganized vasculatures that arise from the surface of the internal walls (thick arrow); the GI-RADS combination with 3D-CEUS system score was 4.

Since its introduction in clinical settings, GI-RADS has been tested extensively in several multicenter studies and shown to be a proper criterion for discriminating between benign and malignant adnexal masses. However, a pilot study reported that a significant number of cystic-solid or solid ovarian masses were confirmed as benign, whereas GI-RADS regarded them as malignant. Thus, the specificity of GI-RADS is still limited.[13] In this research, we sought to demonstrate that combining GI-RADS and 3D-CEUS scoring system could significantly improve the sensitivity, specificity, and accuracy, in comparison with the use of GI-RADS alone.

Previous studies have shown that the use of 3D-US after the administration of microbubble-based contrast agent, called 3D-CEUS, aids in the characterization of ovarian tumors by evaluating their vascular patterns.[14,15] The microvascular distribution of ovarian tumors tend to be distorted, complex, and concentrated in different planes, and 3D-CEUS allows the division of structures into tomographic slices in three orthogonal planes overcoming the shortcoming of one single area of interest with 2D-CEUS, thus providing supplementary information which is unachievable by 2D-CEUS. In addition, a recent study demonstrated that 2D-CEUS has no advantages in ovarian masses containing thick papillary projections, which had been recognized as a malignant sign in comparison with conventional US (P>0.05).[16] By subsequently presenting several slices through TUI and changing the thickness and distances between two slices, 3D-CEUS can make it easier to detect thick papillary projections which US or 2D-CEUS may miss, it also displays the perfusion condition in its different portions.[17] It is of note that the peripheral tissue of ovarian tumors can also be displayed sensitively by contrast media, decreasing the resolution of the morphology of ovarian masses by means of 3D-CEUS, while the morphology of ovarian tumors has a significant effect on determining the tumor's natures.[18] Therefore, combining GI-RADS with 3D-CEUS may help make a comprehensive analysis of the morphologic variations of masses.

To confirm the effectiveness of this advanced scoring system, the number of investigated patients must be increased. In addition, for this purpose, conducting a multicenter study could be efficient. Furthermore, 3D-CEUS cannot show real-time hemodynamic variations in the lesions. This is the reason why we have relied on a sequence of image acquisition to achieve the timing and characteristics of contrast enhancement by comparing with that of the uterus. This limitation similarly affects acquisition on both lesion and uterus. Further studies are required to address these specific issues.

RESUMO

OBJETIVO: *O objetivo deste estudo é avaliar a eficácia da combinação da estratificação por ultrassonografia usando o Sistema de Relatórios e Dados de Imagem Ginecológica (GI-RADS) e ultrassonografia 3D com contraste (3D-CEUS) para diferenciar massas ovarianas benignas de malignas.*

METODOLOGIA: *Neste estudo, 102 pacientes com massas ovarianas foram examinadas usando ultrassonografia bidimensional (2D-US) e 3D-CEUS. As características ultrassonográficas das massas ovarianas obtidas com 3D-CEUS foram analisadas e comparadas com de 2D-US. Todos os pacientes com massas ovarianas tiveram o diagnóstico confirmado pelos resultados de patologia cirúrgica ou acompanhamento de longo prazo.*

RESULTADOS: *(1) O teste qui-quadrado e a regressão logística múltipla confirmaram a existência de apenas oito preditores independentes de massas malignas, incluindo septos espessos (≥3mm), projeções papilares espessas (≥7mm), áreas sólidas, presença de ascite, vascularização central, aumento de contraste, distribuição do agente de contraste e características vasculares da parte sólida e suas razões de possibilidades (OR), que foram 5,52, 5,39, 4,94, 4,34, 5,92, 7,44, 6,09 e 7.67, respectivamente (P< 0,05). (2) Esses oito preditores foram utilizados para combinar o GI-RADS com o sistema de escores da 3D-CEUS, para o qual o valor correspondente da área sob a curva (AUC) foi de 0,969, superior ao uso exclusivo do GI-RADS (valor de Z = 1,64, P < 0,025). Usando 4 pontos como corte, o sistema de escores mostrou que o desempenho foi muito melhor do que com o uso exclusivo do GI-RADS (P < 0,05). (3) O valor de Kappa foi 0,872, obtido por dois médicos diferentes com igual experiência.*

CONCLUSÃO: *A combinação do GI-RADS e do sistema de pontuação da 3D-CEUS é um método mais eficaz para distinguir massas ovarianas benignas de malignas.*

PALAVRAS-CHAVE: *Ovarian neoplasms. Ovarian diseases. Ultrassonografia. Imagem tridimensional/métodos.*

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ORIGINAL ARTICLE

CA 19-9 levels in patients with acute pancreatitis due to gallstone and metabolic/toxic reasons

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SUMMARY

OBJECTIVE: *Acute pancreatitis (AP) is an important clinical event with an increased frequency due to increased life expectancy, obesity, and alcohol use. There are some data about the elevation of carbohydrate antigen (CA) 19-9 levels in benign and malignant pancreaticobiliary events in the literature, but in AP they are limited. The aim of this study was to evaluate the CA 19-9 level in patients with AP and determine its relationship according to the cause.*

METHODS: *Between 2010-2018, 173 patients evaluated with CA 19-9 levels as well as by standard laboratory tests were included in the study. CA 1 9-9 levels and laboratory findings were compared in patients with pancreatitis due to gallstone (group 1) and metabolic/toxic reasons such as hyperlipidemia, alcohol, or drug use (group 2).*

RESULTS: *There were 114 (66%) patients in the group 1 and 59 (34%) patients in the group 2. The majority of patients with high CA 19-9 level were in group 1 (92.1% vs 6.8%). CA 19-9 level, as well as amylase, lipase, AST, ALT and bilirubin levels were found to be statistically higher in patients with AP due to gallstone compared to patients with metabolic/toxic AP.*

CONCLUSIONS: *Patients with AP due to gallstone, were found to have a high level of CA 19-9 at admission. Early stage CA 19-9 levels may contribute to standard laboratory tests in the etiology of the disease in patients diagnosed with AP.*

KEYWORDS: *Pancreatitis. Gallstones. CA-19-9 Antigen.*

INTRODUCTION

Acute pancreatitis (AP) is an important gastrointestinal event commonly encountered all over the world. Although there are regional differences, the first two etiologies that cause AP are gallstone and alcohol (60-80%)[1]. Determining the underlying etiology is important to determine the treatment roadmap and the need for endoscopic retrograde cholangiopancreatography (ERCP). In AP with metabolic and toxic causes, such as alcohol or hyperlipidemia, normal or moderate transaminases and cholestatic enzymes may be elevated, whereas gallstone-associated AP may be associated with increased levels of transaminases and cholestatic enzymes. Even in cases where transaminase and cholestatic enzyme elevations are associated, false positive results may be encountered. In addition, a laboratory parameter alone cannot differentiate between gallstone and other causes. For this reason, additional imaging methods such as magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and ERCP are frequently used.

Carbohydrate antigen (CA) 19-9 is a SiaLe-Lewis blood group antigen which was first described in murine monoclonal antibodies against colorectal carcinoma epithelial cells[2]. In many studies, CA 19-9

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levels have been shown to increase in tumors involving the pancreas and biliary tract[3-7]. In addition, in the patients with malignant tumors such as stomach, ovary, hepatocellular and colorectal carcinomas and in benign cases (pancreatitis, cholangitis, and choledocholithiasis) involving the biliary tree have been shown to increase levels[8-11]. There have also been case reports that found elevated CA 19-9 levels may be seen in cases of tuberculosis, infections, various rheumatological, and benign renal events[12-15].

In this study, we aimed to retrospectively investigate the relationship between CA 19-9 levels and pancreatitis reasons in patients with AP due to gallstone, hyperlipidemia or toxic cause (alcohol and drug), which constitute the first three main etiologies.

METHODS

Patient selection and data collection

Patients who were admitted to the emergency department of our hospital with complaints of abdominal pain between May 2010 and May 2018 and diagnosed with AP were included in the study. After analyzing the exclusion criteria of for the 829 diagnosed patients (Table 1), we found that the CA 19-9 levels were examined in 173 at admission in addition to standard blood tests (Figure 1).

The patients were divided into two groups according to their etiology. The patients with AP due to gallstone were placed in the first group, and patients diagnosed with metabolic/toxic AP such as hyperlipidemia, alcohol, or drug were placed on the second group.

AP etiologies were determined according to history, laboratory findings, imaging methods (ultrasonography, computerized tomography (CT), magnetic resonance imaging (MRI), MRCP, EUS, and ERCP) and, if necessary, pathology results.

Statistical analysis

Continuous variables were expressed as a mean ± standard deviation and categorical variables as a percentage. The chi-square test was used to compare categorical values, and the Mann-Whitney U test was used to compare continuous variables between the groups. The Receiver Operating Characteristics (ROC) curve was used to determine the level of CA19-9 to differentiate gallstone and metabolic/toxic causes with optimum sensitivity and specificity. The area under the curve (AUC), positive (PPV) and negative predictive (NPV) values were obtained. The statistical analysis of the study was done using SPSS 25.0 (IBM Statistical Package for Social Sciences software version 25). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 173 patients (92 female, 81 male) were included in the study. There were 114 (66%; 71 female, 43 male) patients in the first group (gallstone) and 59 (34%; 21 female, 38 male) patients in the second group (metabolic/toxic) (Table 2). There was a statistically significant difference between the groups regarding gender distribution (p=0.001). The mean age of the patients was also a statistically significant difference between the groups (65 vs. 52; $p<0.05$) (Table3). The demographic data of the patients and baseline characteristic findings at the time of the presentation are summarized in Table 2, 3.

TABLE 1. EXCLUSION CRITERIA OF THE STUDY

Exclusion criteria:
Patients with no identified etiology of pancreatitis (idiopathic cases)
Other patients with rare AP reasons except gallstones, alcohol, hyperlipidemia and drugs
Patients with known malignancy or diagnosed with malignancy after admission (papilla, pancreas, bile duct neoplasia, etc.)
Patients with chronic renal failure or active renal disease
Patients with a history of chronic rheumatic disease
Patients with active lung infection at admission
Patients with inflammatory bowel disease
Patients without CA 19-9 levels within 24 hours after AP diagnosis

FIGURE 1. PATIENT SELECTION FLOWCHART.

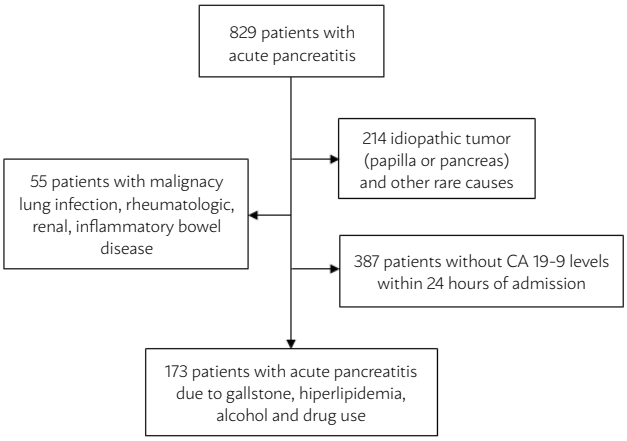


TABLE 2. DISTRIBUTION OF PATIENTS INCLUDED IN THE STUDY

Patient groups	n	%
Gallstone	114	66
Metabolic and toxic reasons - Hyperlipidemia - Toxic reasons (Alcohol + drugs)	59 21 38	34 12 22

TABLE 3. DEMOGRAPHIC DATA AND LABORATORY FINDINGS OF THE PATIENTS AT THE TIME OF ADMISSION

	Gallstone (n:114)	Metabolic/toxic reasons (n:59)	p
Gender			
Male, n	43	38	0.001
Female, n	71	21	
Age, years (range)	65 (22-91)	52 (21-87)	<0.05
Mean CA 19-9 (U/mL), (range)	206.1 (21.6-2,000)	14.6 (0.6-108)	<0.05
Positive CA 19-9, (> 37 U/mL)	105 (92.1%)	4 (6.8%)	<0.05
Amilase (U/L), (range)	1,367 (78-10,541)	948 (67-4,567)	<0.05
Lipase (U/L), (range)	3,790 (205-25,380)	2,322 (174-12,384)	<0.05
*AST (U/L), (range)	297 (17-1,399)	105 (10-1,137)	<0.05
**ALT (U/L), (range)	245 (6-1236)	71 (8-388)	<0.05
Total bilirubin (mg/dL), (range)	3.5 (0.3-12.89)	1.2 (0.6-11.19)	<0.05
Direct bilirubin (mg/dL), (range)	2.07 (0.3-794)	1.01 (0.3-3.67)	<0.05
White blood cell (/mm3), (range)	13,541 (5,400-17,000)	12,182 (5,390-25,000)	0.615
Hematocrit (%), (range)	39.5 (25-50)	42 (32-47)	0.02
Glucose (mg/dL), (range)	143 (55-341)	173 (48-504)	0.111

*AST, aspartate aminotransferase; **ALT, Alanine aminotransferase;

CA 19-9 level between the groups and cut off value for prediction

CA 19-9 was detected in 105 (92.1%) of the patients in the first group, and in 4 (6.8%) of the patients in the second group, more than 37 U/ml (Normal range of CA 19-9: 0-37 U/ml) (p<0.001). There was also a statistically significant difference between the groups regarding mean CA 19-9 values (206.1 vs. 14.6; p <0.005). The box-plot representation between the groups is shown in Figure 2.

When the cut-off value for CA 19-9 was 37 U/ml, the sensitivity and specificity of the values in the prediction of pancreatitis due to gallstone were measured as 92.1% and 93.2%, respectively (AUC 0.925, PPV; 96.3%, NPV; 85.9%) (Figure 3).

High levels of CA19-9 increases the risk of gallstone as AP reason by 160-fold (OR: 160, CI 95%: 47-544).

DISCUSSION

AP is an important clinical event with an increased frequency due to increased life expectancy, obesity, and alcohol use. The most common causes of pancreatitis in the 829 patients who were evaluated in our study were gallstone (58%), hyperlipidemia (8%), alcohol or drug use (8%). In addition, gallstone-induced AP was significantly higher in females, and metabolic/toxic AP was statistically higher in males (p = 0.001). In spite of developing laboratory and imaging methods, idiopathic patients continue to play an important role in the etiology (10-30%)[1]. We could not detect any reason that could cause AP in 17% of the cases. Laboratory tests alone are not sufficient to clarify the etiology in AP patients at admission. Imaging methods such as ultrasonography, CT, MRI, and even EUS are often needed. Especially in AP due to choledocholithiasis, alkaline phosphatase (ALP), bilirubin, gamma-glutamyltransferase (GGT) levels are important markers for pathologies in bile ducts, but it should be kept in mind that false positive and negative results can also be observed.

CA 19-9 is a glycolipid synthesized by the pancreas and ductal epithelial cells, as well as in the stomach, colon, endometrium and salivary gland epithelium cells. The primary role of CA 19-9 level is to evaluate the efficacy of palliative chemotherapy

FIGURE 2. BOX-PLOT REPRESENTATION OF CARBOHYDRATE ANTIGEN (CA) 19-9 LEVELS IN GALLSTONE AND METABOLIC/TOXIC GROUPS.

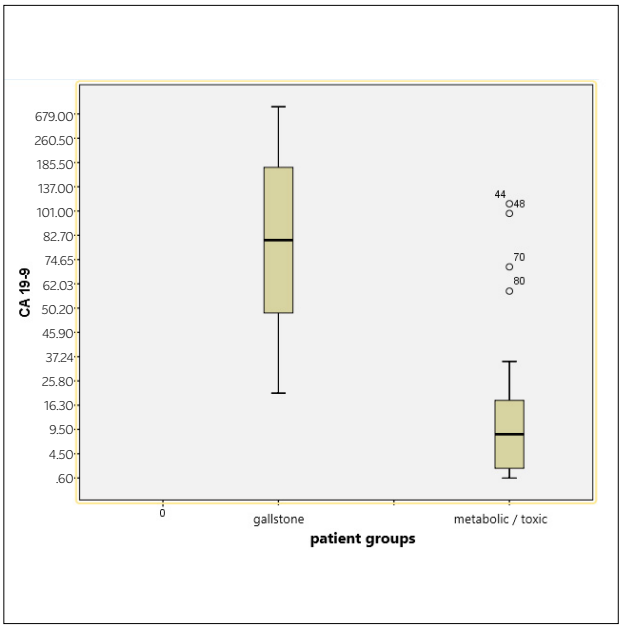
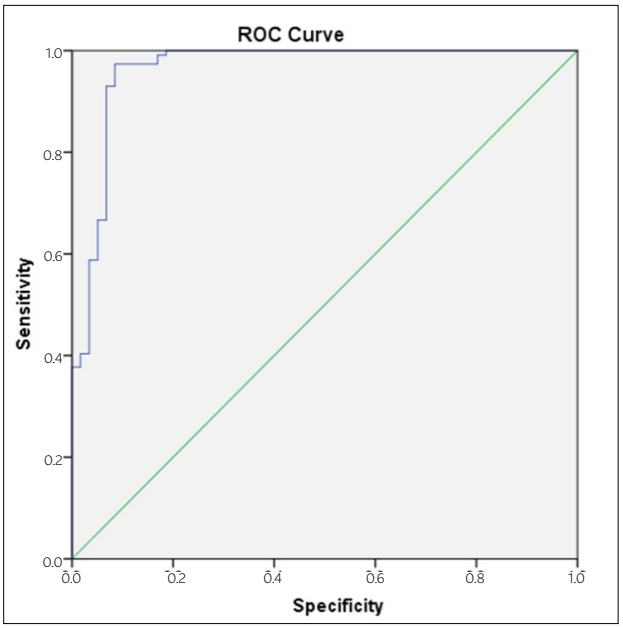


FIGURE 3. ROC CURVE FOR CARBOHYDRATE ANTIGEN 19-9 SENSITIVITY AND SPECIFICITY (CUT-OFF VALUE 37 U/ML).



in hepatobiliary and pancreatic cancers and to follow up after curative surgery. The sensitivity of CA 19-9 in hepatobiliary malignancies was found to be above 90%[4]. However, in addition to elevations in various benign events (Mirizzi syndrome, cholecystitis, choledocholithiasis, autoimmune pancreatitis, benign biliary stricture, among others) in the hepatobiliary system, it has been reported in extra-biliary events such as interstitial lung disease, tuberculosis, pneumonia, rheumatoid arthritis, and renal system malignancies[12-19]. CA 19-9 values above normal limits alone cannot distinguish malignant or benign causes. In a study from Morris-Stiff et al.2 , CA 19-9 levels were detected above normal values in 95.9% of patients with pancreatic adenocarcinoma, 89.5% of patients with cholangiocarcinoma, 44.4% of patients with gallstone, and 27% of patients with chronic pancreatitis. In the study, the sensitivity, specificity, PPV, and NPV values in the differentiation of malignant from benign diseases were calculated as 84.9%, 69.7%, 67.7%, and 86.1%, respectively. According to the ROC curve analysis, the optimal CA 19-9 value for distinguishing malignant and benign events was 70.5 U/ml. Similarly, in a study from Marrelli et al.[20] that evaluated 128 patients with obstructive jaundice (87 pancreatic-biliary malignancy and 41 benign events), the CA 19-9 level was found to be high in 61% of benign events and 86% of malignant events. Kim et al.[21] found CA 19-9 levels above 37 U/ml in 90% of malignant and 59% of benign events. The mean CA 19-9 level in malignant events was 442.4 U/ml, and 67.4 U/ml in benign events. In another similar study, CA 19-9 levels in benign cases were found to be 102 U/ml, and 910 U/ml in pancreaticobiliary tumors[22]. Ong et al.[8] also showed that benign hepatobiliary diseases are associated with an increase in CA 19-9 and bilirubin levels. In a study in which Dogan et al.[23] evaluated CA 19-9 levels in patients with gallstone, high CA 19-9 was detected in 32 of the 70 patients (46%). CA 19-9 levels were not correlated with the number and diameter of the stones but were shown to be higher in patients with cholangitis.

In the literature, there are not many studies about CA 19-9 levels in patients with AP. Teng et al.[5] evaluated CA19-9 levels in 693 of 1609 patients with AP,, and CA 19-9 levels were found above 37 U/ml in 186 (26.8%) patients. CA 19-9 levels were not correlated with AP severity but with serum alkaline phosphatase, alanine aminotransferase, aspartate transaminase, and creatinine levels. In this study, the CA 19-9 level was found to be high in 53.8% of patients with gallstone-induced AP, in 11.3% of patients with alcohol-induced AP, and in 7.5% of patients with hypertriglyceridemia induced AP. However, there is no data about when the evaluation of CA 19-9 was made. In addition, in another prospective study of CA 19-9 and CEA levels in 61 patients with AP, the CA 19-9 level was found to be high in 36% of the patients[24]. There were no significant differences in the rates of CA 19-9 in patients with AP (34 patients), including

pancreatitis due to gallstone and other reasons. The number of patients with metabolic/toxic causes of AP was low (12 patients), and the inclusion of idiopathic patients in the study was seen as a disadvantage.

The CA 19-9 levels of the 173 patients included in our study were evaluated within 24 hours after diagnosis, and CA 19-9 levels were detected high (> 37 U/ml) in 109 (63%) of the cases. In our study, CA 19-9 levels were above 37 U/ml in 92% of patients with AP due to gallstone, and the mean CA 19-9 level was found to be 206.1 U/ml. CA 19-9 levels were in the normal range in 93.2% of the patients who developed pancreatitis due to metabolic/toxic causes, and the mean CA 19-9 level was found to be 14.6 U/ml in these patients. There were also statistically significant differences between the groups in terms of levels of amylase, lipase, AST, ALT, and bilirubin in addition to CA 19-9 levels. These data show that CA 19-9 levels are high in clinical events in the bile ducts not only in patients with biliary tract malignancies but also in patients with stasis like gallstones[25]. It shows that CA 19-9 levels, especially in the early period of AP, are an important predictor for the etiology of pancreatitis.

Our study is retrospective, and prospective studies are needed for CA 19-9 levels in patients with pancreatitis after bile duct drainage and after pancreatitis regression, as well as in all pancreatitis groups. In addition, prospective studies are needed to determine whether CA 19-9 can contribute to diagnostic in idiopathic cases.

CONCLUSION

CA 19-9 levels at an early stage in patients diagnosed with AP may provide an additional contribution to standard laboratory tests. In pancreatitis patients with high CA 19-9 levels, in particular, it is possible to say that there is a clinical event which causes stasis in the biliary tract. We believe that an additional imaging technique for the biliary tract, such as EUS, will be useful before the diagnosis of idiopathic pancreatitis in patients with normal USG, CT, and MRCP findings and high CA 19-9 levels. We think it is appropriate to consider the metabolic/toxic causes of pancreatitis in patients with mild cholestatic enzyme elevation if the CA 19-9 level is normal.

Conflict of interest

None.

Authors' Contribution

Concept: OBB. Design: OBB. Supervision: ZBP. Materials: OBB, ZBP. Data collection and/or processing: ZBP. Analysis and/or interpretation: OBB, ZBP. Literature search: OBB. Writing: OBB. Critical reviews: OBB, ZBP.

RESUMO

OBJETIVO: *A pancreatite aguda (PA) é um evento clínico importante e cada vez mais frequente devido ao aumento da expectativa de vida, obesidade e do consumo de álcool. Existem alguns dados na literatura sobre a elevação dos níveis do antígeno carboidrato (CA) 19-9 em eventos pancreato-biliares benignos e malignos, mas eles são limitados em relação à PA. O objetivo deste estudo foi avaliar o nível de CA 19-9 em pacientes com PA e determinar sua relação com a causa da doença.*

PACIENTES E MÉTODOS: *Entre 2010 e 2018, 173 pacientes submetidos a uma avaliação dos níveis de CA 19-9, bem como testes laboratoriais padrão, foram incluídos no estudo. Os níveis de CA 19-9 e os achados laboratoriais foram comparados em pacientes com pancreatite devido a cálculos biliares (grupo 1) e razões metabólicas/tóxicas, como hiperlipidemia, álcool, ou uso de drogas (grupo 2).*

RESULTADOS: *Um total de 114 (66%) pacientes foi incluído no grupo 1 e 59 (34%) no grupo 2. A maioria dos pacientes com alto nível de CA 19-9 estavam no grupo 1 (92,1% versus 6,8%). O CA 19-9, bem como os níveis de amilase, lipase, AST, ALT e bilirrubina foram estatisticamente mais altos em pacientes com PA devido a cálculos biliares em comparação àqueles com PA devido a alterações metabólicas/tóxicas.*

CONCLUSÃO: *Pacientes com PA devido a cálculos biliares apresentaram um alto nível de CA 19-9 no momento da internação. O nível de CA 19-9 na fase inicial pode contribuir para testes laboratoriais padrão na etiologia da doença em pacientes com diagnóstico de PA.*

PALAVRAS-CHAVE: *Pancreatite necrosante aguda. Pancreatite. Cálculos biliares. Antígeno CA-19-9.*

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ORIGINAL ARTICLE

Relationship of T lymphocytes, cytokines, immunoglobulin E and nitric oxide with otitis media with effusion in children and their clinical significances

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SUMMARY

OBJECTIVE: *To investigate the relations of T lymphocytes, cytokines, immunoglobulin E, and nitric oxide with otitis media with effusion (OME) in children and their clinical significances.*

METHODS: *Fifty children with OME treated in our hospital were enrolled in the study (observation group). Fifty healthy children were selected as control. The percentages of CD_4+ and CD_8+ T lymphocyte and CD_4+/CD_8+ ratio in peripheral blood, and the levels of cytokine (IL)-2, IL-4, IL-6, immunoglobulin E (IgE) and nitric oxide (NO) in peripheral blood and middle ear effusion (MEE) in both groups were detected. The correlations of these indexes with OME were analyzed.*

RESULTS: *The percentage of peripheral blood CD4+ and CD_8+ levels, CD_4+/CD_8 ratio, IgE, and NO levels in the observation group were significantly higher than those in the control group ($P < 0.01$). In the observation group, the IL-2 and IL-6 levels, and IgE and NO levels in the MEE were significantly higher than those in peripheral blood ($P < 0.01$). In addition, in the observation group, the MEE IL-2 and IL-6 levels were positively correlated with peripheral blood CD_4+/CD_8+ ratio, respectively $r = 0.366$, $P = 0.009$; $r = 0.334$, $P = 0.018$.*

CONCLUSIONS: *The levels of peripheral blood CD_4+ and CD_8+ lymphocytes and MEE IL-2, IL-6, IgE, and NO levels are increased in children with OME. These indexes have provided significant clues for the diagnosis of OME in children.*

KEYWORDS: *Otitis media with effusion. T-lymphocytes. Cytokines. Immunoglobulin E. Nitric oxide.*

INTRODUCTION

Otitis media with effusion (OME) is a common disease in otology and one of the main causes of hearing loss. About 50%-90% of preschool children suffer from OME, and patients with recurrent OME account for 30%-40% of total OME patients[1]. The protracted course of OME can easily influence the hearing of children, which seriously threatens their growth and intellectual development[2]. The etiology of OME is

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not yet fully elucidated. Although otology scientists have carried out long and extensive research on this, they have yet to reach a consensus. It is believed that OME is associated with a dysfunctional eustachian tube (including mechanical and non-mechanical obstruction of the eustachian tube), infection, immune response, among others[3]. With the progress of molecular biology and immunology, more and more scholars believe that the immune response is the main reason for the formation of middle ear effusion (MEE) and its retention[4]. MEE comes from the eustachian tube, tympanum, and mastoid air cells mucosa. Whether MEE is serous, mucous, or purulent, its pathological exudation, secretion, and absorption are involved in the process of OME[5]. It is known that OME is related to the inflammatory reaction and immune response of the body[6,7]. Cytokines such as interleukin (IL)-2, IL-4, IL-6, and nitric oxide (NO) are highly expressed in the MEE in adults[8,9]. In addition, there is an abnormity of T lymphocytes and immunoglobulin E (IgE) in patients with OME[10,11]. This further suggests that the immune response is closely related to OME, but the expression and significance of these indicators in children are rarely reported. This study investigated the relationships of T lymphocytes, cytokines, IgE, and NO with OME in children and their clinical significances. The objective was to provide a basis for the diagnosis and prognosis evaluation of OME in children.

METHODS

Subjects

Fifty OME children treated in our hospital were enrolled in this study. There were 26 males and 24 females. Their age was 2-15 years, with an average age of 7.3±3.1 years. They presented various degrees of hearing loss. The clinical manifestations were shouting, no attention, learning disability, need of a high volume when listening on the phone and watching television, among others. The diagnostic criteria of OME were as follows: i) the tympanic membrane protruded outward, or there were visible liquid plane and/or air bubbles; ii) the acoustic impedance test showed B-type or C-type curve; iii) the pure-tone audiometry result was abnormal. All the children were diagnosed with OME. They were treated with tympanic membrane incision and tube operation under general anesthesia. In addition, 50 healthy children were selected as control. There were 28 males and 22 females. Their age was 3-13 years, with an average age of 6.8±2.4 years. They had no history of otitis media or any related disease. There was no significant difference in age or gender between the two groups ($P > 0.05$). This study was approved by the ethics committee of the Shanghai Children's Hospital. Written informed consent was obtained from a family member of all participants.

Collection of specimens

Five milliliters of venous blood was taken from all subjects. Two milliliters of venous blood was placed in the EDTA anticoagulant tube (Sigma-Aldrich Corp., MO, USA) for measurement, and the remaining 3 ml was centrifuged at 2 000 r/min for 10 min. The serum was kept in a cryogenic refrigerator at -20 °C for measurement. In OME children, the cerumen in the external auditory canal was cleaned. The external auditory canal and its outer aperture were wiped with 75% alcohol cotton. The cotton contained 1% Dicaine (Jiangsu Jiuxu Pharmaceutical Co., Ltd., Xuzhou, China) and was gently attached to the ear tympanic membrane to relieve the pain of patients. After 15 min, the cotton piece was removed, and the external auditory canal and its outer aperture were disinfected with cotton and 75% alcohol (Jiangsu Jiuxu Pharmaceutical Co., Ltd.., Xuzhou, China) again. Under photopic vision (frontal mirror) or otoscope, a #5 needle was pierced into the tympanum from underneath the tympanic membrane. The MEM was extracted using 1 ml sterile syringe. The volume and mature of MEM were recorded. The MEM was placed in a sterile tube in the freezer at -20 °C for measurement.

Determination of indexes

The peripheral blood CD_4^+ and CD_8^+ levels were determined using flow cytometry[12]. The peripheral blood and MEM IL-2, IL-4, IL-6, and NO levels were determined using enzyme-linked immunosorbent assay[13]. The peripheral blood and MEM IgE levels were detected by chemiluminescence immunoassay[14]. The operations were followed the instructions of the kit's manufacturers (Sigma-Aldrich Corp., MO, USA).

Statistical analysis

All statistical analyses were carried out using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The data were presented as mean ± SD. Comparisons between the two groups were performed using the t-test. The correlation of continuous variables was investigated

using the Pearson correlation analysis. $P < 0.05$ and $P < 0.01$ were considered statistically significant and highly statistically significant, respectively.

RESULTS

General data of OME children

In 50 OME children, the course of the disease varied from 5 days to 3 years, with an average of 4 months. There were 20 cases with less than 15 days of disease course and 30 with over 15 days. The otoscopy found tympanic membrane sign disappearance and light cone deformation. The acoustic impedance mapping showed 47 cases of B type (38 cases of both ears, 6 cases of right ear, 3 cases of left ear) and 3 cases of C type (1 case of both ears, 2 cases of right ear). The pure-tone audiometry showed a mild or moderate conductive hearing loss. The average language hearing loss was 35-55 dB, and the bone conduction difference was ≥ 30 dB.

Peripheral blood CD_4^+ and CD_8^+ levels in both groups

The peripheral blood CD_4^+ and CD_8^+ levels and CD_4^+/CD_8^+ ratio in the observation group were 12.27±3.67%, 7.78±2.12%, and 1.58±0.32, respectively, which were significantly higher than the 7.46±2.37%, 5.52±2.01%, and 1.35±0.19 found in the control group (all $P < 0.01$).

Peripheral blood and MEE IL-2, IL-4 and IL-6 levels in both groups

The peripheral blood IL-2, IL-4, and IL-6 levels in the observation group were 229.94±89.44 ng/L, 28.93±11.29 ng/L, and 33.18±10.41 ng/L, respectively, while in the control group they were 198.83±75.23 ng/L, 26.04±9.28 ng/L, and 29.88±6.23 ng/L. Each index in the observation group was higher than the same in the control group; however, the difference was not significant (all $P > 0.05$) (Table 1). In addition, in the observation group, the MEE IL-2, IL-4, and IL-6 levels were 705.19±147.37 ng/L, 35.25±23.31 ng/L, and 67.22±21.04 ng/L, respectively, while the peripheral blood IL-2, IL-4, and IL-6 levels were 229.94±89.44 ng/L, 28.93±11.29 ng/L, and 33.18±10.41 ng/L, respectively. In this group, the IL-2 and IL-6 levels in MEE were significantly higher than those in peripheral blood (all $P < 0.01$).

Peripheral blood and MEE IgE and NO levels in both groups

The peripheral blood IgE and NO levels in the observation group were 1245.36±458.46 mg/L and 74.56±23.72 ng/L, respectively, which were significantly higher than the 856.28±201.26 mg/L and 33.36±8.20 ng/L of the control group (all $P < 0.01$) (Table 2). In addition, in the observation group, the IgE and NO levels in MEE were 3205.28±660.39 mg/L

TABLE 1. COMPARISON OF PERIPHERAL BLOOD IL-2, IL-4, AND IL-6 LEVELS BETWEEN THE OBSERVATION AND CONTROL GROUPS

Group	IL-2 (ng/L)	IL-4 (ng/L)	IL-6 (ng/L)
Observation (n = 50)	229.94±89.44	28.93±11.29	33.18±10.41
Control (n = 50)	198.83±75.23	26.04±9.28	29.88±6.23
t	1.882	1.398	1.923
P	0.063	0.165	0.057

IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6.

TABLE 2. COMPARISON OF PERIPHERAL BLOOD IGE AND NO LEVELS BETWEEN THE OBSERVATION AND CONTROL GROUPS

Group	IgE (mg/L)	NO (ng/L)
Observation (n = 50)	1245.36±458.46	74.56±23.72
Control (n = 50)	856.28±201.26	33.36±8.20
t	5.495	11.608
P	< 0.001	< 0.001

IgE, immunoglobulin E; NO, nitric oxide.

and 423.44±67.67 ng/L, respectively, which were significantly higher than the 1245.36±458.46 mg/L and 74.56±23.72 ng/L in peripheral blood (all $P < 0.01$).

Results of the correlation analysis

Pearson correlation analysis showed that, in the 50 OME children, the MEE IL-2 and IL-6 levels were positively correlated with the peripheral blood CD_4^+/CD_8^+ ratio, respectively (IL-2 with CD_4^+/CD_8^+: $r = 0.366$, $P = 0.009$; IL-6 with CD_4^+/CD_8: $r = 0.334$, $P = 0.018$) (Figure 1). There was no significant correlation between the other two indexes ($P > 0.05$).

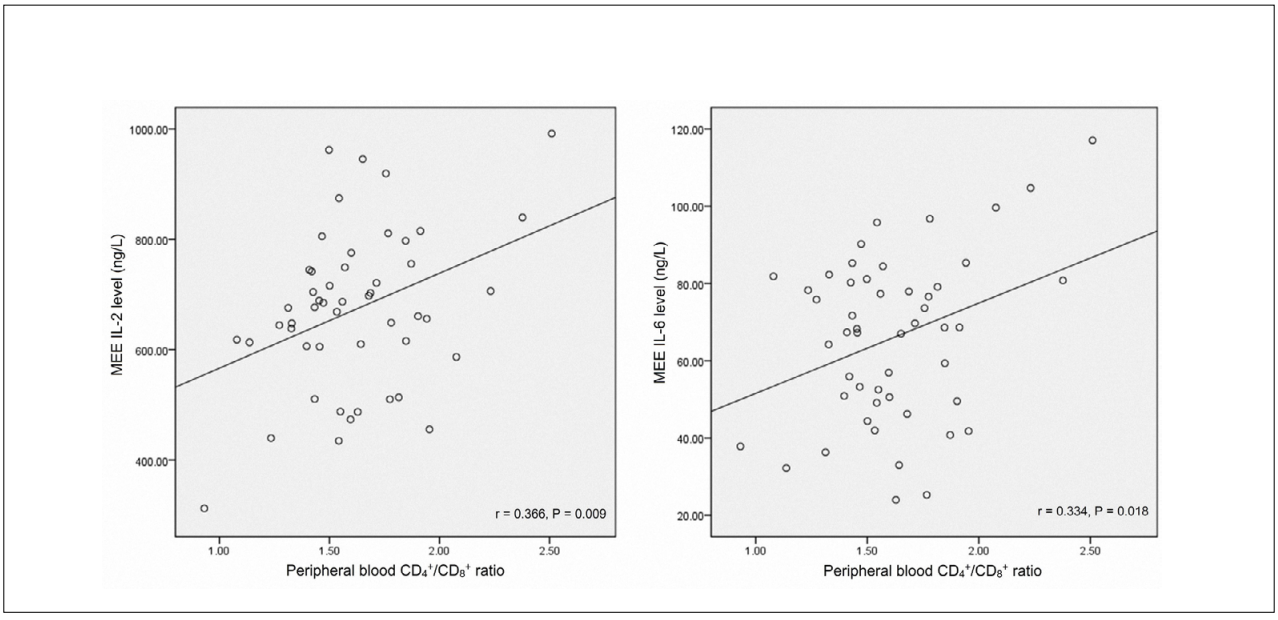
DISCUSSION

It is known that cytokines are cell regulating proteins with a variety of bioactivity that can mediate many immune responses in the body[15]. Generally, the basic functions of IL-2 and IL-4 are to activate immunity and stimulate the differentiation of B cells into plasma cells that produce immunoglobulin[16]. IL-6 is one of the essential factors that induce cell secretion and participates in the body defense reaction[17]. In this study, the peripheral blood IL-2, IL-4, and IL-6 levels in the observation group were higher than those in the control group, but the difference was not significant. In addition, in the observation group, the MEE IL-2 and IL-6 levels were significantly higher than the peripheral blood IL-2 and IL-6 levels. This indicates that in OME children IL-2 and IL-6 do not change in the peripheral blood, but are highly expressed in the MEE.

Hence, OME is related to the immune response of the body, and T lymphocytes are involved in the process of OME. CD_4^+ and CD_8^+ are an important part of the immunoregulation of T cells. CD_4^+ can help T cells produce antibodies, and CD_8^+ can inhibit the proliferation of T cells and the synthesis of antibodies. Both of them are directly or indirectly involved in the immune response[18]. Results of this study showed that the peripheral blood CD_4^+ and CD_8^+ levels and CD_4^+/CD_8^+ ratio in the observation group were significantly higher than those in the control group. This indicates that the inflammatory infection reaction occurs in children with OME, which stimulates the stress response of the body's immune function.

NO is an oxide produced by L-arginine catalyzed by nitric oxide synthase. It has an antimicrobial effect and is also an immunomodulator[19]. However, excessive NO often induces immune and pathological processes and mediates the production of some cytokines and inflammatory mediators, resulting in tissue damage[20]. Lin et al.[20] have reported that NO is highly expressed in the later stage of OME in adults. They speculate that the tissue damage and antibody inhibition caused by NO may be one of the critical factors leading to prolonged immobility of OME. In the present study, the peripheral blood NO level in the

FIGURE 1. CORRELATIONS BETWEEN MEE IL-2 LEVEL AND PERIPHERAL BLOOD CD_4+/CD_8+ RATIO AND BETWEEN MEE IL-6 LEVEL AND PERIPHERAL BLOOD CD_4+/CD_8+ RATIO. MEE, MIDDLE EAR EFFUSION; IL-2, INTERLEUKIN-2; IL-6, INTERLEUKIN-6.



observation group was significantly higher than that in the control group, and in the observation group, the MEE NO level was significantly higher than that in peripheral blood. This indicates that NO is involved in the process of OME in children.

Upper respiratory tract virus infection can cause IgE-mediated reaction, and IgE-mediated hypersensitivity is more likely to occur in patients with a family history of allergy. It often occurs in the nasopharynx, which can easily affect the eustachian tube[21]. In addition to the hypersensitivity reaction, the virus can reduce the function of granulocyte and lymphocyte, and significantly inhibit the cilium movement[22]. All these effects lead to eustachian tube obstruction and increased mucus secretion, as well as the accompanying dysfunction of ventilation and drainage. The results of this study showed that the peripheral blood IgE level in the observation group was significantly higher than that in the control group, while in the observation group, the MEE IgE level was significantly higher than that in peripheral blood. This indicates that IgE is involved in the process of OME in children. IgE mediated hypersensitivity exists in the peripheral blood and MEE in children with OME, which leads to the obstruction of the eustachian tube and increased mucus secretion.

There are certain correlations among T lymphocytes, cytokines, immunoglobulin E, and nitric oxide in the body. Liang et al.[23] found that in rats with moderate and severe traumatic brain damage the serum level of IL-2 is positively correlated with the serum level of CD_4^+/CD_8^+ ratio. Shu et al.[24] found that in early acute pancreatitis patients the serum level of IL-6 is positively correlated with the serum level of CD_4^+/CD_8^+ ratio. The results of Xu and Liu's study[25] have shown that in children with allergic rhinitis the serum IgE level is positively correlated with the CD_4^+/CD_8^+ ratio. In the present study, the correlation analysis showed that in 50 OME children the MEE IL-2 and IL-6 levels were positively correlated with peripheral blood CD_4^+/CD_8^+ ratio. This is consistent with the results previously found.

CONCLUSION

In conclusion, the levels of peripheral blood CD_4^+ and CD_8^+ T lymphocytes, and MEE IL-2, IL-6, IgE, and NO levels are increased in children with OME. These indexes have provided significant clues for the diagnosis of OME in children. This study had some limitations, its sample size is relatively small, which may affect the results. In subsequent studies, the sample size should be increased for more reliable results. In addition, there are many other indexes involved in the process of OME in children. This should be considered in further studies.

Disclosure of conflict of interest: None.

RESUMO

OBJETIVO: *Investigar as relações entre linfócitos T, citocinas, imunoglobulina E e óxido nítrico e a otite média com efusão (OME) em crianças e sua significância clínica.*

MÉTODOS: *Cinquenta crianças com OME tratadas em nosso hospital foram incluídas no estudo (grupo de observação). Selecionamos também 50 crianças saudáveis como controle. As porcentagens de linfócitos T CD_4+ e CD_8+ e a razão CD_4+/CD_8+ no sangue periférico, além dos níveis das citocinas IL-2, IL-4, IL-6, imunoglobulina E (IgE) e óxido nítrico (NO) no sangue periférico e de efusão no ouvido médio (MEE) de ambos os grupos foram medidos. A correlação desses índices com a OME foi analisada.*

RESULTADOS: *A porcentagem dos níveis de CD_4+ e CD_8+, da razão CD_4+/CD_8+, de IgE e NO no sangue periférico do grupo de observação foram significativamente maiores do que no grupo controle (P < 0,01). No grupo de observação, os níveis de IL-2 e IL-6, IgE e NO em MEE foram significativamente maiores do que no sangue periférico (P < 0,01). Além disso, no grupo de observação, foi encontrada uma correlação positiva entre os níveis de IL-2 e IL-6 em MEE e a razão de CD_4+/CD_8+no sangue periférico, respectivamente, r = 0,366, P = 0,009; r = 0,334, P = 0,018.*

CONCLUSÃO: *Os níveis de linfócitos CD_4+ e CD_8+ no sangue periférico e IL-2, IL-6, IgE e NO em MEE são mais altos em crianças com OME. Esses índices forneceram evidências valiosas para o diagnóstico de OME em crianças.*

PALAVRAS-CHAVE: *Otite média com derrame. Linfócitos T. Citocinas. Imunoglobulina E. Óxido nítrico.*

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ORIGINAL ARTICLE

Renal angiomyolipoma

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SUMMARY

INTRODUCTION: *Angiomyolipoma is one of the most common benign solid renal tumors. We investigated the characteristics of renal angiomyolipomas and the clinical outcomes of patients in the last thirteen years.*

METHODS: *The medical records of the patients who underwent nephrectomy were reviewed retrospectively from July 2005 to May 2018. The laboratory data, radiology, and pathology reports were recorded. Patients diagnosed with angiomyolipoma were included in the study.*

RESULTS: *A total of 28 patients were included in the study, eight of them male. The mean age of the patients was 55.89+14.49 years. The patients were treated with open and laparoscopic techniques. Partial nephrectomy was performed in 12 patients(42.85%). After pathological examination, 23 patients were diagnosed as fat rich, four patients as fat poor, and one as epithelioid angiomyolipoma. There were no recurrences in the follow-up 91.21+48.31 months.*

CONCLUSION: *Angiomyolipoma is a rare renal tumor in daily urology practice. Clinicians must be aware of its complications and manage patients well.*

KEYWORDS: *Angiomyolipoma/surgery. Nephrectomy. Kidney Neoplasms.*

INTRODUCTION

Angiomyolipoma is a rare benign tri-phasic soft tissue tumor that contains fat, blood vessels, and smooth muscles in different proportions[1]. Fujii et al.[2] reported that the prevalence of angiomyolipoma (AML) was 0.13% among 17941 patients in Japan. Among benign kidney tumors, AML is the most common type[3] and accounts for 0.3-.3% of all renal masses[4]. Approximately 80% of these tumors occur sporadically. However, the others are associated with tuberous sclerosis complex and predominantly seen in women[5].

Most of the patients are asymptomatic and diagnosed incidentally because of the widespread use of imaging techniques[4]. The classical triad of symptoms

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is flank pain, palpable mass, and hematuria[6]. The main complication of AML is retroperitoneal hemorrhage caused by a rupture of the tumor, which can be life-threatening. Patients with Lenk's triad usually also present acute flank pain, abdominal tenderness, and signs of internal bleeding.

In this study, we aimed to investigate the characteristics of AML patients who underwent nephrectomy in our department.

METHODS

Patients who underwent nephrectomy for renal tumors between July 2005 and May 2018 were reviewed retrospectively using the hospital database. The patients' age, symptoms, laboratory results, need for transfusion in the preoperative and postoperative period, and pathology results were recorded. The follow-up data of both laboratory and ultrasonography-computed tomography results were noted. Patients with missing data and not treated for nephrectomy were excluded.

The pathological examinations were done by a genitourinary pathologist (GG) in the pathology department. Immunohistochemical studies were performed for differential diagnosis. The data were expressed as mean+standard deviation using the MedCalc Statistical Software demo version 17.6 (MedCalc Software bvba, Ostend, Belgium; http :// www.medcalc.org; 2017).

RESULTS

There were 647 patients in the database. Of these, 28 (4.3%) were diagnosed with AML and included in the study. The female:male ratio was 2.5, and the mean age of the patients was 55.89+14.49 years. The patients' characteristics are shown in Table 1. Most of the patients were asymptomatic and diagnosed by ultrasonography. Blood transfusion was needed in three patients preoperatively, and eight postoperatively. The mean tumor size and follow up was 7.84+4.83cm and 91.21+48.31 months. Partial nephrectomy was performed in 12 patients, and 16 underwent radical nephrectomy. No perioperative and postoperative complications occurred.

On radiological examination, ultrasonography was performed in all patients, computed tomography confirmed the diagnosis in 25 patients, and magnetic resonance techniques were used in three patients (Figure 1). The pathological evaluation classified 23 patients as fat rich AML, four as fat poor, and one as epitheloid (Figure2). Immunohistochemical studies were done in ten patients using desmin, actin, SMA, CD34, CD 117, CD68, HMB-45, and others (Figure-3). None of the patients experienced recurrence and nor died with a mean follow-up period of 91.21+48.31 months.

DISCUSSION

Renal angiomyolipoma is one of the most common benign mesenchymal tumors composed of fat cells, smooth muscle cells, and blood vessels[7]. This pathological entity was first defined by Fischer[8], in 1911, and predominantly affected females rather than males[9]. The prevalence of AML is 0.28% in males and 0.6% in females[4]. A proportion of AMLs (20%) is associated with tuberous sclerosis complex (TSC)[9]. Tuberous sclerosis is an autosomal dominant disorder caused by mutations in the TSC1 and TSC2 genes[6]. Patients with TSC have features of epilepsy, mental retardation, and angiofibroma[10]. Most of the patients(80%) with TSC develop AML[6] generally consisting of multifocal, bilateral, bigger lesions[10]. Sporadic cases of AML usually have small(<4 cm) and solitary tumors. Most of the sporadic AML patients(80%) are usually asymptomatic and diagnosed incidentally. The classical triad of symptoms is flank pain, palpable mass, and hematuria. A small proportion of the patients(10%) can present retroperitoneal hematoma or hypovolemic shock as the initial symptom. Wunderlich syndrome is a life-threatening

TABLE 1. THE CHARACTERISTICS OF THE PATIENTS

Number of patients	28
Male n,%	8, 28.57
Female n,%	20 71.42
Age (Mean+SD)	55.89+14.49
Symptoms	
No n,%	24, 85.7
Flank pain n,%	2, 7.14
Hematuria n,%	2, 7.14
Blood transfusion	
Preoperative n,%	3, 10.71
Postoperative n,%	8, 28.57
Tumor size (Mean+SD)	7.84+4.83
Follow-up	91.21+48.31
Treatment	
Open radical nephrectomy	16, 57.14
Open partial nephrectomy	11, 39.28
Laparoscopic partial nephrectomy	1, 3.57

FIGURE 1. MAGNETIC RESONANCE IMAGING OF AML PATIENTS WHO UNDERWENT PARTIAL NEPHRECTOMY

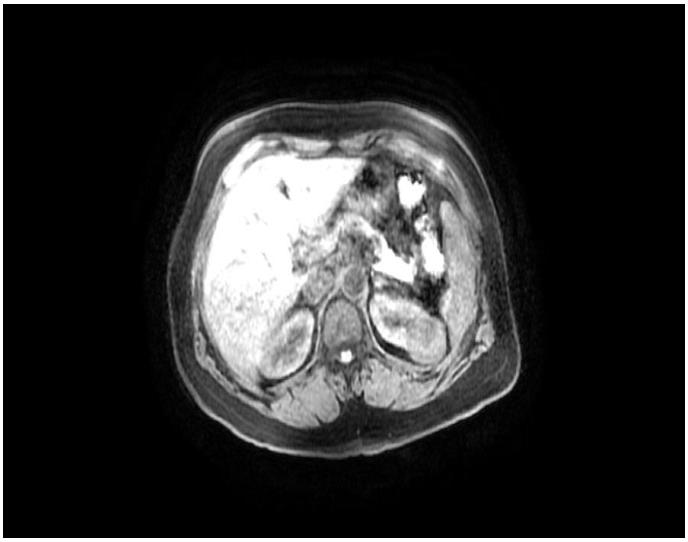


FIGURE 2. FAT-RICH AML INCLUDES FAT TISSUE AND VASCULAR AREA H&E*100

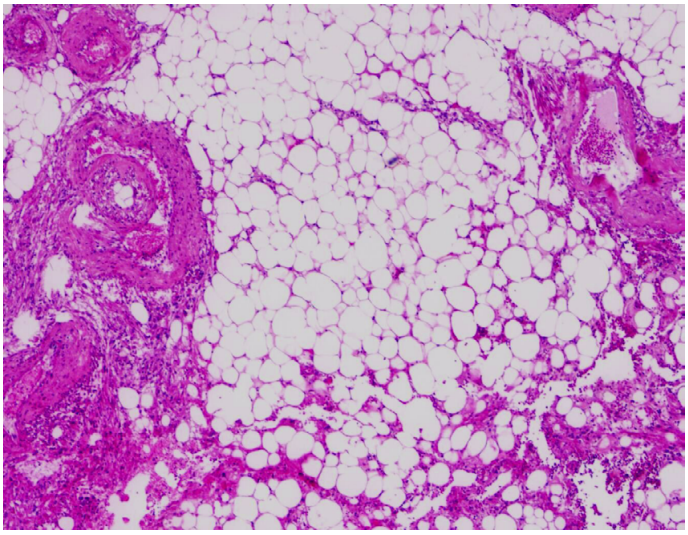
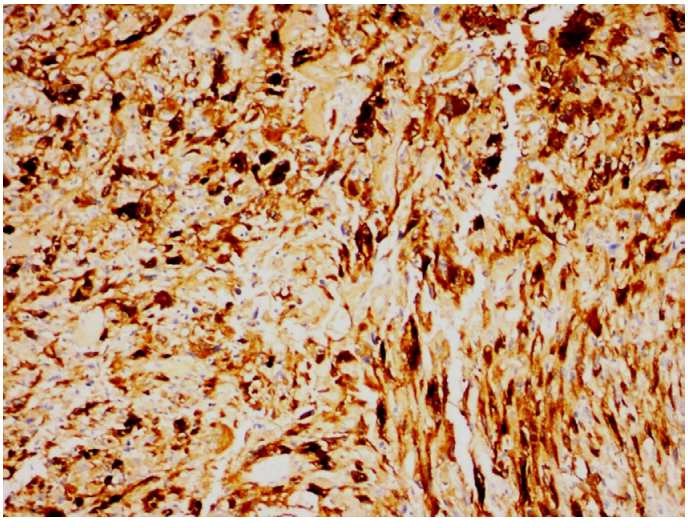


FIGURE 3. EPITHELOID AML WITH POSITIVE STAINING OF HMB- 45 (IMMUNOHISTOCHEMICAL STUDY X 400)



emergency condition characterized by nontraumatic spontaneous hemorrhage in the perinephric space[11]. The patients' symptoms vary and usually include Lenk's triad in addition to acute flank pain, flank mass, and hypovolemic shock. Kim et al.[11] analyzed 26 patients with Wunderlich syndrome and found 12% of them were diagnosed with AML. The age of diagnosis varies; patients with TSC are more likely to develop the condition earlier, such as at the third and fourth decades of life. However, sporadic cases present at the fifth and sixth decades[9]. Similarly to what is found in the literature, most of the patients were female, and their mean age was in the sixth decade.

Ultrasonography is not very sensitive for AML, it usually shows a hyperechoic lesion with acoustic shadowing which cannot be differentiated from other kidney tumors[6]. After the diagnosis of AML, ultrasonography may be used in the follow-up period[9]. Computed tomography (CT) with contrast enhancement is the most commonly used radiologic method to diagnose AML[6]. It has excellent sensitivity, specificity, positive and negative predictive values regarding AML and differentiates it from other lesions. Areas with attenuations less than 10-20 Hounsfield units (HU) are generally considered a diagnostic of macroscopic fat[1]. Some kinds of renal tumors with fat can mimic AML. The other advantages are that it is rapid, cost-effective, and available in most hospitals[9]. Magnetic resonance imaging (MRI) has high sensitivity for detecting fat tissues, so it is useful to differentiate AML from other renal masses[6]. The T1-weighed imaging as hyperintense and T2-weighed as hyposignal on fat-poor AML and epithelioid AML. Israel et al.[12] reported that 'India link artifact' signal has a high sensitivity (100%) and specificity (97.9%) for AML diagnosis. The main disadvantage of MRI is its high cost and being time-consuming when compared to ultrasonography and CT[10].

Most asymptomatic patients with AML can be managed by surveillance[13]. The clear diagnosis of AML needs a biopsy, but it is very rarely used because of the tumor rupture and bleeding risks[6]. Although there is no standard protocol for surveillance, physical examination and CT at 6 months, 12 months and annually is recommended[10]. A close follow-up is necessary for high-risk patients, namely women in childbearing age, larger tumor size, and TSC associated AML[10,13]. Watanabe et al.[14] reported a case of renal AML growth after ovarian stimulation therapy.

Symptomatic renal AML or big tumor size >4-6 cm is widely accepted as an indication of other treatment

modalities including surgery, embolization, and mammalian target of rapamycin(mTOR) inhibitor therapy[4]. For asymptomatic patients of TSC related AML bigger than 3 cm size, mTOR inhibitors are the first line prophylactic treatment[13]. These drugs inhibit vascular epithelial proliferation and reduce tumor size, so the risks of tumor rupture and bleeding decrease[6]. Embolization is the first line treatment for bleeding AML and a preventive method for patients with a high risk of bleeding. This procedure is minimally invasive with a high success rate[13]. Sometimes embolization can be performed to facilitate open and laparoscopic partial nephrectomy procedures.

Nephrectomy, partial or total, was the most common treatment for symptomatic cases, emergency hemorrhage, suspicion of malignancy, and prophylaxis in the early years[13]. Partial nephrectomy is a widely accepted modality for its feasibility, efficacy, and satisfaction for renal preservation[6]. These surgical procedures can be done by laparoscopic and robotic approaches with low complication rates[13]. Liu et al.[5] reported that retroperitoneal laparoscopic partial nephrectomy is a safe, feasible, and effective procedure for large renal AML(>7 cm). Microwave tumor ablation, radiofrequency, and cryoablation are other possible treatments for small tumors[10].

Histologically, there are three types of AML: fat-rich (classical), fat-poor, and epithelioid[3]. These tumors usually exhibit expression of smooth muscle actin, actin, HMB-45, Melan-A, S-100, and CD117[15]. We found that 82.14% of the patients were classified as fat rich AML.

The small number of patients from one center and the retrospective study design are the main limitations of the study. The lack of other patients who were treated with nonsurgical treatment modalities is the other limitation.

CONCLUSION

In conclusion, angiomyolipoma is a benign renal tumor. The characteristics of the tumor must be considered in daily practice because of rupture risk. Clinicians should consider that patients are usually asymptomatic and diagnosed incidentally.

Declaration of Conflicting Interests

The authors declare no conflict of interest.

RESUMO

OBJETIVO: *O angiomiolipoma é um dos tumores renais benignos sólidos mais comuns. Investigamos as características dos angiomiolipomas renais e os desfechos clínicos dos pacientes nos últimos treze anos.*

MÉTODOS: *Os prontuários dos pacientes, para os quais a nefrectomia foi realizada, foram revisados retrospectivamente de 2008 a 2018. Os dados laboratoriais, relatórios de radiologia e patologia foram registrados. Os pacientes diagnosticados como angiomiolipoma foram incluídos no estudo.*

RESULTADOS: *Vinte e oito pacientes foram incluídos no estudo, oito deles do sexo masculino. A média de idade dos pacientes foi de 55,89 + 14,49 anos. Os pacientes foram tratados com técnicas abertas e laparoscópicas. Nefrectomia parcial foi realizada em 12 pacientes (42,85%). Depois de exame patológico, 23 pacientes foram diagnosticados como ricos em gordura, quatro pacientes como gordurosos e um paciente como angiomiolipoma epitelioide. Nenhum paciente teve recorrências no seguimento.*

CONCLUSÕES: *O angiomiolipoma é um tumor renal raro na prática urológica diária. Os médicos devem estar cientes das complicações e gerenciar bem os pacientes.*

PALAVRAS-CHAVE: *Angiomiolipoma/cirurgia. Nefrectomia. Neoplasias renais.*

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ORIGINAL ARTICLE

Evaluation of the efficacy of ropivacaine injection in the anterior and middle scalene muscles guided by ultrasonography in the treatment of Thoracic Outlet Syndrome

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SUMMARY

A clinical, placebo-controlled, randomized, double-blind trial with two parallel groups.

OBJECTIVE: *to evaluate the efficacy of ropivacaine injection in each belly of the anterior and middle scalene muscles, guided by ultrasonography, in the treatment of Nonspecific Thoracic Outlet Syndrome (TOS) compared to cutaneous pressure.*

METHODS: *38 patients, 19 in the control group (skin pressure in each belly of the anterior and middle scalene muscles) and 19 in the intervention group (ropivacaine). Subjects with a diagnosis of Nonspecific Thoracic Outlet Syndrome, pain in upper limbs and/or neck, with no radiculopathy or neurological involvement of the limb affected due to compressive or encephalic root causes were included. The primary endpoint was functionality, evaluated by the Disabilities of the Arm, Shoulder, and Hand - DASH scale validated for use in Brasil. The time of the evaluations were T0 = before the intervention; T1 = immediately after; T2 = 1 week; T3 = 4 weeks; T4 = 12 weeks; for T1, the DASH scale was not applied.*

RESULTS: *Concerning the DASH scale, it is possible to affirm with statistical significance (p> 0.05) that the intervention group presented an improvement of functionality at four weeks, which was maintained by the 12th week.*

CONCLUSION: *In practical terms, we concluded that a 0.375% injection of ropivacaine at doses of 2.5 ml in each belly of the anterior and middle scalene muscles, guided by ultrasonography, in the treatment of Nonspecific Thoracic Outlet Syndrome helps to improve function.*

KEYWORDS: *Thoracic Outlet Syndrome. Myofascial Pain Syndromes. Anesthetics. Ultrasonics. Ultrasonography, Interventional.*

INTRODUCTION

Thoracic Outlet Syndrome (TOS) is a group of disorders characterized by the compression of the brachial plexus and subclavian vessels at any point of the thoracic outlet region[1-3]. It includes painful, sensorial, and motor manifestations on the neck, shoulder, upper limb, and shoulder girdle region. Among the reasons for the symptoms, is the compression of the subclavian vessels and brachial plexus during the journey through the thoracic outlet[1,3,4].

The current medical literature makes a distinction between the vascular and neurogenic syndrome and considers five types of the syndrome, i.e., arterial

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TOS, venous TOS, and traumatic neurovascular TOS, which are of vascular etiology, and those of neurogenic origin, i.e., true neurogenic TOS and disputed TOS[5,6].

However, given that the estimated prevalence of the cervical rib in the general population is 0.5% to 2%[5,7,8] and of neurogenic TOS is 1 per millions[5,9]; statistically, the presence of a cervical rib *per se* does not constitute a diagnosis for neurogenic TOS[9,10].

The neurogenic presentations correspond to up to 95% of TOSs, with no clear quantification between its true and disputed varieties. These presentations are clarified by physical examination, in which the neurogenic variety is associated with complaints such as muscular atrophy and positive electrophysiological examination[4,8,11-13].

The treatment options for TOS may be conservative, such as stretching, massage, compression, drug injections on the trigger point with lidocaine, ropivacaine, bupivacaine, and botulinum toxin[14-17].

In the literature, the most prevalent references of injections in scalene muscles relate to the use of bupivacaine[18-20] or lidocaine[20]. However, there was no sustained improvement of function because there was only a single evaluation immediately after the application. Considering there was no scientific rigor in the studies carried out and their results were not impressive — and, in large part, non-reproducible — in this study, we opted for the use of ropivacaine, due to its lower toxicity than that of bupivacaine.

Therefore, this study sought to answer the following question: What is the efficacy of the treatment based on the ultrasound-guided anesthetic blocking of the anterior and middle scalene muscles for improving functionality and pain in Thoracic Outlet Syndrome patients?

METHODS

This is a randomized, placebo-controlled, double-blind clinical trial with parallel groups.

We included in this study subjects who met the inclusion criteria with pain in the upper limbs and/or neck without radiculopathy or neurological involvement of the limb affected due to compressive encephalic root causes.

Those included were required to undergo a simple radiography examination of the neck at the swimmer's view to verify the presence of a cervical rib.

We excluded subjects with clinical instability and acute medical conditions, hypersensitivity to the medication administered, rotator cuff injury previously diagnosed by an imaging exam that explains the pain, and previously diagnosed fibromyalgia.

For the sample size calculation, we used the values obtained in a single prospective, randomized, double-blind study, conducted with diagnosed TOS patients, with pain for over three months and submitted to an injection of botulinum toxin type A[21]. We assumed a significance (alpha) of 0.05, double-tailed, and a power of 80%. We used the *Stata 10.1™* software. Thus, the sample size calculated was 38 patients, 19 in each group.

The recruitment of participants was carried out by the recruitment center of the Lucy Montoro Rehabilitation Institute, with its research headquarters in the Morumbi Unit, São Paulo/SP.

The process of recruitment, selection, intervention, and evaluation is presented in Figure 1.

Procedure: The procedure was conducted at the Surgical Center of the Institute of Orthopaedics and Traumatology (IOT) of the Medical School of the University of São Paulo. The patient was required to be at the center on the morning of the day of the procedure fasting for 8 hours. Following institutional protocols, all patients waited in a hospital bed until the marking on the skin was made prior to the procedure.

In the surgical center, with the patient lying in dorsal decubitus, a folded sheet was placed under the neck, and head was rotated approximately 20°

FIGURE 1. DISTRIBUTION OF THE VISITS.

Visit I – 1 week before the procedure
- Anamnesis
- Physical examination
- Dash scale
- Wash-out instructions
- Tables of recovery medication and side effects

Visit II – day of the procedure

Visit III – one week after the procedure
- Dash scale

Visit IV – 4 weeks after the procedure
- Dash scale

Visit V – 12 weeks after the procedure
- Dash scale
- Delivery of the tables of recovery medication use and side effects

Source: Prepared by the author.

to 30° contrary to the application side, exposing the sternocleidomastoid muscle region. Using a Sonosite MTurbo ultrasound device and a HFL38x 13-6MHz frequency linear transducer (FujiFilm SonoSite, Inc. 21919 30th Dr. SE, Bothell, WA, 98021, USA) to visualize superficial tissues, a preliminary assessment determined the location of the vascular structures, the anterior and middle scalene muscles, and the brachial plexus trunks.

The scalene muscles were scanned along their craniocaudal extension and better visualized in the images in its lower half. Once the structures were identified, the transducer was placed on both scalene bellies, on a cut in the short axis of the muscles. Before drilling, the Doppler mode was turned on to check for the presence of vessels in the path of the needle. The favorite needle approach to the anterior scalene muscle was in the medial to lateral direction, drilling through the sternocleidomastoid muscle, and medial to lateral for the approach of the middle scalene to decrease the likelihood of vascular lesion. Patients were not submitted to bilateral injections.

All hygiene, asepsis, and antisepsis care measures were performed both in relation to the patient and the research team.

Intervention: Using the hands-free technique, with no guide coupled to the transducer, the needle of the syringe is guided following the transducer plan and keeping the target, the belly of the muscle to be injected, in the center of the screen. The needle moves slowly, allowing for the adjustment of the entry angle, keeping the point under constant ultrasound visualization. Once the tip of the needle is seen in the belly of the target muscle, aspiration is performed to make sure it is not inside of the vessel. Only then, the solution is slowly injected, observing its dispersion in the belly.

The patients were randomized into two groups: intervention and placebo, described below.

TABLE 1. DASH COMPARISON BETWEEN THE CT AND INT GROUPS

Group	CT	INT	p
Initial Dash	66.93±17.04	60.83±12.58	0.161
Dash Visit III	43.68±16.08	42.40±15.62	0.693
Dash Visit IV	49.90±17.62	35.53±21.37	0.034
Dash Visit V	52.09±22.25	39.17±21.04	0.075

Source: Prepared by the author.

Intervention group (1): The patients in this group received an ultrasound-guided injection in the anterior and middle scalene muscles, on the side where there was a complaint of pain, with 2.5 ml of a 0.375% ropivacaine solution in each belly, totaling 5 ml of the solution. The dilution was made with the aspiration of 2.5 ml of saline 0.9% and 2.5 ml of 7.5 mg/ml (0.75%) ropivacaine in a 5-ml syringe.

Placebo group (2): The patients in this group received skin pressure at the same locations of the ultrasound-guided applications, on the anterior and middle scalene muscles, on the side in which there was a complaint of pain, with the same needle-syringe assembly; however, without piercing the skin. The syringe for the control group was filled only with saline solution.

The evaluations were made before the procedure (T1), one hour after the procedure (T2), then at one week (T3), four weeks (T4) and 12 weeks (T5). The instrument used to assess the functional outcome was the Dash questionnaire (Disabilities of the Arm, Shoulder, and hand), validated and adapted for use in Brasil[22].

This study was submitted to and approved by the Research Ethics Committee of the Hospital das Clínicas - CAPPesq - FMUSP, CAAE: 01232012.0.0000.0068, under the opinion No 19568 on 09.05.2012 and by the Scientific Committee of the Department of Orthopaedics and Traumatology of the Medical Faculty of the University of São Paulo on the Official Communication/CC-DOT/160/2012, of 27.06.2012. All participants signed the informed consent form, authorizing their participation in the research, which was performed following the ethical standards required by Resolution no. 466/2012 (National Health Committee).

RESULTS AND DISCUSSION

Patients and controls were compared in relation to the variables age, gender, formal education, body mass index (BMI), physical activity, smoking, associated chronic diseases ($p>0.05$). In relation to gender, the predominance was of females in both groups, which is compatible with the results found by Finlayson et al.[21], who found a female percentage of 82%.

The Dash scale was evaluated before the beginning of treatment (initial visit) and in three subsequent moments (visitations III, IV, and V). There were no statistically significant differences between the CT and INT groups on the Dash scale at the initial moment

and on visit III (a week after the intervention). On the other hand, we found that the Dash was significantly lower in the INT group on visits IV, and marginally significant on visit V (Table 1).

Since Dash is a scale, it is characterized as an ordinal numeric variable and, therefore, used to compare the groups in a non-parametric statistical test (Mann-Whitney).

The scale Dash measures the functionality of the upper limbs, including shoulder and arm. We observed the surprising and unique improvement evolution of the participants in the intervention group. In the initial assessment and one week after the procedure, no difference was observed between the groups. However, there was a significant reduction in both groups after one week, with no difference between them. However, on visit IV, it was possible to see a bigger difference between the groups, with greater improvement on the intervention group compared to the control, which was maintained on visit V, after 12 weeks.

In a statistically significant manner, it is possible to state that the intervention group showed a functionality improvement by the fourth week, and the improvement was maintained by the12th week. In addition, the intervention group also showed a statistical advantage over the control group.

Confirming the trend of improvement, the cohort published in 2015 by Braun et al.[23] used a isokinetic test before and after a lidocaine 1% injection administered without any imaging method for the scalene topography and found an improvement of various parameters.

After checking the percentage of improvement on the Dash scale, it is possible to observe two interesting and satisfactory results. There was a significant improvement in the control group by the last visit. The second piece of data, which was unexpected, was the improvement on the Dash scale of the intervention group, which was statistically significantly higher than on the control group.

On visit I, one week before the procedure, and on visit III, one week after the procedure, there was no difference between the Dash values of both groups, but there was an improvement in the Dash scale, with a reduction in values. Initially, the values in the intervention and control groups were 66 and 60 points, respectively, with no statistical difference between them. On the visit one week after the procedure, there was an improvement in both groups, now with 43 and 42 points, respectively. The minimum values for a detectable improvement on the Dash scale are from 7.9 to 14.8 points. Therefore, there was a satisfactory detectable improvement, with a difference of 23 points in the control group, and 18 points in the intervention, values that exceed the minimum necessary to verify a detectable improvement.

However, on visit IV, after four weeks, the results were quite different. Whereas on the first week after the procedure, the values were similar and showed improvement, on visit IV, there was an antagonistic movement of the Dash values. While the Dash value in the intervention group continued to improve, with a reduction of the value, the control group showed worsening in relation to visit III, at one week. Moving forward to visit V, 12 weeks after the procedure, the values stabilized, with a slight worsening in both groups.

At this time, after 12 weeks, it was possible to see an improvement in the intervention group compared to the control, which was statistically significant even though the P-value was marginal (*P*=0.072) and there was an expressive percentage reduction in the Dash improvement in the intervention group, 38.65%, whereas in the control group there was improvement of 22.61%.

Since there is no parallel for these values in the literature, it is difficult to seek comparisons. The improvement of performance in work and power shown by Braun et al.[23] happened after a non-ultrasound-guided lidocaine injection in the scalene muscles, with a single evaluation and no control group. Other authors who have proposed to register a randomized, double-blind study and verified functionality using the Dash tool, *i.e.,* Finlayson et al.[21], did not see any improvement after the same period. By the end of 12 weeks, these authors found disappointing results, in which the negative variation, i.e., the Dash improvement, was less than 1 point in the control group, whereas in the control group submitted only to the injection of saline solution, the variation was 3.2 points of improvement on a Dash scale of 0-100 points. Among the groups, there was no improvement or statistical difference after six months.

CONCLUSION

In practical terms, it can be concluded that the injection of 0.375% ropivacaine in doses of 2.5 ml in each belly of the anterior and middle scalene muscles, guided by ultrasound, in the treatment of Disputed

Neurogenic Thoracic Outlet Syndrome, assists in the improvement of function (primary outcome). The measurement of functionality using the Dash tool was considered an objective measure.

The intervention group showed a significant improvement in the Dash scale by the end of the 12 weeks. On the first assessment after the procedure, there was a decrease in values, representing an improvement of function. However, the improvement was global, with no distinction between the groups. In subsequent evaluations, after four and 12 weeks, there was a greater difference in the values between the groups in a reverse movement: while the intervention group remained improving, the control group interrupted its curve of improvement and started presenting worsening values.

This study contributed in practice by presenting a proposal for an alternative method to improve the functionality of patients with Neurogenic Thoracic Outlet Syndrome, demonstrating that muscular blocking with anesthetics is an effective alternative in the TOS approach, in addition to describing the safety of ultrasound-guided therapeutic procedures.

Among the limitations, is the lack of literature to support the findings. The approaches proposed include the use of anesthetics, not restricted to only one of them, as well as the unjustified use of steroidal anti-inflammatory and botulinum toxin. Not only is the literature scarce, but there is also a lack of scientific rigor in the production of publications about non-surgical treatments.

Another point is the difficulty in the recruitment of patients, perhaps due to the lack of consensus and training of medical professionals for proper diagnosis of the syndrome, since there is still controversy in the literature.

RESUMO

Ensaio clínico, controlado por placebo, aleatorizado, duplo-cego, com dois braços paralelos.

OBJETIVO: *Avaliar a eficácia da injeção de ropivacaína em cada ventre dos músculos escalenos anterior e médio, guiada por ultrassonografia, no tratamento da Síndrome do Desfiladeiro Torácico Neurogênico inespecífico comparado com o toque cutâneo.*

MÉTODOS: *Trinta e oito pacientes, sendo 19 no grupo controle (toque cutâneo em cada ventre dos músculos escalenos anterior e médio) e 19 no grupo intervenção (ropivacaína). Foram incluídos sujeitos com diagnóstico de Síndrome do Desfiladeiro Torácico Neurogênico inespecífico com dor em membros superiores e/ou cervicalgia sem radiculopatia ou comprometimento neurológico do membro em questão por causas radiculares compressivas ou encefálicas. O desfecho primário foi a funcionalidade avaliada pela escala Disabilitie of the Arm, Shoulder and Hand – Dash, validada no Brasil. O tempo das avaliações foram T0 = antes da intervenção; T1 = imediatamente após, T2 = 1 semana, T3 = 4 semanas e T4 = 12 semanas, sendo que para o T1 não foi aplicado o Dash.*

RESULTADOS: *Com relação ao Dash, de forma estatisticamente significante (p>0,05), é possível afirmar que o grupo intervenção apresentou melhora da funcionalidade a partir de quatro semanas, e essa melhora se manteve até a 12ª semana.*

CONCLUSÃO: *Em termos práticos, conclui-se que a injeção de ropivacaína 0,375% nas doses de 2,5 ml em cada ventre dos músculos escalenos anterior e médio, guiada por ultrassonografia, no tratamento da Síndrome do Desfiladeiro Torácico Neurogênico inespecífico auxilia na melhora da função.*

PALAVRAS-CHAVE: *Síndrome do Desfiladeiro Torácico. Síndrome da Dor Miofascial. Anestésicos. Ultrassom. Ultrassonografia de intervenção.*

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ORIGINAL ARTICLE

Low triiodothyronine syndrome is associated with platelet function in patients with nephrotic syndrome

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SUMMARY

OBJECTIVE: *The objective of this study was to investigate the effects of low triiodothyronine syndrome (LT3S) on platelet function and clotting factors in patients with nephrotic syndrome(NS).*

METHODS: *Patients with primary nephrotic syndrome were divided into two groups, normal thyroid function (group A) and LT3S (group B), based on whether they had LT3S or not. Healthy subjects were selected as the control group (group C). Blood coagulation function was detected in each group. The platelet activation function (CD62P, CD63) was determined by flow cytometry. The platelet aggregation rate was detected by an optical method using adenosine diphosphate and arachidonic acid as inducers.*

RESULTS: *The proportion of primary nephrotic syndrome with LT3S was 23.2% (69/298). Compared with group C, group A had higher CD62P and PAgTADP, and group B had higher CD62P, CD63, PAgTAA, and PAgTADP; the difference was statistically significant (all $P < 0.05$). There was no significant difference in renal pathology between group A and group B ($X2 = 4.957$, $P = 0.421$). Compared with group A, the 24-hour urine protein, CD63, PAgTAA, and PAgTADP were higher in group B, and APTT and Alb were lower. The difference was statistically significant ($P < 0.05$). Logistic regression analysis showed that LT3S was associated with CD36 (OR: 3.516; 95% CI: 1.742~8.186; $P = 0.004$) and PAgTAA (OR: 0.442; 95% CI: 1.001~1.251; $P = 0.037$).*

CONCLUSION: *NS patients are prone to LT3S. Patients with LT3S may have abnormal platelet activation and increase of platelet aggregation.*

KEY WORDS: *Nephrotic syndrome; low triiodothyronine syndrome; platelet activation; platelet aggregation*

INTRODUCTION

Nephrotic syndrome (NS) is characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. The loss of anticoagulant substances from urine, abnormal platelet function, hyperlipidemia and blood concentration, and the use of hormones and diuretics in clinical treatment cause NS patients to have hypercoagulability and the complication of thromboembolism.[1,2] Platelet dysfunction is one of the main causes of thrombosis, which can manifest as abnormal activation of platelets and hyperfunction of platelet aggregation.[3] Low thyroid hormone concentrations, especially low serum T3 levels are a common finding in NS patients. The primary pathophysiological mechanism underlying low circulating T3 is the reduced enzyme activity of 5'-monodeiodinase responsible for converting T4 into T3 in peripheral tissues. Low triiodothyronine syndrome (LT3S) has commonly been interpreted by the medical community as a

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euthyroid sick syndrome, which is widely believed to be an adaptive mechanism for energy conservation.[4] At present, there are few studies on the relationship between LT3S and platelet function in NS patients. The purpose of this study is to evaluate thyroid function, nutritional status, platelet activation function, and platelet aggregation function. The objective is to provide a reference for future clinical work.

METHODS

Patients and inclusion criteria

From January 2016 to May 2018, patients with primary nephrotic syndrome treated in the Department of Nephrology of the Affiliated Hospital to Nantong University were enrolled. Diagnostic criteria for NS[5]: 1) urine protein greater than 3.5 g / d; 2) plasma albumin lower than 30 g / L; 3) edemas; 4) elevated blood lipids. Items 1 and 2 are required for diagnosis. Exclusion criteria: 1) heart, liver, lung, and other major organ diseases; 2) primary thyroid disease; 3) secondary nephrotic syndrome; 4) mental illness or inability to cooperate. Thyroid function was detected after admission. Patients with primary nephrotic syndrome were grouped according to whether they had LT3S or not. Normal thyroid function group (Group A): Normal free triiodothyronine (FT3), normal free thyroid hormone (FT4), and normal hypersensitivity human thyroid-stimulating hormone (TSH). LT3S group (Group B): FT3 < 3.8pmo1/L and normal TSH. In addition, 60 healthy subjects were selected as the control group. All the subjects in the control group did not have any history of kidney disease or severe diseases.

Outcome measures

General data were collected, such as sex and age, as well as thyroid and blood coagulation function, blood cytology and blood biochemical indexes, including FT3, FT4, TSH, prothrombin time (PT), activated partial thrombin time (APTT), fibrinogen (Fib), thrombin time (TT), platelet count (PLT), hemoglobin (Hb), serum albumin (Alb), 24h urine protein, serum creatinine (SCr) and urea (BUN).

Platelet function tests

Platelet Activation: 1 ml of blood was collected using a vacuum blood collection tube containing 3.18% sodium citrate 0.3 ml. Platelet-rich plasma was extracted by centrifugation, fixed with 1% paraformaldehyde, and labeled with fluorescein isothiocyanate (FITC). CD62P and CD63 were labeled as CD62P-FITC and CD63-FITC, and IgG-FITC was used as a negative control (reagents were purchased from Beekman, USA). Flow cytometry (Beckman Coulter Epics XL) counted 5,000-10,000 platelets and determined the percentage of fluorescently labeled platelets.

Platelet aggregation: 2.7 ml of blood was taken using a vacuum blood collection tube containing 3.18% sodium citrate 0.3 ml. Platelet-rich plasma and platelet-poor plasma were extracted by centrifugation. The platelet-poor plasma was used as a negative control and placed in a platelet aggregation instrument (Beijing Plymouth LBY-NJ2). The platelet aggregation rate (PAgT) was determined by preheating at 37 °C for 3 min with 0.5 mol/L arachidonic acid (AA) and 10 μmol/L adenosine diphosphate (ADP) as inducers. Both AA and ADP were purchased from Shanghai Dusheng Biological Company.

Statistical analyses

The main statistical indicators were used to test for normality. The measurement data were expressed as mean ± standard deviation ($\overline{X} \pm S$ SD), the count data were analyzed by X^2 test. The t-test was used for comparison between the groups, and logistic regression was used to analyze influencing factors. Statistics were made using the SPSS 20 software package. $P < 0.05$ was statistically significant.

RESULTS

General Information

A total of 298 NS patients were enrolled in this study, with 229 cases of normal thyroid function (group A), of which 94 cases (41%) were women, with an average age of 46.8 ± 14.3 years. There were 69 cases of LT3S (group B). The proportion of NS with low LT3S was 23.2% (69/298), including 28 cases (40.1%) in women, with an average age of 44.3±14.2 years. There were 60 patients in the control group, including 26 women (43.3%), with an average age of 45.5±14.8 years. There was no significant difference in gender and age distribution between the three groups. Compared with group C, 24-hour urine protein, PLT, SCr, BUN were higher in group A and group B, and Alb and APTT were lower; the difference was statistically significant ($P < 0.05$). The urine protein level of patients in group B was higher than that in group A. APTT and Alb were lower than in group A, and the difference was statistically significant ($P < 0.05$), as showed in Table 1.

Renal Pathology Composition

In group A, 66 cases (28.82%) were minimal change disease (MCD), 18 (7.86%) were focal segmental glomerulosclerosis (FSGS), 57 (24.89%) non-IgA mesangial glomerulonephritis (MsPGN), 22 (9.61%) IgA nephropathy (IgAN), 59 (25.76%) membranous nephropathy (MN), and 4 cases (2.63%) were membranous proliferative glomerulonephritis (MPGN). Of the patients in group B, 18 (26.01%) were MCD, 6 (8.70%) FSGS, 13 (18.85%) MsPGN, 7 (10.15%) IgAN, 19 (27.54%) MN, and 6 (8.69%) MPGN. There was no significant difference in the distribution of renal pathology types between the two groups (X2=4.957, P=0.421), as shown in Fig. 1.

Comparison of platelet function

Compared with group C, CD62P and PAgTADP were higher in group A, while CD62P, CD63, PAgTAA, and PAgTADP were higher in group B; the difference was statistically significant (all $P < 0.05$); Compared with patients in group A, patients in group B had higher levels of CD63, PAgTAA, and PAgTADP, and the difference was statistically significant (all $P < 0.05$), as shown in Fig. 2.

Regression analysis

CD62P, CD63, PAgTAA, 24-hour urine protein, APTT, and Alb were used as independent variables, and LT3S was used as the dependent variable for logistic regression analysis. The results showed an association with CD36 (OR:3.516; 95%CI:1.742~8.186; $P = 0.004$) and PAgTAA (OR:0.442; 95%CI:1.001~1.251; $P = 0.037$) after correction for age, gender and other related factors (Table 2).

DISCUSSION

LT3S is an abnormal level of serum thyroid hormone caused by non-thyroid diseases, with a decline in FT3 and normal or reduced TSH, often associated with systemic disease.[6] Under normal physiological conditions, T3 exists in both free and bound states, with the state of binding to thyroid-binding globulin

TABLE 1. COMPARISON OF GENERAL DATA

Group	Group A (n = 229)	Group B (n = 69)	Group C (n = 60)
Age (year)	46.8 ± 14.3	44.3 ± 14.2	15.5 ± 14.8
Women (cases,%)	62 (41.0%)	28 (40.1)	17 (43.3)
Prothrombin time (S)	11.40 ± 2.98	10.78 ± 3.06	12.02 ± 2.92
Activated partial thromboplastin time (S)	24.86 ± 4.54*	23.75 ± 6.00*#	28.32 ± 7.03
Fibrinogen (g / L)	2.61 ± 0.72	2.69 ± 0.66	2.88 ± 0.69
Thrombin time (S)	18.46 ± 3.00	18.82 ± 3.32	19.00 ± 4.15
Platelets (109 / L)	236.3 ± 49.22*	249.02 ± 51.60*	173.45 ± 46.73
Hemoglobin (g / L)	123.03 ± 22.91*	125.14 ± 25.01*	138.12 ± 24.24
Serum albumin (g / L)	22.78 ± 4.83*	21.01 ± 5.14* #	41.02 ± 7.75
24h urine protein (g / day)	4.81 ± 0.93 *	5.55 ± 1.06* #	0.13 ± 0.03
Serum creatinine (μmol / L)	75.13 ± 13.92*	82.02 ± 16.52*	70.44 ± 16.66
Urea (mmol / L)	6.19 ± 1.84*	6.43 ± 2.54*	4.96 ± 2.22

Note: compared with group C* P <0.05, compared with group A#P <0.05; Group A: normal thyroid function, Group B: Low triiodothyronine syndrome group, Group C: control group.

FIGURE 1

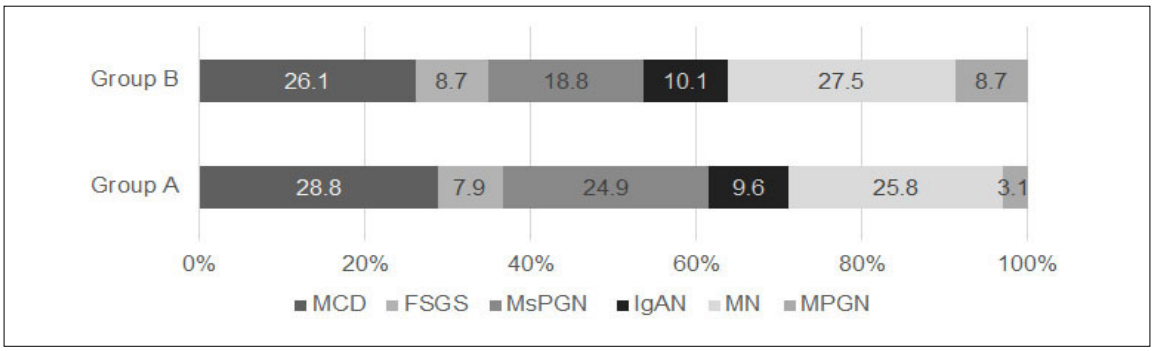

FIGURE 2

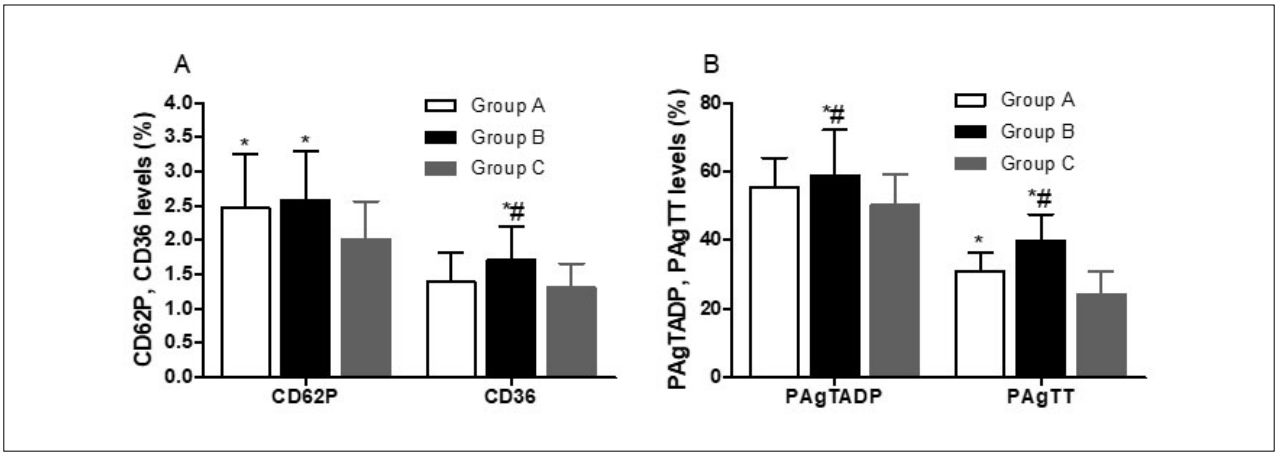

TABLE 2. INFLUENTIAL FACTORS OF NS WITH LOW T3 SYNDROME

Arguments	B	Wals	P	OR	95% CI
APTT	-0.402	23.443	0.000	0.635	0.547 ~ 0.851
Alb	-0.146	6.924	0.005	0.799	0.697 ~ 0.913
24h urine protein	0.816	11.074	0.001	2.636	1.196 ~ 3.467
CD36	1.401	0.445	0.004	3.516	1.742 ~ 8.186
PAgTAA	0.107	4.141	0.037	0.442	1.001 to 1.251

(TBG). Patients with NS may have LT3S due to the loss of various hormone-binding proteins including albumin, thyroid-binding protein, and thyroxine transporter from urine. This study showed that the incidence of LT3S in NS patients was 23.2% (69/298). There was no significant difference in the distribution of renal pathology types in the two groups. Our further studies showed that the 24-hour urine protein in the patients with LT3S was higher, and the serum albumin was lower. The results of our study are similar to those of previous reports.[7] The results indicate that LT3S is associated with the severity of the disease in NS patients, suggesting that LT3S may be a self-protective mechanism under the disease state. By reducing the concentration of thyroid hormone, protein catabolism is reduced, resulting in a decrease in the basal metabolic rate and reduced energy consumption.[8,9]

Thrombosis in NS patients is closely related to a proteinuria-related imbalance of thrombosis inhibition and thrombotropic factor[10,11] and abnormal platelet function [3]. Platelet hyperfunction can lead to the sustained expression of platelet surface activation markers, increased release of active substances, and increased platelet aggregation. Platelet activation is the starting factor of thrombosis. When platelets are activated, the pipeline system is open, and the internal alpha particles are fused with the plasma membrane to increase the expression of platelet membrane glycoprotein CD62P and CD63. Thus, CD62P and CD63 are considered specific markers of platelet activation.[12,13] The platelet aggregation rate (PAgT) was determined by an optical method with adenosine diphosphate (ADP) and arachidonic acid (AA) as inducers, so PAgTAA and PAgTADP could evaluate the platelet aggregation function. Recently studies have concluded that low serum albumin is an independent correlator of platelet hyperactivity in NS patients.[14] Similar to this result, our study also found that patients with LT3S had higher 24h urinary protein and lower serum albumin. Our further studies showed that patients with LT3S had lower APTT, higher CD63, PAgTAA, and PAgTADP. Logistic regression adjusted for age, gender, and other related factors showed that LT3S was associated with APTT, CD36, and PAgTAA, suggesting that patients with LT3S have abnormal platelet activation and increased platelet aggregation. Prior studies show that LT3S is a common complication, and patients after stroke are associated with greater stroke severity and worse outcomes.[15,16] Findings of the present report suggest that pro-coagulative state associated with LT3S can be a significant underlying factor of the observed associations in strokes. LT3S may affect platelet function in NS patients by the following mechanisms: on the one hand, albumin can bind free arachidonic acid (AA) in a normal physiological state, inhibiting its conversion to thromboxane A2 (TXA2) and platelet metabolism. The low bioavailability of free arachidonic acid increases the production of thromboxane A2 under the action of platelet activator, further promoting platelet activation and aggregation.[17] On the other hand, low T3 levels can

lead to abnormal relaxation of vascular smooth muscle cells, inhibit the use of endothelial cells on vasodilator nitric oxide, and reduce the formation of nitric oxide to cause endothelial dysfunction, collagen exposure after vascular endothelial injury initiates endogenous and exogenous coagulation pathways, resulting in abnormal activation of platelets and hyperfunction of platelet aggregation.[18] It is well known that patients with membranous nephropathy are prone to thrombosis complications, but our study did not find LT3S to be associated with renal pathology. This study is single centered with few enrolled patients, so it is necessary to further expand the sample size and conduct a comprehensive and in-depth multi-center study.

CONCLUSION

In conclusion, our findings suggest that NS patients are prone to complications with LT3S, and patients with LT3S have abnormal platelet activation and platelet aggregation. NS patients with LT3S should be monitored for platelet function and treated accordingly.

RESUMO

OBJETIVO: *O objetivo deste estudo foi investigar os efeitos da síndrome do baixo triiodotironina (LT3S) na função plaquetária e nos fatores de coagulação em pacientes com síndrome nefrótica (SN).*

MÉTODOS: *Pacientes com síndrome nefrótica primária foram divididos em dois grupos, função tireoidiana normal (grupo A) e LT3S (grupo B), com base na presença ou não de LT3S. Indivíduos saudáveis foram selecionados como grupo de controle (grupo C). A função de coagulação do sangue foi analisada em cada grupo. A função de ativação plaquetária (CD62P, CD63) foi determinada por citometria de fluxo. A taxa de agregação plaquetária foi detectada por um método óptico usando adenosina difosfato e ácido araquidônico como indutores.*

RESULTADOS: *A proporção de síndrome nefrótica primária com LT3S foi de 23,2% (69/298). Em comparação com o grupo C, o grupo A apresentou níveis mais altos de CD62P e PAgTADP, e o grupo B apresentou maiores CD62P, CD63, PAgTAA e PAgTADP; a diferença teve significância estatística (P < 0,05). Não houve diferença significativa na patologia renal entre o grupo A e o grupo B (X^2 = 4,957, P = 0,421). Em comparação com o grupo A, a proteína em urina de 24 horas, CD63, PAgTAA e PAgTADP foram maiores no grupo B, já APTT e Alb foram mais baixos. A diferença apresentou significância estatística (P < 0,05). A análise de regressão logística mostrou uma associação entre LT3S e CD36 (OR: 3,516; 95% IC: 1,742~8,186; P = 0,004) e PAgTAA (OR: 0,442; 95% IC: 1,001~1,251; P = 0,037).*

CONCLUSÃO: *Pacientes com síndrome nefrótica estão propensos à síndrome do baixo triiodotironina (LT3S). Pacientes com LT3S podem ter ativação plaquetária anormal e aumento da agregação plaquetária.*

PALAVRAS-CHAVE: *síndrome nefrótica; Baixa triiodotironina, síndrome de ativação plaquetária; agregação plaquetária.*

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Comments: "Low triiodothyronine syndrome is associated with platelet function in patients with nephrotic syndrome"

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Low triiodothyronine (TL3) syndrome is a common complication of critical illnesses and has been documented as an independent predictor of greater severity and unfavorable prognosis [1]. Impaired thyroxin to T3 5'-deiodination in peripheral tissues and the brain was implicated as the major mechanism underlying the development of LT3 syndrome. T3 is the most potent of the two thyroid gland hormones, and reduced concentrations of T3 can significantly impair cell metabolism. Mechanisms underlying the association of LT3 syndrome with unfavorable outcomes remain largely unknown, and the treatment for LT3 syndrome has not been shown to improve outcomes of critically ill patients with reduced T3 concentrations. Furthermore, it is also argued that LT3 syndrome can be an adaptive response to conserve energy in severely ill patients.

A study by Wu et al.[2] on patients with nephrotic syndrome suggests that LT3 syndrome is associated with a pro-coagulative and pro-thrombotic state. Specifically, they found that nephrotic disease patients with LT3 syndrome, compared with patients with no LT3 syndrome, have prolonged activated partial thrombin time (APTT), greater platelet activation (CD63 measured with flow cytometry), and adenosine diphosphate-induced platelet aggregation rate (PAgTAA), which is indicative of a pro-coagulative and pro-thrombotic state.

Greater platelet aggregation and pro-coagulative state associated with LT3 syndrome can be an important and previously undescribed mechanism underlying the well-documented, strong and independent association of LT3 syndrome with greater disease severity, mortality, and unfavorable prognosis of patients with vascular disorders, including stroke[3] and myocardial infarction[4]. These findings suggest that patients with acute vascular disorders (MI and stroke) who develop LT3 syndrome are at high risk of developing a pro-coagulative and pro-thrombotic state that can subsequentially cause propagation of blood clots within the affected artery, resulting in recruitment of branching vessels and, consequentially, in greater volume of infarcted myocardium or brain tissue. Greater end-organ damage subsequently correlates with worse clinical status, limited efficacy of commonly used therapeutic interventions, and worse overall outcomes. At subacute disease phases, thromboembolic complications (such as deep vein thrombosis and pulmonary embolism) can be serious, potentially fatal, and sometimes occur despite pharmacologic and mechanical preventive measures. Hence, it is possible that untreated LT3 syndrome can place critically ill patients at high risk of thromboembolic complications at sub-acute disease phases and, thus, result in devastating outcomes, impaired recovery, and limited participation in rehabilitation.

Ischemic stroke patients with LT3 syndrome also have worse cognitive outcomes when compared to patients with no LT3 syndrome, an association independent from stroke severity and patient age[5]. It can be hypothesized that a pro-coagulative and pro-thrombotic state associated with LT3 syndrome

can predispose microvascular circulation impairment in brain areas responsible to cognitive functioning, such as the limbic system, and remote from the stroke territory.

Further studies exploring pro-coagulative and pro-thrombotic state as a possible underlying complication of LT3 syndrome in patients with acute cerebrovascular and cardiovascular disorders are strongly encouraged as they could provide a potentially actionable target for treatment with safe and widely used hormone replacement therapy[5].

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ORIGINAL ARTICLE

Performance of the STOP-Bang in the Detection of OSA, a Brazilian study

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SUMMARY

OBJECTIVES: *Assess the performance of the Stop-Bang questionnaire in Brazilian patients for the screening of OSA.*

METHODS: *A cross-sectional study with historical and consecutive analysis of all patients who underwent polysomnography tests in the Sleeping Sector of the Ear, Nose, and Throat, and Cardiopulmonary (LabSono) Departments of the Gaffrée and Guinle University Hospital (HUGG), from 10/17/2011 to 04/16/2015. The variables relating to the SB questionnaire were collected by direct research from the medical records of patients.*

RESULTS: *In a series of 83 patients, we found that our sample were similar to other studies conducted in specialized centers of Sleep Medicine, and the population presented characteristics similar to those found by studies in Latin America. Men and women only behaved similarly in relation to the presence of Observed Apnea and body mass index, with a predominance of women who had systemic hypertension over men. In our study, the discriminatory value of 4 or more positive answers to the questionnaire had the best performance in identifying patients with an hourly Apnea-Hypopnea Index greater than 15/h, with a sensitivity of 72.97% (55.9% - 86.2%) and specificity of 67.39% (52.0% - 80.5%).*

CONCLUSIONS: *The Stop-Bang questionnaire proved to be, in our sample, a good screening instrument for diagnosing OSA Syndrome.*

KEYWORDS: *Sleep Apnea, OSA Syndromes. Surveys and Questionnaires. Polysomnography. Diagnosis.*

INTRODUCTION

The prevalence of Obstructive Sleep Apnea (OSA) is still controversial. It is estimated at an average of 22% among men and 17% among women[1]. Many cases still remain with no definite diagnosis[2]. Full-night polysomnography (PSG), at specialized sleep laboratory and in the presence of a qualified technician, is the chosen method (gold standard) for diagnosing respiratory sleep disorders[3]. However, it is expensive, time-consuming, and uncomfortable, in addition to not being affordable for the majority of the population[4,5]. That is why several alternative methods for screening and diagnosis are being researched, from simple questionnaires to smaller and portable devices.

In 2008, Dr. Frances Chung's group, from the Department of Anesthesia of the Toronto Western Hospital, Canada, published an article presenting a questionnaire approach to the screening, the Stop questionnaire. It is a quick and simple questionnaire

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with straightforward yes/no questions that has been used in different scenarios. This tool has changed and condensed the Berlin Questionnaire (BQ) in four items, with special care to have a questionnaire that is concise and easy to use[6]. More than two positive answers in the Stop questionnaire mean a significant risk for OSA. Subsequently, the inclusion of four objective measures was analyzed, resulting finally in a method that is easy to use, with high sensitivity and negative predictive value, especially for cases of moderate and severe OSA[7,8], which are desirable characteristics in screening tests. This questionnaire has already been validated for Brasil[9].

The current study aims to evaluate the behavior of the variables present in the Stop-Bang (SB) Questionnaire in Brazilian patients who underwent PSG in a university hospital in Rio de Janeiro and check its performance for OSA screening in the sample studied.

METHODS

A cross-sectional study, with historical and consecutive analysis of all 110 patients who underwent polysomnography exams at the Sleep Department (LabSono) of the University Hospital Gaffrée e Guinle (HUGG), from 17/10/2011 to 16/04/2015. All patients who underwent the PSG were informed about the possibility of their data being used in scientific studies, respecting their privacy, and signed the informed consent form (CNS Resolution no. 196/1996). This study is part of a larger project (*Study of predisposing conditions and comorbidities associated with sleep disorders*) that was submitted to and approved by the Research Ethics Committee of the HUGG under No 37/2011.

We included all patients 20 years old or older with complaints related to OSA and who, therefore, were forwarded to the PSG. We exclude those who did not sign the informed consent form and patients with morbid obesity (BMI>40 kg/m^2). All the examination reports were done manually, according to criteria previously described by the American Academy of Sleep[10].

The variables related to the SB were collected by direct research in the patient's medical records and defined as follows:

Original Stop-Bang questionnaire[11]:

1. S*noring*: Do you snore loudly (loud enough to be heard outside your bedroom with the door closed?

2. T*ired*: Do you feel tired frequently, sleepy during the day?

3. O*bserved*: Has anyone ever noticed your breathing stopping while you sleep?

4. *Blood* P*ressure*: Do you have or are on treatment for high blood pressure?

5. BMI: Is your BMI greater than 35 kg/m^2?

6. A*ge*: Are you older than 50 years? Yes or No

7. N*eck circumference*: Is your neck circumference greater than 40 cm?

8. G*ender*: Are you a male?

Since the data collection was retrospective in medical records, some changes were necessary, as listed below:

Presence of snoring. In this study, we considered the answer to be positive in the presence of any report of snoring.

The PSG was performed using the BrainNet BNT 36 device, with 32 channels, on adequate beds, in a location with appropriate levels of noise, light, and temperature. The results of this test, especially the hourly Apnea-Hypopnea Index (AHI), remained unknown to the researcher until the moment of analysis.

The severity of the Obstructive Sleep Apnea was graded into three cutoff points 5/h, 15/h, and 30/h.

The data from the SB questionnaires and the PSG were transcribed into an electronic spreadsheet (Microsoft Excel®) and subsequently analyzed using the MedCalc® software[12].

We calculated the absolute and relative frequencies of nominal variables and central and dispersion measures, and the amplitude of the continuous variables to present the sample and variables characteristics per selected groups.

The sensitivity (S), specificity (E) and the likelihood ratios (LR+ and LR-) for the diagnosis of OSA, defined by an AHI >15/h were calculated based on 2X2 contingency tables. The cut off value (DV) of the SB was analyzed by ROC Curve (receiver operating characteristic plots)[13-15]. The significance level was set at less than or equal to 5% ($a \leq 0.05$) to reject the null hypothesis in a two-tailed test. The values are presented with the respective confidence interval at 95% (95% CI), which expresses with 95% certainty the range of values within which the true value lies in the population.

RESULTS

LabSono/Unirio performed 110 examinations by the end of the current study. A total of 27 patients were excluded, 16 due to low technical quality, four

TABLE 1. CENTRAL VALUES AND DISPERSION OF THE VARIABLES THAT CHARACTERIZE THE SAMPLE.

	Average	SD	Median	Minimum	Maximum	25-75P	Normal Dist.
Age	48.2	11.3	50.0	22.0	69.0	40.2 a 56.0	<0.0001
BMI	30.0	5.7	29.0	17.7	47.9	26.1 a 33.3	<0.0001
Neck circumference	39.7	4.3	39.0	30.0	49.0	37.2 a 42.0	<0.0001
AHI	23.2/h	25.0/h	11.4/h	0.0/h	113.5/h	5.2/h to 33.7/h	<0.0001

Legend: SD - standard deviation, AHI - hourly Apnea-Hypopnea Index, BMI - Body Mass Index (kg/m²), 25-75P - percentile between 25% and 75% of the sample, Normal Dist. - normal distribution.

TABLE 2. ABSOLUTE AND RELATIVE FREQUENCY DISTRIBUTION OF THE STOP-BANG VARIABLES ACCORDING TO GENDER.

Translation	Total	%	95%CI	♂	%	♀	%	p-value
Snoring	79	95.2	75.3 -100	47	100	32	88.8	0.0199
Tiredness	58	69.9	53.0 -90.3	28	59.5	30	83.3	0.0201
Apn. Witn.	53	63.9	47.8 -83.5	32	68.1	21	58.3	0.3623
Hypertension	33	39.8	27.3-55.8	11	23.4	22	61.1	0.0005
BMI>35	17	20.5	11.9 -32.7	9	19.1	8	22.2	0.7325
Age>50	45	54.2	39.5 -72.5	21	44.6	24	66.6	0.0477
NC>40	38	45.8	32.4 -62.8	27	57.4	11	30.5	0.0154
Gender ♂	47	56.6	41.6-75.3					

Legend: Apn. Witn. - Observed Apnea, NC- neck circumference (cm), Hypertension, IC95% confidence interval, BMI - Body Mass Index (kg/m²).

TABLE 3. CHARACTERISTICS OF EACH RANGE OF POSITIVE ANSWERS TO THE STOP-BANG QUESTIONNAIRE AND THE AVERAGE OF THE AHI.

Stop-Bang	2+	3+	4+	5+	6+	7+
Snoring	66.6%	100%	100%	100%	93.3%	100%
Tiredness	55.5%	50.0%	68.1%	69.5%	86.6%	100%
Apnea	0.0%	50.0%	63.6%	82.6%	73.3%	100%
Hypertension	77.7%	10.0%	27.2%	47.8%	66.6%	75.0%
BMI>35	0.0%	0.0%	0.0%	13.0%	66.6%	100%
Age>50	44.4%	20.0%	63.6%	52.1%	66.6%	75.0%
NC>40	0.0%	20.0%	22.7%	60.8%	86.6%	100%
Men	11.1%	50.0%	59.0%	73.9%	60.0%	50.0%
Average AHI	6.8/h	17.2/h	10.2/h	27.1/h	42.3/h	52.7/h

Legend: CC - Cervical Circumference, Hypertension, AHI - hourly Apnea-Hypopnea Index, BMI - Body Mass Index.

TABLE 4. SENSITIVITY AND SPECIFICITY OF THE STOP-BANG VALUES, CONSIDERING AHI>15 INDICATIVE OF OSA PRESENCE.

S-B	S	95%CI	E	95%CI	LR+	95%CI	LR-	95%CI
2	97.3	85.8- 99.9	17.3	7.8- 31.4	1.1	1.0- 1.4	0.1	0.0- 1.2
3	86.4	71.2- 95.5	30.4	17.7- 45.8	1.2	1.0- 1.6	0.4	0.2- 1.1
4	72.9	55.9- 86.2	67.3	52.0- 80.5	2.2	1.4- 3.5	0.4	0.2- 0.7
5	37.8	22.5- 55.2	89.1	76.4- 96.4	3.4	1.4- 8.8	0.7	0.5- 0.9
6	8.1	1.7- 21.9	97.8	88.5- 99.9	3.7	0.4- 34.4	0.9	0.8- 1.0
≥7	0.0	0.0- 9.5	100	92.3- 100			1	1.0- 1.0

Legend: E - specificity, 95% CI - confidence interval, S - sensitivity, LR - likelihood ratio (positive and negative), S-B - Stop-Bang.

TABLE 5. PERFORMANCE OF DISCRIMINATORY VALUES OF THE STOP-BANG.

Variable	DV	Clas. OSA	S	95%CI	E	95%CI	LR+	LR-
		AHI> 5/h	60.8	48.4- 72.4	100	76.8- 100		0.3
Stop-Bang	≥4	AHI> 15/h	72.9	55.9- 86.2	67.3	52.0- 80.5	2.2	0.4
		AHI> 30/h	81.8	59.7 - 94.8	60.6	47.3 - 72.9	2.0	0.3

Legend: Clas. OSA - Classification of Obstructive Sleep Apnea, E - specificity, 95% CI - confidence interval, LR - likelihood ratio (positive and negative), S - sensitivity, DV - cut off value.

had duplicate exams, and seven for lack of data in the medical records. We were left with a sample of 83 individuals, with full clinical data relating to the SB, in addition to polysomnographic records of good technical standards.

In Table 1, we find the characteristics of the sample in relation to the quantitative variables. It is worth noting that none of these showed normal distribution, despite the values not being too diverse for the respective mean and median.

Qualitative variables that are part of the SB are described in Table 2. Our sample is formed by 56.6% men, all of which reported snoring, and only four women, who denied the symptom. Few patients met the obesity criterion, but the discriminatory value considered was 35.0 kg/m^2. However, 65.1% had a BMI in the overweight or pre-obesity range. Fatigue was reported by 69.9% of individuals. We also found that 37.3% had neck circumference (NC) greater than 40 cm. Apnea witnessed by a third party was reported by 63.9% of the individuals investigated. Regarding the presence of Hypertension, 39.8% had a positive record. The presence frequencies of the SB variables and their comparisons by gender are described in Table 2, in which we see that only BMI and Observed Apnea behaved similarly between men and women.

We found 89.0% of the patients had ≥3 positive answers to the SB, and 50.5% had ≥5 positive answers.

In Table 3, we can see the relative frequencies and averages of the SB items for each of the ranges of positive responses. As expected, in most cases, there is an elevation of the values with the increase of positive answers, although, in some items, we did not observe this behavior.

Only 16.9% of the cases had a negative diagnosis for OSA (AHI>5/h) based on the PSG; 32 patients (39%) had an AHI between 5 and 15/h, 16 (19%) were between 16 and 30/h, and 21 (25%) had an AHI greater than 30/h. If we analyze the DV of AHI>15/h, we find a total of 44.5% of the exams that fall into this category.

The SB performance in our sample, using AHI>15/h as reference, is described in Table 4, with the respective sensitivity, specificity, and likelihood ratios for each DV.

An SB value greater than or equal to four positive answers showed satisfatory accuracy, considering an AHI greater than 5/h,15/h, or 30/h (Table 5). The best balance between S and E, with an AUC of 0.73 with 95% CI from 0.619 to 0.835, was obtained with four positive answers to the SB in all three AHI cutoff values.

DISCUSSION

The characteristics of our sample regarding the predominance of men, overweight, median age and AHI>15/h were similar to those found in a similar study conducted in a population from a Sleep Disorder Clinic in Latin America[16]. Other studies found in our literature review also used samples with similar characteristics to ours[2,17-19].

All patients in the sample had some complaint, sign, or symptom related to OSA. Knowing that an AHI>5/h in the presence of symptoms is already a diagnostic criterion for the syndrome, our sample showed a high probability for the disease. One of the possible biases in this study was the fact that most of our patients were diagnosed with moderate and severe OSA. We attribute this predominance to the clinical selection for the PSG by our professionals in the Sleep Clinic, who prioritize more severe patients, due to the great difficulty to perform the examination, a problem that is present in the entire Brazilian public health system. Another possible problem is the low number of individuals with PSG that excluded an OSA diagnosis. Thus, we chose to evaluate the criteria in relation to an AHI>15/h, so that the sample is more equally distributed regarding the number of cases in each group and given the ability of the PSG alone to identify the disease with a value of AHI>15/h.

In our study, we found 89.1% of patients had three or more positive answers to the questionnaire, thus considered in the OSA high-risk range. A possible explanation is the fact that this study was carried out in a care center specialized in Sleep Medicine.

For the SB, the DV of ≥4 positive answers was found to have the highest accuracy for all values of AHI. We believe, however, that the ≥3 value is likely to be adequate to maintain a greater sensitivity for a screening test. For a discriminatory value ≥4, we found sensitivities of 60.8%, 72.9%, and 81.8%, and specificities of 100%, 67.3%, and 60.6% for AHI>5/h, >15/h, and >30/h, respectively. Our findings differ from those of the original study, which presented, for a DV of three or more positive SB answers, greater sensitivity of 83.6%, 92.9%, and 100%, and a lower specificity: 56.4%, 43.0%, and 37.0% for the same values of AHI[8]. However, there was an overlap in the confidence intervals, which shows that the difference may not exist. In addition, the sample of the other study comprised a pre-operative population, not from a sleep clinic. Although we found a different DV, if we look at the sensitivity and specificity in our sample at ≥3 positive SB answers, we would have S = 84.5%, 86.4%, and 91.3%; E = 57.1%, 30.4%, and 28.3% for the same AHIs, which are more similar to the sample of said study. In a review article of the SB criteria, the accuracy of a DV ≥4 positive answers is described with a sensitivity of 60.1%, 68.0%, and 79.1%, and specificity of 58.8%, 55.2%, and 51.4%[11], thus a sensitivity very similar to ours, but some differences in the specificities, although there was some overlapping in the confidence interval.

A very recent study from Minneapolis, Minnesota, with 234 patients, identified in its sample a mean age of 55.9 years, the prevalence of males (67.1% of the sample), excessive daytime sleepiness in 86.8% of the patients, Hypertension in 50.9%, and 64.9% of patients tested with a type III apparatus presented respiratory disorders (AHI)>15/h. All these parameters are higher than those found by us, with the exception of the presence of snoring and Observed Apnea, which in our sample were more prevalent. The study concluded that the Stop-Bang is a poor instrument to discriminate patients with RDI>15/h because its AUC ROC was 0.62 with 95% CI of 0.55 to 0.68[20]. We found a higher AUC of 0.73 with 95% CI from 0.619 to 0.835, unlike the study described.

Our results make us continue to understand that the SB screening to identify OSA patients has a predictive value, even though we know that data provided by sleep monitoring equipment have better performance in the diagnosis. However, the SB is easier, more convenient, and quicker to obtain. So, if it can be used to at least rule out patients, we can spare the need for more exams in a given group of individuals[20].

CONCLUSION

We conclude that the number of positive answers to the SB provides us safe parameters that can be used as screening instruments for Sleep Apnea Syndrome and guide the initial conduct of cases. In our sample, the value of four or more positive answers had the best performance in identifying patients with an AHI>15/h.

RESUMO

OBJETIVO: *Avaliar o desempenho no Questionário Stop-Bang (QSB) em pacientes brasileiros para rastrear a Apneia Obstrutiva do Sono.*

MÉTODO: *Estudo transversal, com análise histórica e consecutiva de todos os pacientes que realizaram exames de polissonografia pelo Setor de Sono da Otorrinolaringologia e da Cardiopulmonar (LabSono) do Hospital Universitário Gaffrée e Guinle (HUGG), no período de 17/10/2011 a 16/04/2015. As variáveis referentes ao QSB foram colhidas por pesquisa direta nos prontuários dos pacientes.*

RESULTADOS: *Numa casuística de 83 pacientes, encontramos amostras semelhantes a outros estudos realizados em Centros Especializados em Medicina do Sono, com características da população semelhantes aos estudos feitos na América Latina. Homens e mulheres só se comportaram de forma semelhante em relação à presença de apneias presenciadas e o índice de massa corporal, com um predomínio de mulheres com hipertensão arterial sistêmica sobre os homens. Em nosso estudo, o valor discriminatório de quatro ou mais respostas positivas ao questionário mostrou o melhor desempenho em identificar pacientes com um índice de apneia/hipopneia por hora maior do que 15/h, obtendo sensibilidade de 72,97% (55,9% - 86,2%) e especificidade de 67,39% (52,0% - 80,5%).*

CONCLUSÕES: *O QSB mostrou-se, em nossa amostra, um bom instrumento de rastreio da Síndrome da Apneia Obstrutiva do Sono.*

PALAVRAS-CHAVE: *Apneia obstrutiva do sono. Síndromes da apneia do sono. Inquéritos e questionários. Polissonografia. Diagnóstico.*

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ORIGINAL ARTICLE

Evolution and projection of knee arthroplasties from 2003 to 2030 in the state of São Paulo

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SUMMARY

OBJECTIVE: *Analyze data regarding total knee arthroplasty (TKA) carried out by the Public Health System (SUS) in the state of São Paulo from 2003 to 2010 and determine the projections expected for 2030.*

METHODS: *A cross-sectional study (observational). We analyzed 10,952 patients who underwent primary total knee arthroplasty (PTKA) and revision total knee arthroplasty (RTKA) in the state of São Paulo between 2003 and 2010. The collection of data based on ICD-10 and HAA (Hospital Admission Authorization) were provided by the Tabnet and Sigtap software (Management System for the Table of Procedures, Medications, and OPM by SUS). The following variables were analyzed: gender, number of PTKAs and RTKAs, and their projections. The information collected formed a database developed in Excel® for Windows, and the statistical analysis was performed by the Stata® 11 SE and Minitab 16 software.*

RESULTS: *There was a significant difference in the prevalence of TKA between genders (p<0.0001); most of the patients were females (7,891; 72%). The projection for 2030 when compared with the first year of the series, 2003, indicates a growth of 428% for PTKA and 1,380% for RTKA, with a greater increase percentage of RTKA in males than in females (1,558% and 1,318%, respectively).*

CONCLUSION: *The proportions of the RTKA projection are much greater than those of PTKA by 2030, with a greater percentage of increase of RTKA in males than in females.*

KEYWORDS: *Osteoarthrosis. Arthroplasty. Knee. Forecasting.*

INTRODUCTION

Over the past decades, there has been an increase in the longevity and life expectancy of the people in the state of São Paulo[1]. In 2000, the state's population was approximately 37 million inhabitants, of which 8.9% were elderly individuals (over 60 years)[1]. In 2014, this percentage increased to 11.89% of the more than 44 million inhabitants of São Paulo[1]. For 2030, it is expected that 21% of a total population of 48 million will be elderly individuals[1]. Recently, with the absolute number increase of the elderly population, the number of patients with osteoarthritis of the knee (OAK), particularly in the most populous Brazilian state[2]. Among the therapeutic options available for treating symptomatic advanced TKA, there is total knee arthroplasty (TKA)[2]. This surgery represents a technological breakthrough in OAK surgical procedures; it is effective to

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reduce pain, realign the affected lower limb, restore function, and optimize the decreased articular mobility[3]. TKA allows a functional improvement in around 90% of the patients, with implants durability at around 95% in 15 years and 91% in 21 years[2].

The development of instrumental support and particular devices, in addition to the improvement of surgical techniques and anesthetic procedures, broadened the indication criteria for KTA, including the age range over 40 years old, provided the procedure's eligibility conditions are met by younger and more active OAK patients[4,5]. The increase of TKA indications in the fifth and sixth decades of life has been reported in other countries, with emphasis on the public health system[6,7]. The increased number of people in their 80's and 90's in clinical conditions to become TKA surgery candidates and the increased prevalence of obesity in the Brazilian population, which is a risk factor for OAK progression, has caused an increasing demand for TKA, and consequently of TKA revision cases (RTKA), thus determining a tendency of increased number of these surgeries in the coming years, especially in reference centers[4,8,9]. The greater number of indications for these types of arthroplasty will increase the health system's financial expenditures related to these primary interventions (ATKs) and surgical re-interventions in the coming decades[2,4].

Thus, there was an expansion of the number of PTKAs and, consequently, an increase in revisions and the possibility of an even greater rise in numbers over the next 30 years[10,11]. Among the primary etiologies for RTKA, periprosthetic joint infection stands out, presenting an unfavorable impact on the functional clinical outcomes, increased hospital costs, and mortality rates in patients infected[12,14]. Other etiologies responsible for revisions are the loosening of the implants, instability, joint stiffness, and pain after the TKA[12,15].

The objective of this study is to analyze data regarding total knee arthroplasty (TKA) carried out by the Public Health System (SUS) in the state of São Paulo from 2003 to 2010 and determine the projections expected for 2030.

METHODS

This study was conducted with the approval of the institution's ethics committee (CAAE: 48693115.1.0000.5463).

The data available were collected from the Tabnet software (a software developed to allow the technical staff of the Ministry of Health, State and Municipal Health Departments quickly tabulate files in DBF format - dbFast, which constitutes the basic components of the SUS Information Systems in their intranet or on their websites) and Sigtap system (Management System for the Table of Procedures, Medications, and OPM by SUS) concerning the epidemiological assessment of TKAs performed in the state of São Paulo, from 2003 to 2010. This time interval was selected due to the redefinition of the strategy for increased access to elective surgical procedures under the SUS in 2011 and regulated by Decree 1,340, of 29 June 2012, of the Ministry of Health, which encompassed knee arthroplasties. These programs are administered by the Hospital Information System of SUS - SIH/SUS, managed by the Ministry of Health, through the Department of Health Assistance, along with State and Municipal Health Departments, and processed by the Datasus - Department of Informatics of SUS, of the Executive Secretariat of the Ministry of Health. The instruments used to record the patients included in the program were the HAAs (Hospital Admission Authorization) of patients admitted with the underlying disease, according to the International Classification of Diseases (ICD - 10). The ICDs selected were M17 for knee arthrosis and T84 for complications of prosthetic devices.

The hypothesis is that the demand for PTKA and RTKA will increase substantially by the year 2030. To test this hypothesis, we performed statistical projections, by means of linear regression, of the total number of PTKAs and RTKAs between 2011 and 2030 based on the medical records available in the database of the Unified Health System (SUS) for the state of São Paulo, between January 2003 and December 2010.

We analyzed data concerning TKAs (primary and revision) performed by SUS in the state of São Paulo, between January 2003 and December 2010, to determine the expected trends and projections of these arthroplasties by 2030. The variables evaluated in this study were the type of arthroplasty, the date of surgery and gender, which were presented in tables with absolute and relative frequency distribution. The normality of the variables was tested using the Shapiro Wilk test[10], and the proportion comparison of the variables was performed using the Test for the Equality of Two Proportions[16]. The trend analysis was performed by polynomial regression models. All analyses were performed with a significance level of 5%; therefore, results were considered statistically significant when p-value < 0.05, always considering two-tailed alternative hypotheses.

The information collected formed a database developed in Excel® for Windows, and the statistical analysis was performed by the Stata® 11 SE and Minitab 16 software.

RESULTS

This study analyzed 10,952 patients who underwent TKA between January 2003 and December 2010. There was a significant difference in prevalence between genders (p<0.0001), with mostly female patients (7,891; 72%), i.e., there were, on average, 2.6 times more procedures of TKA performed in women than in men (Table 1).

There was a significant increase in PTKA and RTKA surgeries (p<0.0001) in the period analyzed. In 2003, the first year analyzed, 830 TKAs and RTKAs 91 were performed. In the last year analyzed, 2010, 1,839 TKAs and 420 RTKAs were performed, an increase of 122% and 362%, respectively, in the number of surgeries performed between the first and the last year analyzed (Table 2).

As for the projections, the results showed that by 2030, the number of TKAs would increase with statistical significance (p<0.0001). When compared with the first year of the series, 2003, the projection indicates a growth of 428% for PTKAs and 1,380% for RTKAs (Table 3 and Figure 1). It should be noted that the proportion ratio between the types of surgery is decreasing: in 2003, the proportion ratio between PTKA and RTKA was 9.1:1, i.e., nine primary surgeries were performed, on average, for each revision surgery. In the projection for 2030, the proportion dropped to 3.3:1, i.e., it indicates that for every three primary surgeries, one revision surgery will be performed.

The result showed that, for 2030, the number of PTKAs increased with statistical significance (p<0.0001) for the female gender. When compared with the first year of the series, 2003, the projection indicates a growth of 388% for PTKAs and 1,318% for RTKAs, with a 3.2:1 ratio for the projections.

The results showed that, for 2030, the number of TKA increased with statistical significance (p<0.0001) for males. When compared with the first year of the series, 2003, the projection indicates a growth of 552% for PTKAs and 1,558% for RTKAs, with a 3.3:1 ratio for the projections (Figure 2).

DISCUSSION

The most important finding of this study was that the TKA demand , for both primary and revision, has a growing trend, with a projected increase of 428% for the primary type and 1,380% for revisions, by 2030. Although primary prosthesis are more frequent, the ratio between the proportion of primary prostheses and revisions is decreasing considerably (9.1:1 in 2003 and 3.3:1 in 2030).

Our study showed an increasing trend of TKA, which was also found in studies conducted in other countries. In the United States, a study carried out over a similar period of time found that the demand

TABLE 1. DISTRIBUTION OF TKAs PER GENDER, FROM 2003 TO 2010.

Gender	No.	%	p
Fem	7,891	72%	<0.0001
Male	3,061	28%	
Total	10,952	100%	

TABLE 2. DISTRIBUTION OF TKAs PER GENDER, FROM 2003 TO 2010.

Type of ATK	Year								Growth % (initial year x final year)
	2003	2004	2005	2006	2007	2008	2009	2010	
Primary	830	840	917	1001	1105	1187	1552	1839	122%
Revision	91	102	116	133	169	333	317	420	362%
Total	921	942	1033	1134	1274	1520	1869	2259	145%

TABLE 3. ATKS EVOLUTION FROM 2003 TO 2010, AND PROJECTIONS BY 2030.

Type of ATK	Historical series								Projections				Growth % (initial x final)
	2003	2004	2005	2006	2007	2008	2009	2010	2015	2020	2025	2030	
Primary	830	840	917	1001	1105	1187	1152	1839	2326	3013	3700	4386	428%
Revision	91	102	116	133	169	333	317	420	621	863	1105	1347	1380%
Primary ratio	9.1:1	8.2:1	7.9:1	7.5:1	6.5:1	3.6:1	4.9:1	4.4:1	3.7:1	3.5:1	3.3:1	3.3:1	-

for PTKA and RTKA is expected to grow 673% and 601%, respectively, between 2005 and 2030[11,17]. Data analyses relating to England and Wales suggest that, by 2030, the volume of TKAs and RTKAs will have increased by 117% and 332%, respectively, between 2012 and 2030[18]. Another European study presented data that predict a 297% demographic projection for the number of TKAs by 2030 in the Netherlands[19]. Another study showed that TKAs would increase by 45% over the next three decades in Italy[20].

FIGURE 1. ATKS EVOLUTION FROM 2003 TO 2010 AND PROJECTIONS BY 2030.

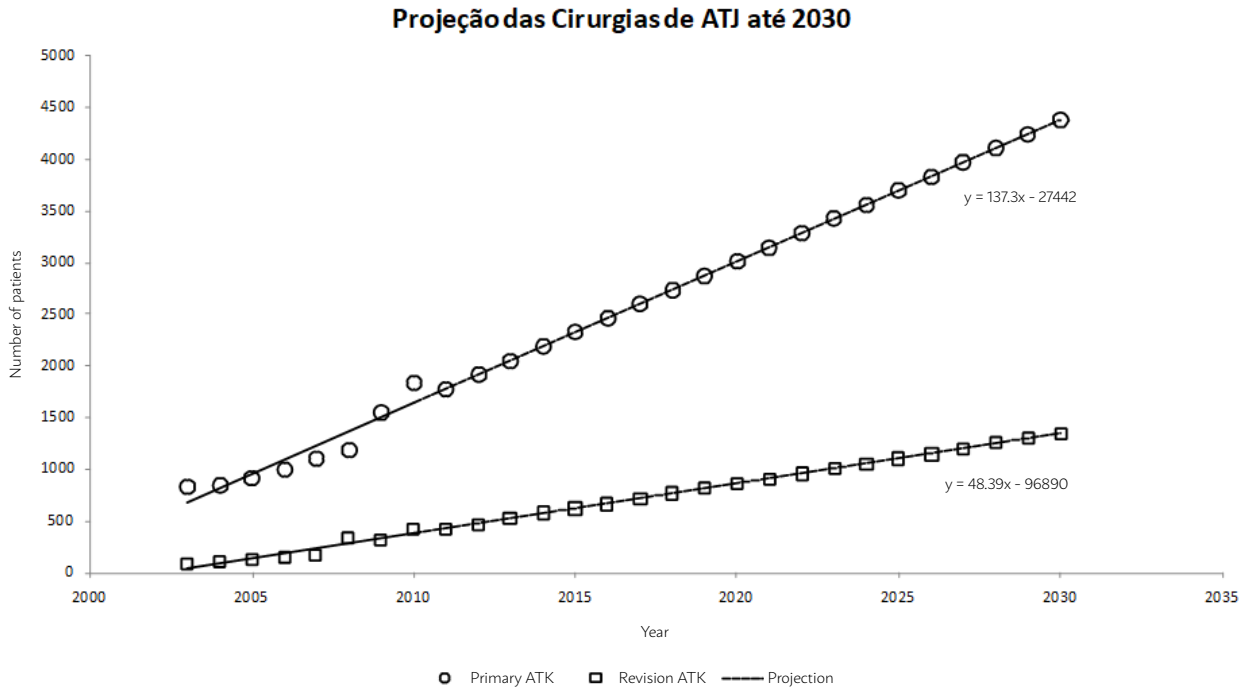
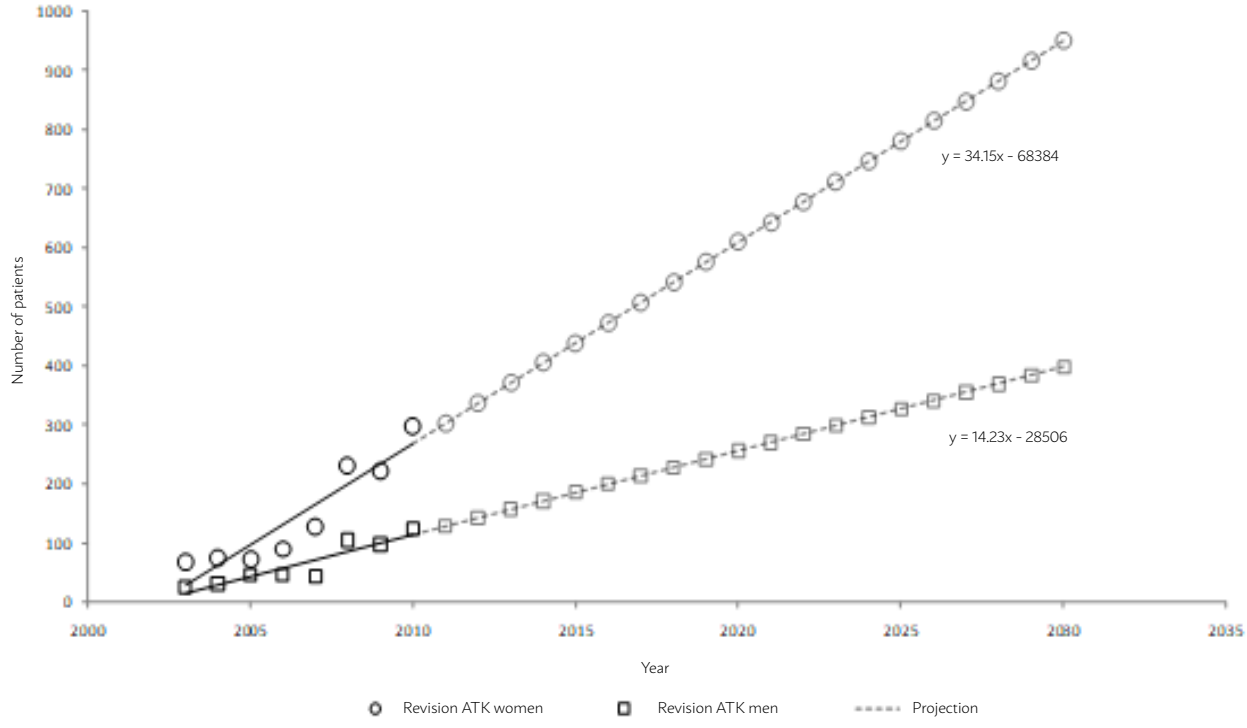


FIGURE 2. RATKS EVOLUTION FROM 2003 TO 2010 AND PROJECTIONS BY 2030, PER GENDER



Another study reports that event young patients (under 65 years) will have an increase in the number of prosthesis and revisions by 2030, and highlights the weight that young patients may represent in the future of the demand for primary and revision surgery[21]. A study conducted in the United States and in Ontario, Canada, demonstrated that the rates of TKA have increased in North America, with the contribution of the increased number of young people undergoing prosthetic replacement of joints, which indicated an expansion of indications[22]. Another international study corroborates the increased projection, estimating a 183% growth of TKAs by 2026[23]. This increase in the demand for TKAs and RTKAs will create a significant socioeconomic burden and require planned and programmed health strategies to ensure the necessary resources are allocated to meet the demand of the population affected by OAK[17,23].

In the gender analysis, when confronted with other international case series, we found an increase proportionally similar for men and women[23]. However, after analyzing the procedures based on type and gender, we saw a greater percentage increase in RTKA in males than in females (1,558% and 1,318%, respectively). This disparity justifies further research to determine the extent to which it reflects changes in the risk of the disease or inequalities in public health services. Women usually seek early medical care due to functional disabilities associated mainly to complaints of pain during walking and daily living activities, while men postpone medical assistance and complain about the deleterious effects of OAK on leisure activities[24]. Women have a longer life expectancy and have presented increased use of TKA in recent years, but face greater barriers to access to the surgical treatment[2,5,25]. Women are willing to undergo surgery, just like men, but are less likely to receive an indication to a specialist in comparison with men with advanced OAK[25].

Additional national epidemiological data, such as the latest updated projections of this study, provide a forecast for surgeons, hospitals, health services and the formulators of public policies to plan for the future demand for ATKs and RTKAs over the next decades[2,26]. The data relating to projections made in this study identified a proportional increase of RTKA indications in comparison with to TKA over the next decade, allowing for a planned health budget and the development of strategic measures to encompass this increased demand for knee arthroplasty surgeries.

Among the possible etiologies responsible for the increased number of RTKAs in the sample analyzed, periprosthetic joint infection (PJI) stands out in several different stages, i.e., early (less than three months), intermediate (between 3 and 24 months) and late (after 24 months), according to the classification proposed by Zimmerli et al.[27]. The lack of standardization and multi-professional teams specialized in the diagnosis and treatment of PJI made the follow-up of these patients in SUS even more difficult. Two national studies conducted in public hospitals in São Paulo, which included part of the period of time analyzed in our study, corroborated this possibility[28,29]. Since then, protocols have been implemented and developed jointly by infectologists, anesthesiologists, and nursing professionals to prevent, diagnose, monitor, and optimize therapeutic strategies to minimize such complication[30].

The increase of prosthetic knee joint replacement surgeries is an urgent reality and requires improvements in the management of hospitals, training of medical professionals, and specialized nursing teams, due to the positive association between the experience of the surgeon and the surgical volume of knee arthroplasties performed at referral centers with more favorable outcomes, lower rate of complications, and lower costs[2,9,11,14]. The projections in this study are limited to an extrapolation of historical data. The trends established may not persist in the future because of the influence of certain factors, such as improvements in the implant technology or new pharmaceutical discoveries that may impact the physiopathology and progression of OAK.

The weaknesses of this study are the lack of standardization of surgical techniques, the absence of data such as patient age and comorbidities, which could identify risk factors for arthroplasties, absence of etiologies and indications for the surgery, complications related to the procedure and the lack of knowledge of materials and implants used for the knee prostheses. These data were not collected due to the diversity of information from medical records and absence of interviews with the patients who underwent surgery.

CONCLUSION

The projected proportions of revision prosthesis are much greater than those of primary prosthesis by 2030. The increasing percentage of RTKAs was greater in males when compared with females.

RESUMO

OBJETIVO: *Analisar os dados referentes às artroplastias totais de joelho (ATJ) realizadas pelo Sistema Público de Saúde (SUS) no estado de São Paulo de 2003 a 2010 e determinar as projeções esperadas para 2030.*

MÉTODOS: *Estudo transversal (observacional). Foram analisados 10.952 pacientes que realizaram artroplastia total de joelho primária (ATJP) e revisão (ATJR) no estado de São Paulo entre 2003 e 2010. A coleta de dados baseados no CID-10 e AIH (Autorização de Internação Hospitalar) foram fornecidos pelo programa Tabnet e Sigtap (Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS). Foram analisadas as seguintes variáveis: gênero, número de ATJP e número de ATJR, além de suas projeções. As informações coletadas formaram um banco de dados desenvolvido no programa Excel® for Windows e a análise estatística foi realizada pelos softwares Stata® 11 SE e Minitab 16.*

RESULTADOS: *Houve diferença significativa na prevalência da ATJ entre os gêneros (p<0,0001), sendo a maioria do gênero feminino (7.891; 72%). A projeção para 2030 quando comparado com o primeiro ano da série, 2003, indica um crescimento de 428% para as ATJP e 1.380% nas ATJR, com uma porcentagem de aumento maior nas ATJR no gênero masculino do que no feminino (1.558% e 1.318%, respectivamente).*

CONCLUSÃO: *As proporções de projeção da ATJR se mostram muito maiores do que nas ATJP até o ano de 2030, percebendo-se uma porcentagem de aumento maior de ATJR no gênero masculino comparado ao feminino.*

PALAVRAS-CHAVE: *Osteoartrose. Artroplastia. Joelho. Previsões.*

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Comments: "Evolution and projection of knee arthroplasty from 2003 to 2030 in the state of São Paulo"

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The aging of the Brazilian population, as a result of increased life expectancy, contributes to the increase of the arthroplasties at a national level.[1-3] Several studies have demonstrated that this increase reflects a worldwide trend. Other places, such as the United Kingdom and Australia, saw an increase in the number of arthroplasties during the same period, even though life expectancy there is greater than in Brasil.[2-5] Over 76 years, from 1940 to 2016, the life expectancy of the Brazilians at birth increased in more than 30 years and today is 75.8 years, an increase of 3 months and 11 days compared to 2015, according to the Brazilian Institute of Geography and Statistics (IBGE). Data from the 2016 Mortality Table showed that, on average, women live longer than men. While the life expectancy of men, in 2016, was 72.9 years, women's reached 79.4 years.[1] These potential patients need public policies for the prevention and treatment of osteoarthritis. The treatment of osteoarthritis is of fundamental importance to public health and surgery is only one many treatment possibilities; however, it is the most expensive and with the greatest rate of complications. The procedure complications are related to factors concerning the material and technique used.[6] The knowledge on how arthroplasty surgeries behave in our midst provides important material for health policies and exposes the need for trained specialists and more tertiary health care centers, which could enable these individuals to resume their productive activities, an essential outcome to the national economic scenario and an important psychosocial factor. Therefore, the discussion on the necessity of a National Arthroplasty Record is of the utmost importance. In July 2015, in Brasilia, an inter-institutional working group on prostheses and special materials published its final report, in which they stress this need. The knowledge of how Brazilian surgeons treat their patients, the type of implant, brand, complications, and survival of these procedures provide basic information so that the most interested party in this whole process, the patient, can truly benefit from it,by being completely included in society, in full activity.[7]

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ORIGINAL ARTICLE

Melatonin may prevent or reverse polycystic ovary syndrome in rats

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SUMMARY

OBJECTIVE: *To evaluate the ovarian effects of melatonin (Mel) in a rat model of polycystic-ovary-syndrome (PCOS) before and after permanent estrus induction.*

METHODS: *Thirty-two adult-female rats with regular estrous cycle were equally divided into four groups: 1) GCtrl – at estrous phase. 2) GPCOS - at permanent-estrous phase. 3) GMel1 – treated for 60 days with Mel (0.4 mg/Kg) during permanent estrus induction and 4) GMel2 – rats with PCOS and treated for 60 days with Mel. After that, the animals were euthanized, and the ovaries were removed and processed for paraffin embedding. Sections were stained with H.E. for histomorphometry or subjected to immunohistochemistry for Ki-67 and cleaved caspase-3 (Casp-3) detections.*

RESULTS: *The GPCOS showed lack of corpus luteum and several ovarian cysts, as well as interstitial-like cells. The presence of corpus luteum and a significant increase in primary and antral follicles were observed in Mel-treated groups, which also showed a decrease in the number of ovarian cysts and in the area occupied by interstitial-like cells. These results were more evident in GMel1. The percentage of Ki-67-positive cells was significantly higher in the Mel-treated groups, mainly in the GMel2, as compared to GPCOS. On the other hand, the percentage of Casp-3-positive cells was significantly lower in granulosa cells of GMel1, whereas it was significantly higher in the interstitial-like cells of GMel2, in comparison to GPCOS.*

CONCLUSION: *Melatonin administration prevents the permanent estrus state in the PCOS rat model. This effect is more efficient when melatonin is administered before permanent estrus induction.*

KEYWORDS: *Ovary. Melatonin. Polycystic Ovary Syndrome. Estrous cycle. Rats.*

INTRODUCTION

Among several causes of infertility, PCOS stands out due to its frequency, as it affects nearly 5 to 10% of women during reproductive life[1,2]. Various animal models have been developed to mimic PCOS, among them PCOS induction through continuous illumination exposure is widely used. This induces the animal to an estrous-permanent condition, associated with anovulation, presence of multiple cysts, and an increase in

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androgens and estrogens serum levels, along with the reduction in melatonin synthesis[3].

Studies have been suggested that the reduction of melatonin levels would be responsible for the development of ovarian cysts[4]. In a previous study carried out by our group, we observed an increase in the area occupied by interstitial cells, as well as the lack of *corpus luteum* in ovaries of rats in the estrous-permanent condition, induced by continuous light exposure. It was also suggested that the interstitial cells of the polycystic ovary of rats probably come from ovarian cysts, due to the degeneration of granulosa cells and the differentiation of theca interna cells[5]. An increase in cleaved caspase-3 immunoreactivity in the granulosa cells of ovarian cysts and the lack of Ki-67 immunolabeling in ovarian interstitial cells have also been identified, suggesting that these cells may originate from another cell type[6].

Animal and human studies indicate that there is a direct action of melatonin on ovarian function, including a systematic alteration in ovarian steroidogenesis, mainly progesterone synthesis. Pinealectomized rats displayed fertility reduction with a decrease in the number of oocytes, in addition to problems during the gestation period and melatonin serum levels reduction. It has been demonstrated that melatonin treatment is safe due to its low toxicity, even when high doses are administered. Moreover, its administration seems to display satisfactory results in the protection and treatment of reproductive dysfunctions[7]. However, the effects of melatonin in the prevention and treatment of PCOS are still poorly understood.

Thus, this study aims to evaluate the ovarian effects of melatonin (Mel) in a rat model of polycystic ovary syndrome before and after permanent estrus induction.

METHODS

Study design

This prospective experimental study used thirty-two and three-months-old virgin female rats (*Rattus norvegicus albinus*) with ± 250g of body weight, provided by the Center for the Development of Experimental Models (CEDEME) at the São Paulo School of medicine, Federal University of São Paulo (UNIFESP/ EPM). This study was initially approved by the Research Ethics Committee at UNIFESP/EPM (Report nº 0179/12), following the guidelines of the Canadian Council on Animal Care[8].

After a period of seven days of adaptation to the new environment, all animals were subjected to a daily collection of vaginal secretions, for seven consecutive days, in order to evaluate ovarian function. Based on the result of this examination it was possible to observe regular estrous cycles, demonstrating normal ovarian functions. Only rats with regular estrous cycles were included in the study. Then, the rats were randomly divided into four groups: 1) GCtrl - at physiological-estrous phase. 2) GPCOS - at permanent-estrous phase induced by 60 days of continuous illumination (rats with PCOS). 3) GMel1 – PCOS rats daily treated with Mel (0.4 mg/Kg diluted in 500ml of drinking water) during 60 consecutive days, preemptively, and 4) GMel2 – PCOS rats, which remained exposed to 60 days of continuous illumination and treated with Mel[9]. It is noteworthy that the animals of the GMel2 group remained under continuous illumination during a total period of 120 days (60 initial days for the induction of the estrous-permanent condition and 60 additional days during the treatment period).

To obtain animals with PCOS, the rats were placed in wooden boxes, kept in a vivarium under continuous artificial lighting using lamps (Philips, Daylight Model, 40W) that provided about 400 Lux in the region occupied by the rats over a period of 60 consecutive days. The GPCOS animals remained in the same standard vivarium conditions, but their lighting period was from 7 am to 7 pm. After that, the collection of vaginal secretions for seven consecutive days was carried out again, in order to analyze the phases of the estrous cycle. Then, only the animals of the GCtrl that showed regular estrous cycle, as well as the ones of the GPCOS group that were at estrous-permanent condition were used.

Afterward, the animals were anesthetized with 15 mg/kg xylazine (Rompun®, SP, Brasil) associated with 30 mg/kg ketamine (Ketalar®, SP, Brasil) intraperitoneally and placed in a supine position. Subsequently, after a longitudinal median incision made at the abdomen, the ovaries were removed and immediately fixed for 24 h in 10% formaldehyde (PBS 10mM, pH 7.2). Subsequently, the ovaries were dehydrated in ascending concentrations of ethanol, cleared in xylene, and embedded in paraffin. By using a microtome (Minot, Leica) 5µm-sections were obtained from the paraffin blocks, with a distance of 50µm from each section. Sections were collected on histological slides and subsequently stained with hematoxylin and eosin (HE), whereas others were subjected to immunohistochemical methods.

After removing the ovaries, the animals were euthanized by deepening the plane of anesthesia and disposed of following current standards at the São Paulo School of medicine (UNIFESP/EPM).

Morphological and morphometric analyses

The evaluation of the slides was carried out at the laboratory of Histology/ UNIFESP/EPM. For the quantification of the parameters evaluated, images were captured by using a high-resolution camera (AxioCam-MCR, Carl Zeiss) adapted to a light microscope (Axiolab, Carl Zeiss) adjusted to a 40X objective lenses and were transmitted to a computer with AxioVision Rel 4.2 software (Carl Zeiss). For the estimation of nuclear volumes of interstitial cells, ten images of each ovary of each rat were obtained, comprising 80 images per group. Posteriorly, the lower and the larger diameter of 10 cells/images were measured and applied to the following formula: $v = a^2.b/1.91$ wherein a = lower diameter and b = larger diameter, and 1.91 represents a constant[5]. The determination of the occupied area by interstitial cells was expressed as a percentage, under objective lenses of 10x. Initially, the total ovarian area and the area occupied by interstitial cells in 10 slices of each ovary/animal were measured. Then, the proportion of the area occupied by interstitial cells in relation to the total ovarian area was calculated as a percentage in each section. In this same magnification, the number of ovarian follicles presented in 10 sections of each ovary/animal was counted and classified as primary and antral follicles.

Immunohistochemical analysis

Immunohistochemical reactions for the detection of Ki-67 and Casp-3 were carried out to analyze cell proliferation and apoptosis, respectively[6]. Sections were collected on silanized slides and subsequently dewaxed in xylene and hydrated in decreasing concentrations of ethanol. The endogenous peroxidase activity was blocked by incubating the sections with

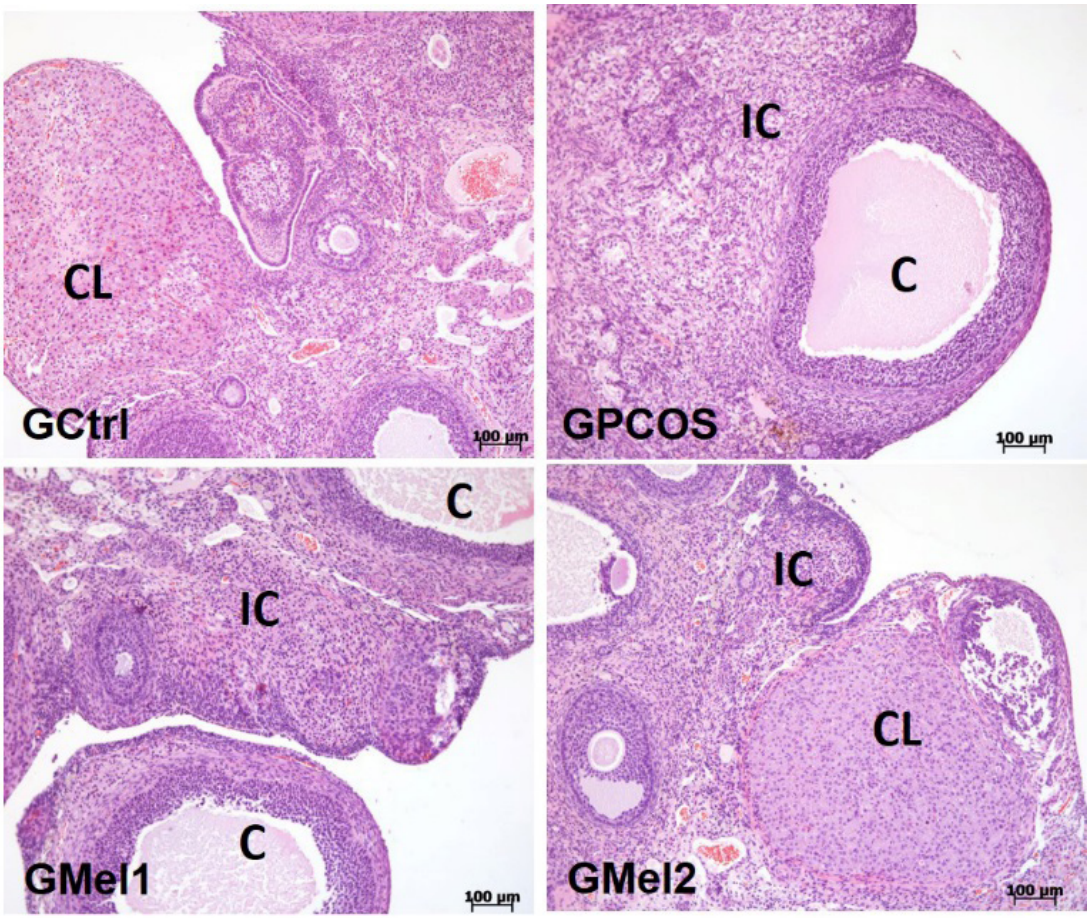

FIGURE 1. Photomicrographs of histological sections of ovarian regions from all groups. It is possible to see a portion of a corpus luteum (CL) of the GCtrl group; and the presence of a cyst in GPCOS (C). In GPCOS, GMel 1, and GMe2, we see the presence of interstitial cells (IC) and corpora lutea in the GMel2. H.E staining.

3% hydrogen peroxide for 5 minutes. The sections were incubated in a sodium citrate buffer (pH 6.0), 10 mM at 95ºC for 20 minutes and non-specific binding sites were blocked with 2% PBS-BSA for 1 hour. Sections were then incubated overnight in the following primary antibodies: anti-Ki-67 (MIB-5, Dako, Denmark, United Kingdom) and anti-cleaved caspase-3 (Asp175-antibody #9661, Cell Signaling Technology, Beverly, USA), diluted at 1:200 and 1:100, respectively. Afterward, the sections were incubated in a biotinylated goat anti-mouse/rabbit (Ig, Duet kit Dako) secondary antibody; reactions were revealed with the streptavidin-peroxidase system (Dako Cytomation, USA) using 3,3'-diamino-benzidine (DAB) as a chromogen and counter-stained with hematoxylin. As a negative control, primary antibodies were replaced by non-specific immunoglobulin (DAKO Cytomation, USA). The frequency of Ki-67 and cleaved caspase-3 immunolabeled cells were expressed as a percentage (%), and a last 500 cells/animal were counted.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation and evaluated by ANOVA test, followed by Tukey test (using the "*GraphPad* 5 *Prism*" software. The rejection level for the null hypothesis was set at 1% ($p<0.01$), and significant values were marked with an asterisk.

RESULTS

Morphological and morphometric analyses

The morphological results showed lack of *corpus luteum* and the presence of multiple ovarian cysts in the GPCOS group. Numerous groups of cells containing large and bulky nuclei and well-evident nucleoli were also observed in the GPCOS group. These cells were organized as spherical and cord-like structures with epithelioid aspect, which are typical characteristics of interstitial cells (Fig.1). On the other hand, the Mel-treated groups showed the presence of *corpus luteum*, as well as an increase in the number of primary and antral follicles, mainly in the Mel1 group (Fig.1 and Table 1). A significant reduction in the number of cysts and in the area occupied by interstitial cells, as well as a decrease in nuclear volume of these cells, were noticed in the Mel-treated groups, mainly in the Mel1 group (Table 1).

TABLE 1. MEAN AND STANDARD DEVIATION (M±SD) OF THE MORPHOMETRIC PARAMETERS OBTAINED IN THE OVARIES OF THE NORMAL ESTROUS CYCLE (GCTRL), ESTROUS-PERMANENT RATS (GPCOS), MEL-TREATED RATS AS PREVENTION (GMEL1) OR AFTER THE INDUCTION OF PERMANENT ESTRUS (GMEL2).

Parameters	GCtrl	GPCOS	GMel1	GMel2
Nº Cysts/Ovary	0^{c}	5.50 ± 0.36^{a}	4.15 ± 0.20^{b}	4.20 ± 0.16^{b}
Nº Corpus luteum/Ovary	4.61 ± 0.80^{a}	0^{c}	4.24 ± 0.70^{a}	3.50 ± 0.16^{b}
Nº Primary follicles/0.04mm²	32.15 ± 0.15^{a}	20.88 ± 0.89^{c}	26.40 ± 0.86^{b}	25.00 ± 0.91^{b}
Nº Antral follicles/0.59mm²	4.45 ± 0.65^{a}	1.02 ± 0.03^{c}	4.30 ± 0.33a	2.85 ± 0.06^{b}
% Area of Interstitial Cells	19.33 ± 1.07^{d}	52.11 ± 1.03^{a}	26.60 ± 2.04^{c}	34.28 ± 1.20^{b}
Nuclear volume of Interstitial Cells/µm³	7.40 ± 0.83^{c}	15.40 ± 1.37^{a}	8.63 ± 0.90^{c}	10.23 ± 0.77^{b}

Note: a>b>c>d. *p≤0.05

TABLE 2. MEAN AND STANDARD DEVIATION (M±SD) EXPRESSED AS A PERCENTAGE (%) OBTAINED FROM THE IMMUNOHISTOCHEMICAL ANALYSIS OF NORMAL ESTROUS CYCLE (GCTRL), ESTROUS-PERMANENT RATS (GPCOS), MEL-TREATED RATS AS PREVENTION (GMEL1), OR AFTER THE INDUCTION OF PERMANENT ESTRUS (GMEL2).

Parameters	GCtrl	GPCOS	GMel1	GMel2
% Apoptosis of theca cells	0.01±0.02	0.02±0.01	0.01±0.01	0.01±0.01
% Apoptosis of granulosa cells	1.50±0.02c	89.05 ± 7.80^{a}	32.50 ± 3.80^{b}	86.09 ± 1.80^{a}
% Apoptosis of interstitial cells	0.15 ± 0.62^{c}	2.20 ± 0.50^{c}	4.20 ± 0.40^{b}	34.04 ± 2.80^{a}
% Proliferation of theca cells	2.01±0.12	2.05±0.12	2.03±0.10	2.02±0.13
% Proliferation of granulosa cells	95.05 ± 0.20^{a}	5.07 ± 0.18^{c}	78.07 ± 0.22^{b}	92.80 ± 0.20^{a}
% Proliferation of interstitial cells	0	0	0	0

Note: a>b>c>d. *p≤0.05

Immunohistochemical analysis

The percentage of Ki-67-positive cells (cell proliferation marker) was significantly higher in granulosa cells of the Mel-treated groups when compared to GPCOS group, mainly in the GMel2. Cell proliferation was not observed in interstitial cells of all groups. A weak and not significant Ki-67 immunostaining in the theca cells was also observed in all groups. Conversely, the percentage of Casp-3-positive cells (apoptosis marker) was significantly lower in the granulosa cells of GMel1 (32.50± 3.8), in comparison with the PCOS group, whereas it was significantly higher in the interstitial cells of GMel2 (34.04 ± 2.80) when compared to the PCOS group. In addition, a weak and not significant Casp-3 immunoreactivity in the theca cells was noticed in all groups (Table 2).

DISCUSSION

One of the critical hormonal factors in the regulation of follicular development is melatonin. Several authors have demonstrated the presence of their receptors (MT1 and MT2) in the ovarian follicle and support the hypothesis of their role in ovarian physiology[9,10].

Melatonin may also stimulate follicular development by promoting increased production of insulin-like growth factor I (IGF-I), a major mitogenic growth factor in granulosa cells[11]. Studies have also demonstrated the effect of melatonin (0.1 mM) on IGF-I receptor expression[12]. Our results showed that rats treated with melatonin presented a greater amount of primary and antral follicles, especially when administered before induction to permanent estrus.

Studies have detected the presence of melatonin in follicular fluid from human preovulatory follicles at concentrations higher than serum levels. High levels of melatonin in follicular fluid seem to play an essential role in the growth and proper maturation of ovarian follicles; in contrast, low concentrations may cause anovulation associated with poor oocyte quality in women with PCOS[13]. However, Shi et al.[14] reported that small swine follicles (<3 mm) contained significantly higher concentrations of melatonin than medium (3 - 8 mm) and large (<8 mm) follicles, which may be related to species-specific reproductive characteristics.

Melatonin has an important antioxidant, antiapoptotic, and anti-inflammatory role[15]. These effects act as a potential factor to protect the oocyte and its surrounding cells against damage caused by oxidative stress, thus inhibiting follicular atresia[16]. According to Sun et al.[17] oxidative stress can cause damage to granulosa cells, increasing the rate of apoptosis of these cells, as well as causing damage to the DNA of oocytes. Our results showed an increase in the number of antral and primary follicles in the melatonin-treated animals when compared to the control group. Moreover, a higher number of ovarian follicles was noticed in the ovaries of animals that received melatonin before induction of permanent estrus state (GMel1). Such findings reinforce the protective effects of melatonin in granulosa cells and ovarian follicles.

High concentrations of melatonin in the preovulatory follicle may be involved with progesterone production, resulting in ovulation and luteinization[18]. In our study, we observed an increase in the number of corpora lutea in melatonin-treated animals, which was more evident in the animals that received melatonin before permanent estrus induction. Zhang et al.[16] demonstrated in humans the action of melatonin on the production of progesterone in granule-lutein cells. This seems to be mediated in part by the increased melatonin-elicited *luteinizing hormone* (LH) receptor expression[19]. Woo et al.[19] demonstrated the action of melatonin on the modulation of follicular response to LH by increasing the expression of mRNA of LH receptors in granulosa cells in humans. The antral follicles recruited for growth are characterized by the increased expression of mRNA for steroidogenic enzymes, receptors for gonadotrophins, and local regulatory factors.

Studies have demonstrated the action of melatonin on the prevention of apoptosis (cell death mechanism) by inducing Bcl2 expression and reducing the activity of the cleaved caspase-3[19,20]. Such data corroborate our immunohistochemical findings, which showed a significant decrease in cleaved caspase-3 immunoexpression in granulosa cells in animals receiving melatonin before induction to permanent estrus (GMel1). In their study, Sun et al.[17] also observed relatively low positivity of internal theca cells to the TUNEL method (apoptosis/necrosis) in ovarian cysts of sows. Foghi et al.[21] also describe the role of Bcl-2 in the apoptosis of theca cells and interstitial cells in rat atretic follicles. Nevertheless, to our knowledge, there are no papers in the literature that clearly describe the apoptosis process of these cells in rats with polycystic ovaries.

A lower Cyp17a1 immunoexpression in theca interna cells has been observed in rats treated with

melatonin, as compared to the control group. However, in granulosa cells and interstitial cells, the authors did not observe statistically significant differences between melatonin-treated and control groups. In the same study, the authors did not observe differences in the immunoexpression for Cyp19a1 in inner theca cells, granulosa cells, and interstitial cells[22]. These data also corroborate with our morphometric results, where a significant reduction in nuclear volume and area occupied by interstitial cells was observed in the melatonin-treated and control groups, suggesting that melatonin administration induced a decrease in androgen production by interstitial cells, especially in animals that received melatonin as prevention (GMel1).

Studies have suggested a stimulatory effect of melatonin on estrogen production in pig and human granulosa cells[16]. In addition, melatonin has been shown to reduce the expression of PCNA in hormone-dependent tumors of mice, indicating that melatonin has an antiproliferative effect. Such effect does not appear to occur in granulosa cells of rats in permanent estrus or under the stimulus for the induction of permanent estrous state since our results showed a significant increase in Ki-67 expression in granulosa cells.

According to our results, melatonin appears to reestablish the normal process of granulosa cell proliferation in the rat model of PCOS (permanent estrus). Melatonin treatment is safe, accessible, and has low toxicity. Our data indicate that melatonin exerts positive effects on the protection and treatment of reproductive dysfunctions in PCOS.

CONCLUSIONS

Melatonin administration prevented the permanent estrus state in the PCOS rat model. This effect is more efficient when melatonin is administered before permanent estrus induction.

RESUMO

OBJETIVO: *Avaliar os efeitos ovarianos da melatonina (Mel) em ratas com síndrome dos ovários policísticos (SOP) antes e após a indução do estro-permanente.*

MÉTODOS: *Trinta e duas ratas com ciclos estrais regulares foram igualmente divididas em quatro grupos: 1) GCtrl - fase de estro. 2) GSOP - fase de estro-permanente. 3) GMel1 – tratadas por 60 dias com Mel (0,4 mg/kg) durante a indução do estro-permanente e 4) GMel2 – ratas com SOP e tratadas com Mel. Após eutanásia dos animais, os ovários foram processados para inclusão em parafina. Cortes foram corados com H.E ou submetidos à imuno-histoquímica para detecção de Ki-67 e caspase-3 clivada (Casp-3).*

RESULTADOS: *O GSOP mostrou ausência de corpos lúteos e vários cistos ovarianos, além de inúmeras células intersticiais. A presença de corpos lúteos e o aumento significativo dos folículos primários e antrais foram observados nos grupos tratados com Mel, os quais também mostraram diminuição no número de cistos ovarianos e na área ocupada pelas células intersticiais. Esses resultados foram mais evidentes no GMel1 do que no GMel2. A porcentagem de células Ki-67 positivas foi significativamente maior no GMel1 e no GMel2, sendo mais evidente no GMel2, em comparação ao GSOP. Por outro lado, a porcentagem de células positivas à Casp-3 foi menor nas células da granulosa do GMel1 e maior nas células intersticiais do GMel2, em comparação ao GSOP.*

CONCLUSÃO: *A administração de melatonina previne o estado de estro-permanente em ratas com SOP. Esse efeito é mais eficiente quando a melatonina é administrada após indução do estado de estro-permanente.*

PALAVRAS-CHAVE: *Ovário. Melatonina. Síndrome do ovário policístico. Ciclo estral. Ratos.*

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REVIEW ARTICLE

The impact of intensive care admission criteria on elderly mortality

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SUMMARY

OBJECTIVE: *To review systematically the influence of admission criteria on the mortality of elderly patients under intensive therapy.*

METHODS: *We performed a search on the PUBMED and BIREME databases by using the MeSH and DeCS terms "intensive care units", "patient admission", and "aged" in Portuguese, English, and Spanish. Only prospective and retrospective cohort studies were included. We analyzed the severity score, type of hospital admission, quality of life, co-morbidities, functionality, and elderly institutionalization.*

RESULTS: *Of the 1,276 articles found, thirteen were selected after evaluation of the inclusion and exclusion criteria. It was observed that the severity score, functionality, and co-morbidities had an impact on mortality. It was not possible to determine which severity score was more suitable.*

CONCLUSION: *We suggest that analysis of functionality, co-morbidities, and severity scores should be conducted to estimate the elderly mortality in relation to the admission to intensive care units.*

KEYWORDS: *Patient selection. Aged. Critical care. Hospital mortality. Intensive care units.*

INTRODUCTION

Population aging represents a challenge to healthcare systems worldwide, particularly regarding issues related to healthcare financing and professional qualification. The care for elderly patients differs from that for adult patients at all levels of medical assistance, including intensive care[1].

In 2010, the number of individuals aged 65 years or older reached 524 million people, approximately 8% of the world's population. By 2050, it is estimated that the elderly population will reach 2 billion people, that is, 22% of the world's population. In the period from 2010 to 2050, the population growth rate will be 22% for the age group between 0 and 64 years, whereas for the elderly population that rate will be 188%, reaching up to 351% in the population older than 85 years[2,3].

In Brasil, the demographic transition is occurring rapidly. While in France it took 150 years for the per-

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centage of the elderly population to double from 10% to 20%, in Brasil this phenomenon will happen only within two decades[3]. In 2014, people older than 60 years reached 13.7% of the population of Brasil[3]. The age group above 80 years old is the one that increases most in the country as its growth rate has been above 4% a year for the past two decades[4].

The mean age of the patients admitted for intensive care is also a reflection of population aging. A study of 35 intensive care units (ICUs) in the region of Paris, France, demonstrated an increase in the mean age from 52.1 to 57.1 years old between 1993 and 2004. In the past decade, the mean age of the intensive care patients increased at a rate of 6 months a year, whereas in the general population that rate was lower, only 3 months a year[5]. Recent studies have indicated that half of ICU admissions are of patients older than 65 years, with 10% older than 80 years, and 5-6% older than 85 years[5,6].

This rapid demographic transition without the due preparation of intensive care units has stimulated changes in their profile, which in turn explains the admission of elderly patients with no well-defined literature-based criteria, including the use of empirical procedures and application of protocols derived from studies, which excludes the majority of the elderly people[1].

Therefore, the objective of this study was to review systematically the influence of admission criteria on the mortality among elderly patients under intensive therapy.

METHODS

In 2015, the authors conducted a search for articles published on the PUBMED and BIREME databases using the MeSH terms "intensive care units", AND "patient admission" AND "aged" as well as DeCS terms "*terapia intensive*" AND "*idoso*" AND "*admissão de paciente*". Articles written in English, Portuguese and Spanish were searched. All the studies found in the literature had their abstracts read critically, and their references were used to search for other works, which had not been selected from the above-cited databases.

Only prospective and retrospective cohort studies using criteria for admission to intensive care units were selected; those including patients younger than 18 years old in their samples were excluded. Nevertheless, articles comparing elderly patients to subjects younger than 60 years old were evaluated. In addition, studies specifically addressing age as a unique variable for risk factor of mortality in ICU patients or assessing outcomes exclusively related to a disease or specifically related to a type of surgery were also excluded. Studies using no multivariate analysis of the results were not included either. All the studies meeting the inclusion criteria were fully read.

For evaluation of the criteria for patient admission to intensive care units, the following items were analyzed: quality of life, co-morbidities, severity scores measured at ICU admission, type of admission (surgical *versus* clinical and elective *versus* urgent/emergency patients), and comparison between institutionalized (those attending long-term care institutions for the elderly) *versus* non-institutionalized patients. In all articles published, the impact of the variables on mortality was investigated on a long-term and intra-hospital basis.

RESULTS

As observed in Figure 1, a total of 1,361 articles published in the MEDLINE and BIREME databases were selected by using the above-cited descriptors. Eighty-five publications were found to be repeated, thus totaling 1,276 studies whose abstracts were critically read. Of these, only those with prospective or retrospective cohort design and presenting a theme related to the admission criteria for intensive care were selected for review, resulting in 34 publications for full reading. In the end, thirteen studies met all the inclusion criteria described above.

All the selected studies assessed the impact of severity scores, which had been measured at admission, on the mortality in intensive care units on a long-term and intra-hospital basis. The same could not be described regarding the other variables evaluated, particularly quality of life and care for institutionalized patients, which were addressed by only one article each (Table 1). Methodological aspects of the selected publications were also listed in Table 1. A summary of the results found will be described below according to the variables analyzed.

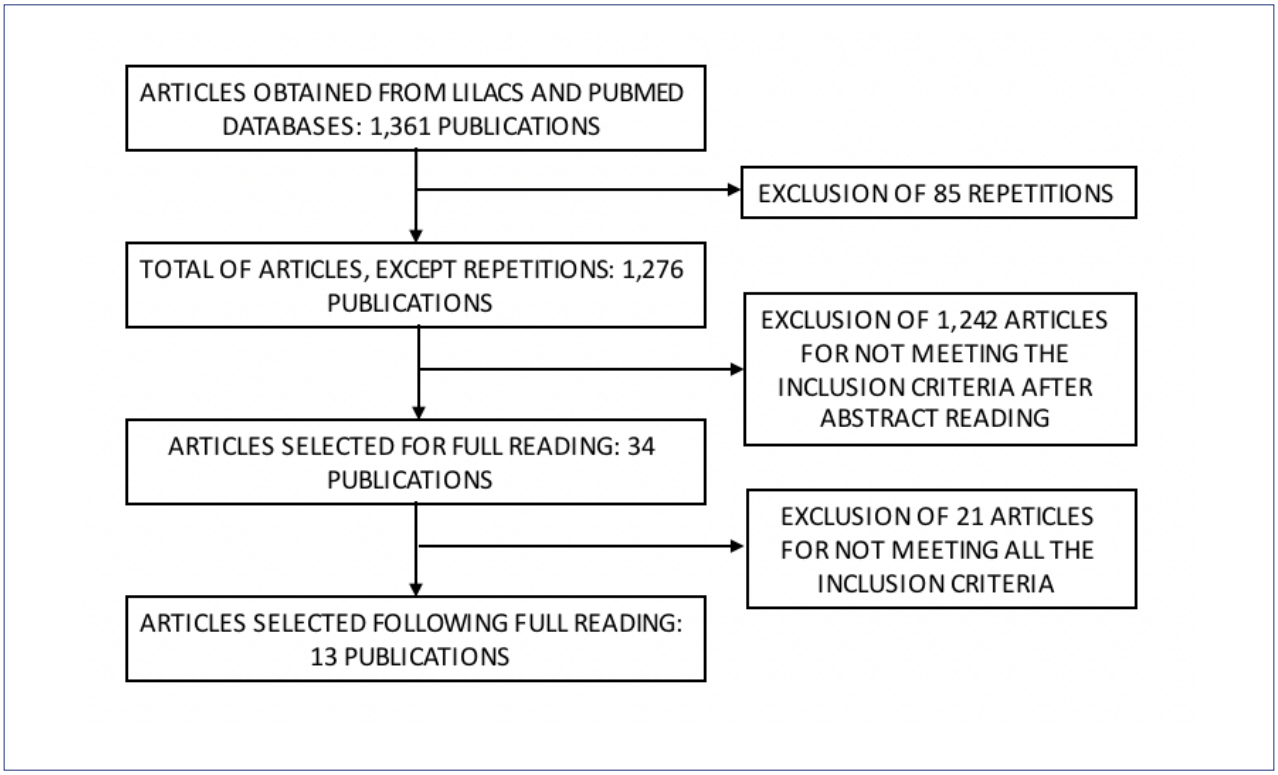
INSTITUTIONALIZATION

Only the study by Bagshaw et al.[12] evaluated the impact of patient admission to ICUs based on individuals attending long-term care institutions

TABLE 1. METHODOLOGY AND VARIABLES RELATED TO ADMISSION OF ELDERLY PATIENTS TO INTENSIVE CARE IN THE STUDIES SELECTED

	Sample number of patients	Methodology	Institutionalisation	Type of admission	Functionality	Severity Score	Comorbidities	Quality of life
Lown DJ et al.[7] (2013)	506	Retrospective Cohort				x	x	
Fuchs L et al.[8] (2012)	7265	Prospective Cohort		x		x	x	
Nasa P et al.[9] (2012)	132	Prospective Cohort				x		
Roch A et al.[10] (2011)	299	Prospective Cohort			x	x	x	
Burkmar JA & Iyengar R[11] (2011)	599	Prospective Cohort				x		
Bagshaw SM et al.[12] (2009)	15640	Retrospective Cohort	x	x		x	x	
Sacanella E et al.[13] (2009)	230	Prospective Cohort			x	x	x	x
Nannings B et al.[14] (2008)	12993	Retrospective Cohort				x		
Ryan D et al.[15] (2008)	245	Retrospective Cohort		x		x		
Brunner-Ziegler S et al.[16] (2007)	3069	Prospective Cohort				x		
Vosylius S et al.[6] (2005)	2067	Prospective Cohort		x		x	x	
Boumendil A et al.[17] (2004)	233	Prospective Cohort			x	x	x	
Mahul P et al.[18] (1991)	295	Prospective Cohort		x	x	x		

FIGURE 1. ORGANOGRAM FOR PUBLICATION SELECTION.



for the elderly. Of the 120,123 patients evaluated, 1.3% was from these institutions. Being an institutionalized individual was associated with higher intra-hospital mortality (OR 1.35; 95%CI 1.09-1.67; p=0.005) and lower survival time after discharge ($p < 0.001$)[12].

TYPE OF ADMISSION

This variable was evaluated in five publications, among which three found no association between type of admission (surgical *versus* clinical and elective *versus* urgent/emergency patients) and mortality, namely, Fuchs et al.[8], Vosylius et al.[6], and Mahul et al.[18].

Bagshaw et al.[12], however, reported that individuals older than 80 years admitted to ICUs on an emergency basis due to surgical reasons or who need hospitalization for non-surgical conditions show higher intra-hospital mortality ($p < 0.001$). Similar results were described by Ryan et al.[15], who related them to mortality among patients older than 65 years during the intensive care unit stay ($p < 0.001$).

FUNCTIONALITY

The functionality at the ICU admission was addressed by four studies, which used the Karnofsky index, Knaus classification, pre-admission health status (PHS), and Barthel and Lawton-Brody scales. Of these publications, only that by Roch et al.[10], who used multivariate analysis, found no association between functionality at ICU admission and high mortality.

Mahul et al.[18] reported an association between functional decline at admission and higher mortality within 1 year after ICU discharge ($p < 0.001$). According to Sacanella et al.[13], the Lawton-Brody scale is associated with higher cumulative mortality (intra-hospital mortality added to that after hospital discharge) in the multivariate analysis ($p = 0.047$). Boumendil et al.[17] reported an association between decline in daily-life activities (DLAs) and higher mortality after ICU discharge ($p < 0.010$), with a decrease in survival time among elderly patients from 851 to 106 days.

SEVERITY SCORE

All the articles selected assessed severity scores in elderly patients at ICU admission. In two of these studies, Burkmar & Iyengar[11] and Nannings et al.[14], the effectiveness of severity scores was assessed, whereas the other works addressed the association between results obtained and mortality.

The following scales were used by the studies reviewed: Simplified Acute Physiology Score I (SAPS I)[8,18], Simplified Acute Physiology Score II (SAPS II)[6,10,14,16,17], Acute Physiology and Chronic Health Disease Classification System II (APACHE II)[7,9,11-13,15], Acute Physiology and Chronic Health Disease Classification System III (APACHE III)[7,12], Acute Physiology and Chronic Health Disease Classification System IV (APACHE IV)[11], OMEGA Score System[13], Palliative Performance Index (PPI)[11], Sequential Organ Failure Assessment (SOFA)[6,8,13], and Patient Rule Induction Method (PRIM)[14].

Of the twelve studies assessing the above-cited scales in relation to mortality, seven showed an association with hospital and/or long-term mortality[6,8,10,12,15,16,18]. Only three studies reported no such association[7,9,17]. On the other hand, Sacanella et al.[13] demonstrated an association with higher hospital mortality and no association with cumulative mortality (intra-hospital mortality added to that after hospital discharge).

Burkmar & Iyengar[11] compared the effectiveness of APACHE IV to that of PPI in relation to the mortality. The authors reported higher sensitivity and higher negative predictive value for APACHE IV compared to PPI and when compared to the association of APACHE IV with PPI. Nannings et al.[14] used PRIM to screen subgroups of patients older than 80 years at high risk of ICU mortality, reporting effectiveness similar to that of SPAS II, although fewer data were needed and the groups were more homogeneous.

CO-MORBIDITIES

The co-morbidities were addressed by seven articles selected. The studies used the McCabe, Charlson, and Elixhauser scales to quantify the number of co-morbidities or assess them individually in the statistical analyses. Of these studies, two found no association between co-morbidities and higher mortality among elderly patients in ICUs, namely, Sacanella et al.[13] using the Charlson scale and Vosylius et al.[6] evaluating cardiac, respiratory, renal, and hepatic diseases in conjunction. Fuchs et al.[8] used the Elixhauser scale and reported that co-morbidities at ICU admission were associated with higher mortality within 28 days ($p < 0.001$) and 1 year ($p < 0.001$). Roch et al.[10] and Boumendil et al.[17], who used the McCabe scale, reported higher long-term mortality when the patient had a potentially fatal co-morbidity, with p values of 0.018 and 0.0001, respectively. Roch et al.[10] also evaluated the hospital mortality and reported a p-value < 0.001.

Lown et al.[7] studied the impact of several co-morbidities on mortality and reported that the diagnosis of coronary arterial disease changed the ICU mortality at the statistical threshold ($p = 0.055$), but without altering the long-term mortality. Bagshaw et al.[12] reported that the presence of two or more co-morbidities was associated with higher hospital mortality in individuals older than 80 years ($p = 0.001$).

QUALITY OF LIFE

A study by Sacanella et al.[13] assessed the influence of quality of life on the ICU mortality in elderly patients by using the EuroQoL-5D instrument. In multivariate analysis, the quality of life decreased at admission was found to be independently associated with higher cumulative mortality at p = 0.005[13].

DISCUSSION

The majority of the variables studied to define ICU admission criteria for elderly patients have not been extensively investigated in the literature. One can highlight that the influence of both quality of life and admission of institutionalized elderly patients were explored only in a single article despite the significant association with higher ICU mortality[12,13]. However, it is early to draw any conclusion on these topics.

The majority of articles on type of admission, namely, surgical *versus* clinical and elective *versus* urgent/emergency patients, show conflicting results and therefore, we do not recommend this type of evaluation for estimation of mortality prior to admission of elderly patients until new studies determine the effectiveness this type of analysis[6,8,12,15,18].

Functionality represents a very interesting alternative for screening ICU patients with better prognosis. The majority of the authors reported that functional decrease was significantly associated with mortality[13,17,18]. It is suggested that functionality should be evaluated by analyzing DLAs before admission to ICU.

Another relevant issue is that an association of the number of co-morbidities and their severity with mortality was observed in the majority of the studies reviewed. Therefore, it is recommended that an analysis of the co-morbidities in elderly patients should be performed as a criterion for ICU admission[7,8,10,12,17].

All the articles selected evaluated severity scores in elderly patients at ICU admission. The majority of the studies demonstrated an association of this variable with mortality, thus indicating that this score is useful for screening elderly patients for intensive care[6,10,12,13,15,16,18]. Despite the existence of several valid scales, there are few studies comparing these instruments to each other, and consequently, it is impossible to determine which is the most suitable severity score for the elderly[11,14]. SOFA is currently the most widely used and recommended instrument for assessing the severity of organ dysfunction in patients with infection, with the cut-off point of two above the patient's baseline score[19].

The present study has limitations. One of them is related to the restriction to three languages and to two databases (i.e. PUBMED and BIREME) for selection of the scientific articles, which might have reduced the number of relevant publications. Another limitation is that the variables studied were specifically assessed in relation to the mortality without analyzing the quality of life and functionality after hospital discharge, which might also have contributed to the exclusion of relevant publications.

CONCLUSION

We have concluded that the analysis of functionality and co-morbidities should be part of the evaluation of elderly patients before admission to intensive care in order to screen those individuals who can benefit from this type of assistance. The clinical severity scores should be part of this analysis. However, it is not possible to state which is the best instrument to use for the elderly. In fact, there is a lack of studies determining whether analysis of quality of life, type of admission, and patient institutionalization should be routinely performed as a criterion for ICU admission.

Conflict(s) of interest: none

RESUMO

OBJETIVO: *Revisar sistematicamente a influência dos critérios de admissão na mortalidade em pacientes idosos em terapia intensiva.*

MÉTODOS: *Realizamos uma busca nas bases de dados PubMed e Bireme, utilizando os termos MeSH e DeCS "intensive care units", "patient admission" e "aged" em português, inglês e espanhol. Somente estudos de coorte prospectivos e retrospectivos foram incluídos. Foram analisados o escore de gravidade, tipo de internação hospitalar, qualidade de vida, comorbidades, funcionalidade e institucionalização do idoso.*

RESULTADOS: *Dos 1.276 artigos encontrados, 13 foram selecionados após avaliação de seus critérios de inclusão e exclusão. Observou-se que o escore de gravidade, a funcionalidade e as comorbidades tiveram impacto na mortalidade. Não foi possível determinar qual escore de gravidade foi mais adequado.*

CONCLUSÃO: *Sugerimos que a análise da funcionalidade, de comorbidades e de escores de gravidade seja realizada para estimar a mortalidade dos idosos em relação à internação em unidades de terapia intensiva.*

PALAVRAS-CHAVE: *Seleção de pacientes. Idoso. Cuidados críticos. Mortalidade hospitalar. Unidades de terapia intensiva.*

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COMMENTARY

Comments: "The impact of intensive care admission criteria on elderly mortality"

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Cintra MTG et al.[1] study addresses a topic of importance to the association between functionality, co-morbidities, severity scores, and the estimate of elderly mortality concerning admission to intensive care units. The overall sample size is large, and the findings suggest an interesting association. However, a significant study limitation limit enthusiasm. This is well described in the discussion.

As we know, the geriatric functional scale is a self-report questionnaire for comorbidity screening. Therefore, the accuracy of diagnosis/comorbidity in this study is very doubtful.

The association between clinical data, functional decline and life-quality with social/environmental factors is an important challenge in geriatric medicine.

This study reviewed systematically the influence of admission criteria on mortality, functional decline, and life-quality among elderly patients under intensive therapy. It is important to emphasize the paradigm shift in aging populations. New research should be encouraged after this paper.

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REVIEW ARTICLE

Effect of the fatty acid composition of meals on postprandial energy expenditure: a systematic review

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SUMMARY

The energy imbalance produced by an increase in caloric intake and/or decrease in energy expenditure induces obesity. However, the fatty acid composition of a diet can affect the metabolism in different ways, having a role in the development of obesity.

AIM: *To determine the effect of different fatty acids types and composition on Diet-Induced Thermogenesis (DIT) and postprandial energy expenditure in humans.*

METHODS: *A search in the PubMed and Web of Science databases, yielded a total of 269 potential articles as a first result; 254 were excluded according to the criteria.*

RESULTS: *Fifteen articles were used for this systematic review. The studies analyzed report different effects of the fatty acids of the treatment on the diet-induced thermogenesis. Evidence indicates that the consumption of polyunsaturated fatty acids causes a greater DIT than saturated fatty acids. Also, the consumption of medium-chain fatty acids compared to long-chain fatty acids has been shown to increase DIT. Likewise, the use of certain oils has shown positive effects on postprandial energy expenditure, as is the case of olive oil, compared to rapeseed oil.*

CONCLUSIONS: *The use of specific types of fatty acids in the everyday diet can increase postprandial energy expenditure in humans. Nevertheless, longer-term studies are required.*

KEY WORDS: *Diet induced thermogenesis; thermic effect of food; fatty acids; energy expenditure; postprandial energy expenditure.*

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INTRODUCTION

The energy imbalance produced by a caloric intake increment and/or a decrease in energy expenditure induces obesity. However, the diet's fatty acid composition can affect the metabolism in different ways, playing a role in its development.[1,2]

AIM

This systematic review analyzes research performed on different fatty acids to determine their effect on Diet Induced Thermogenesis (DIT), also called Thermic Effect of Food (TEF), and energy expenditure in humans.

METHODS

For this review, the search for articles lasted four months (August to November 2017) and was conducted on the PubMed and Web of Science databases. We used the MeSH terms "Diet induced thermogenesis" AND "fatty acids" OR "fatty acid" OR "fats". Additionally, searches with the terms "Thermic effect of food" OR "Thermogenic effect of food" AND "fatty acids" OR "fats" OR "fat" were used. Article selection was performed taking into consideration the following inclusion criteria: the study needed to a) have been performed in humans, b) be original, c) have used at least one diet or food that includes fatty acids, d) report the fat composition of the diet or food used, e) have measured postprandial energy expenditure. Other characteristics used as eligibility criteria were publication date between 1997 and 2017 and in the English language.

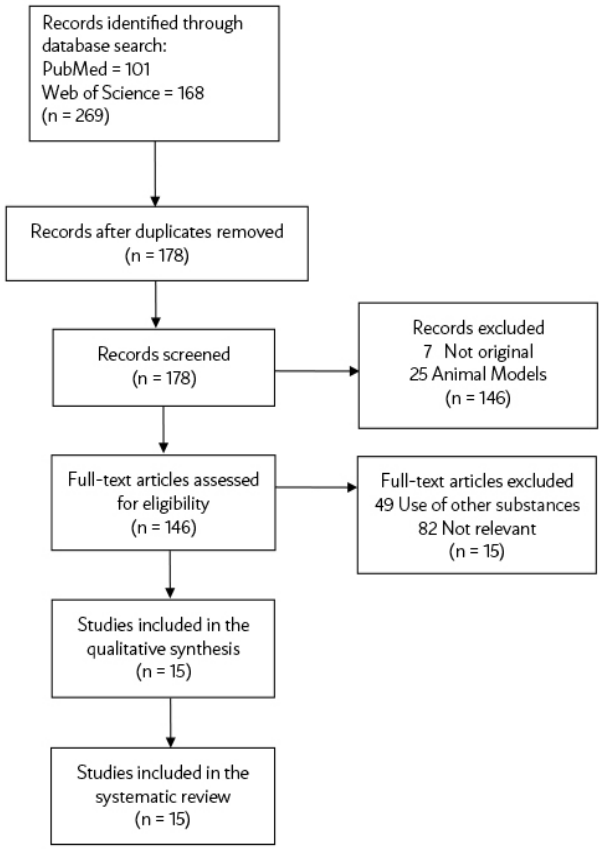
One hundred and one articles were identified in the PubMed database, of which were excluded a) 44 because they were duplicates and b) 43 for not being relevant to the topic. A total of 14 articles from this database were used. Regarding the research in the Web of Science database, from the 168 articles originally identified: a) 31 were excluded due to duplication in different searches in the database, b) 16 because they were repeated between the two databases used, c) 88 were not relevant for the subject, d) 21 were performed in animal models, and e) 7 were not original. Finally, one article from this database was used. Fifteen original articles were included in this systematic review (Figure 1). The main data of the studies can be found in the data matrix (Table 1) made using a data extraction form in duplicate. This systematic review did not require any personal information and therefore, did not require approval by the Institutional Review Board. The review protocol was made using the PRISMA reporting checklist and flowchart[3] as the basis, except for the PROSPERO registry.

RESULTS

Fifteen publications were analyzed (Table 1), seven of which were performed specifically in men,[1,4,5-9] six were carried out only with women.[2,10-14] One publication reported two experiments, one of which was made exclusively in men while the other was made exclusively in women[15] Finally, just one study included men and women.[16]

Among the eight studies that included women, it should be noted that two reported performing the interventions on days 3-9 of the participant's menstrual cycle.[2,10] In another publication, experimental sessions were described to have taken place two days in a week, with one- or two-day intervals to synchronize with either the highest or lowest temperature point in the menstrual cycle.[15] Two studies reported as

FIGURE 1. STUDY SELECTION FLOWCHART



Flow chart of the selection of papers for the systematic review of the effects of the fatty acid composition of foods on diet-induced thermogenesis and postprandial energy expenditure in humans. The papers considered not relevant did not meet any of the other inclusion criteria.

one of the participant's characteristics 28 days menstrual cycles, and interventions were made 14 days of washout apart, ensuring their participants would be in the same point of the menstrual cycle in both crossover treatments.[12,14] In one of the studies, participants were in a postmenopausal stage.[13] Finally, two of the interventions did not report controlling or recording this variable.[11,16] The study that reported the highest number of participants was performed with 71 males,[5] followed by two studies with 20 participants each.[11,16] In a decreasing order, we found one study with 19 participants,[1] two studies with 16 participants each,[10,15] and two with 15.[2,6] Among the studies with less than 15 participants, a study with 14 subjects was found,[8] as well as three with 12,[12-14] one with 11[4] and lastly, the studies with the lowest number of participants had 6 each.[7,9]

Participants ages in the different researches ranged from 18 years old for the youngest[2,10] to 73 for the oldest.[13] However, most studies had participants with an average age between 22 and 29 ranges,[2,4-6,10-12,15,16] average and standard deviation for each study are presented in Table 1.

Regarding the participant's conditions, six of the 15 publications had participants whose Body Mass Index (BMI) classified them as obese and/or overweight.[5,7,8,10,11,13] One of the studies also included among the subject's characteristics the presence of metabolic syndrome,[7] while another worked with postmenopausal participants.[13] In one of the studies, the participant's body weight was at the threshold between normal and overweight with an average BMI of 23 ± 2.6.[1] Seven of the investigations reported participants with normal BM.[2,4,6,12,14-16] Finally, one of the studies didn't report any information regarding this important variable.[9]

The studies design and length where diverse, except for two,[7,16] most studies selected for this review were randomized.[1,2,4-6,8-15] Eleven of the 15 studies had a crossover design,[1,2,4,6,9-12,14-16] two were paired comparisons,[8,13] one was a pilot study[7], and one was a one-day intervention essay.[5]

The studies were carried out in one,[5] two,[8,13,15,16] three[2,6,10] or four[4] experimental sessions, lasting from less than one day each for the shortest, to a study with a total duration of 23 weeks, which included two intervention periods of 10 weeks separated by a three-week washout for the longest.[11] Between these two extremes, we found studies with interventions of two weeks each, with an intermediate washout period of two.[1,9,12,14] Within this length of intervention periods, we can mention a pilot study that had 14 days of intervention.[7]

About the diets, eleven of the 15 studies selected indicated that participants continued with their usual diet.[1,2,5-8,10-13,15,16] At this point, it should be clarified that most of these studies carried out interventions in one or more sessions, in which the participants consumed a test food containing the fatty acids whose effects were being studied. Subsequently, measurements of postprandial energy expenditure were taken.[2,5,6,8,10,13,15,16]

In the two studies that indicated a routine diet, the supplement or food that contained the fatty acids whose effects was studied consisted either of 1,440kJ of raw unsalted almonds, [10] or 2.0 g of Eicosapentaenoic Acid (EPA) and Docosahexaenoic acid (DHA) polyunsaturated fatty acids, which should be included in said diet.[7] Three studies indicated a controlled diet.[4,12,14] In one of them a maintenance diet containing 15% proteins, 45% carbohydrates, and 40% fats was provided; 80% of the fats were part of the experimental treatment.[12] In the other, the day before each measurement, a standardized diet was provided, according to the energy requirements of each participant, with 50% of energy obtained from carbohydrates, 37% from fat and 13% from protein.[4] Finally, in the third controlled diet research, an isoenergetic diet was indicated with 40% of the energy coming from fats, 80% of which was the treatment fat.[14]

As additional information regarding the diet variable, one of the studies that indicated a routine diet provided a controlled diet during the last week of each treatment (week 10) to determine the metabolizable energy of the experimental food (1440kJ of raw unsalted almonds). However, calorimetry measurements were carried out in week one and eight, when the diet was not controlled and the routine diet was followed, with or without the almonds, according to the phase.[11] The investigation didn't specify any type of diet or dietary restriction.[9]

The treatments in six studies were described based on the saturation of the fatty acids provided.[2,7-10,13] Among them, two compared saturated fatty acids (SFA) with polyunsaturated (PUFA) and monounsaturated (MUFA) fats, using liquid isocaloric foods with an average of 735 kcal, 8 fl oz (237 ml), with 70% energy provided by fats, around 515 kcal, 40% of which (approximately 200 kcal) came from the fat used for the intervention, that is to

TABLE 1. STUDIES THAT EVALUATED THE EFFECT OF DIET'S FATTY ACID COMPOSITION ON THE THERMIC EFFECT OF FOODS.

Reference	Type of study (duration)	Groups (n)	BMI Kg/m²	Sex W/M	Age (range) years	Diet	Type and/or fatty acids amount	Intervention time before measurements	Test meal	Energy expenditure estimation method	Effect on DIT (Other variables)
Ando et al. 2016	Randomized, placebo-controlled, double-blind, crossover (2- 2w interventions, 2w wash out)	TAG (19)	23 ± 2.6	0/19	40 ± 8	Routine + TAG or ALA-DAG	5 g TAG rapeseed oil	2 w	583 kcal, 15% PS, 34% LPS, 51% CH including 5 g of TAG or ALA-DAG	Indirect calorimetry ARCO 2000	
		ALA-DAG (19)					5 g ALA-DAG				(↑* fat oxidation) (↑*PEE)
Bendixen et al. 2002	Randomized, double-blind, crossover (4separete tests for 2 to 4 w)	Conventional (11)	22.5 ± 0.6	0/11	25.1 ± 0.5	Standardized provided by the researchers	Rapeseed oil	Same day	34% CH, 60% LPS 32(91% test fat), 6% PS. Composed of bread, jam, 2 orange slices, and a chocolate drink with the test fat	Indirect calorimetry with an open-air- circuit	
		Lipase-structured (11)					Lipase-structured fat				
		Chemically-structured (11)					Chemically structured fat				↑*
		Physically-mixed (11)					Physically mixed fat: rapeseed oil and trioctanoate				
Clevenger et al. 2014	Randomized, single-blinded, cross-over (3 sessions with at least 4 d between sessions)	MUFA (15)	21.5 ± 1.9	15/0	24.5 ± 4.3 (18-35)	Routine	735 kcal 70% fat = 42% MUFA or 42% PUFA or 40% SFA	Same day	Liquid meals (735 kcal) 8 fl oz (237 ml) Ensure, soy lecithin and Nesquik, 70% fat = 42% MUFA or 42% PUFA or 40% SFA)	Indirect calorimetry ParvoMedics TrueOne 2400 Canopy System (ParvoMedics, Sandy, UT, USA)	
		PUFA (15)									↑ *
		SFA (15)									
Clevenger et al. 2015	Single-blinded randomized cross-over (3 sessions with at least 4 d between sessions)	MUFA (16)	30-40	16/0	23.6 ± 6 (18-39)	Routine	MUFA: canola and olive oil	Same day	Liquid meals (735 kcal) 8 fl oz (237 ml) Ensure®, soy lecithin and Nesquik®, 70% fat = 42% MUFA or 42% PUFA or 40% SFA)	Indirect calorimetry ParvoMedics True-One® 2400 Canopy System (ParvoMedics, Sandy, UT)	NS
		PUFA (16)					PUFA: sunflower and linen oil				
		SFA (16)					SFA: butter, palm, and coconut oil				
Duarte Moreira Alves et al. 2014	Randomized trial (One-day)	Control (CT) (24)	(26 to 35) 29.8 ± 0.3	0/71	27.1 ± 0.9	Routine	Control biscuits	Same day	56 g of peanuts, CVP or HOP	Indirect calorimetry: Deltatrac II, MBM-200; Datex Instrumentarium Corporation	
		Conventional peanuts (CVP) (23)					56 g of CVP				
		High-oleic peanuts (HOP) (24)					56 g of HOP				↑* (↑*PEE VS CVP)

Reference	Type of study (duration)	Groups (n)	BMI Kg/m²	Sex W/M	Age (range) years	Diet	Type and/or fatty acids amount	Intervention time before measurements	Test meal	Energy expenditure estimation method	Effect on DIT (Other variables)
Hollis & Mattes 2007	Randomized cross-over (2-10 w interventions, 3 w wash out)	Control (20)	23 – 30	20/0	24 ± 9		Routine Routine diet	10 w	1672kJ portion of almonds and 250 ml of water within a 15 min period	Indirect calorimetry SensorMedics Vmax 29 n metabolic cart (SensorMedics, Anaheim, CA, USA)	NS
		Almond (20)					Habitual diet + 1440kJ portion of raw, unsalted almonds each day				
Jones et al. 2008	Randomized crossover design (3-1 d sessions)	Olive oil (15)	23 ± 1.9 (20 - 25)	0/15	28.6 ± 6.2	Routine	Olive oil rich in oleic acid (18:1n-9)	Same day	Identical in composition except for the type of oil. 60% LPS, 30% CH, and 10% PS	Indirect calorimetry (Deltatrac Metabolic Monitor) (Sensormedics, Anaheim, CA)	(↑* EE VS flaxseed oil) (↑ EE VS sunflower oil)
		Sunflower oil (15)					Sunflower oil rich in linoleic acid (18:2n-6)				(↑ EE VS flaxseed oil)
		Flaxseed oil (15)					Flaxseed oil rich in linolenic acid (18:3n-3)				
Kasai et al. 2002	Double-blind, crossover (Study 1: 3 d at 1 or 2 d intervals. Study 2: 2 d in a week at 1 or 2 d intervals)	10M (8)	Males: 22.7± 0.8	0/8	Males: 26.8 ± 0.7	Routine	10 g MCT	Same day	Liquid meal containing 10 g MCT or 5 g MCT and 5 g LCT or 10 g LCT	Aeromonitor AE-300S (Minato Medical Science, Osaka, Japan)	↑ ** VS 10L
		5M5L (8)					Mixture: 5 g MCT and 5 g LCT				↑ * VS 10L
		10L (8)					10 g LCT				
		Mayonnaise (7)	Females: 18.8 ± 0.4	8/0	Females: 28.1 ± 1.4		5 g of MCT		Sandwich with mayonnaise or clear soup with margarine		↑ * VS LCT
		Margarine (8)					5 g of LCT				
Matheson et al. 2011	Pilot study (2 w)	Intervention group (6)	37.2 ± 5.60 obese	0/6	46.7 ± 12.1	Routine + 2 g per day of EPA and DHA	2.0 g per day of n-3 PUFA	2 w	250 mL of Break-free Omega-3 eggs, 200 g of strawberry yogurt, 1 Cali-Wrap tortilla, and 250 mL orange juice	Indirect calorimetry (MAX II Metabolic System, AEI Technologies, Napierville, IL)	↑ *
Ogawa et al. 2007	Double-blind cross-over (2 experimental sessions separated by 2 days or more)	LCT (20)	21.7 ± 0.3	11/9	24.0 ± 0.9	Routine	14 g of Long-chain Triacylglycerols	Same day	Liquid meal 500 Kcal 14.8% PS, 25.2% GS, 60% CH. Including 14 g of LCT or MLCT	(Innovision A/S, Denmark)	
		MLCT (20)					14 g of Medium- and Long Chain Triacylglycerols				↑ *
Papamandjaris et al. 1999	Randomized cross-over (2- 2 w feeding periods separated by a 2 w washout)	MCT (12)	21.5 ± 0.8	12/0	22.7 ± 0.7	WM diet: 15% Ps, 45% Ch, and 40% fat, 80% of which was treatment fat	26%(MCFA) and 74% (LCFA)	Day 7 and 14	Scheduled breakfast	RGE (Deltatrac Metabolic monitor, Sensormedics, Anaheim, California, USA)	NS
		LCT (12)					2% MCFA and 98% LCFA				

Reference	Type of study (duration)	Groups (n)	BMI Kg/m²	Sex W/M	Age (range) years	Diet	Type and/or fatty acids amount	Intervention time before measurements	Test meal	Energy expenditure estimation method	Effect on DIT (Other variables)
Piers et al. 2002	Randomized, paired comparison (2 intervention sessions separated by 1-2 w)	SFA (14)	27.8 ± 3.2 (21.1 – 32.0)	0/14	38 ± 9 (24–49)	Routine	SFA breakfast: 92 g of muesli, 57 g of cream and 275 g of skim milk	Same day	SFA breakfast: 92 g of muesli, 57 g of cream and 275 g of skim milk	Indirect calorimetry Deltatrac II metabolic monitor (Datex, Finland)	
		MUFA (14)					MUFA breakfast: 285 g of skim milk and 96 g of baked muesli with 20 g of EVOO		MUFA breakfast: 285 g of skim milk and 96 g of baked muesli with 20 g of EVOO		↑ * in subjects HWC ≥ 99 cm
Soares et al. 2004	Single-blinded, randomized, paired comparison (2 trials, 1 to 4w interval between them)	Cream (12)	21·9–38·3	12/0	64 ± 4.5 (57–73)	Routine	65 g natural Swiss muesli, 40 g thickened cream and 188 g skimmed milk	Same day	65 g natural Swiss muesli, 40 g thickened cream and 188 g skimmed milk	Indirect calorimetry Vmax-29 metabolic monitor (Sensor Medics)	NS
		Extra virgin olive oil (12)					66 g and 195 g of the same brand of muesli and skimmed milk, 15 g Extra virgin olive oil		66 g and 195 g of the same brand of muesli and skimmed milk, 15 g Extra virgin olive oil		
Van Marken Lichtenbelt et al. 1997	Randomized crossover (2-2w intervention, 2 w wash out)	High P/S ratio (6)	NE	0/6	25-48	NE	P/S ratio 1.67	2 w	46% LPS, 37% CH, 17% PS	Indirect calorimetry (ventilated hood)	↑ *
		Low P/S ratio (6)					P/S ratio 0.19				
White et al. 1999	Single-blinded randomized crossover (2-2w intervention, 2 w wash out)	MCT-enriched diet (12)	21.4 ± 2.0	12/0	22.8 ± 2.2	Isoenergetic diets 40% of energy as fat (80% of which was the treatment fat)	MCT-enriched diet 80% of the diet's fat	7 and 14 d	Standardized breakfast	Indirect calorimetry Deltatrac metabolic monitor (Sensormedics, Anaheim, CA)	(↑*BMR) (↑*TEE day 7) (↑TEE day 14)
		LCT-enriched diets (12)					LCT-enriched diet 80% of the diet's fat	7 and 14 d			

ABBREVIATIONS:
* Statistically significant differences between groups (p<0,05)
** Statistically significant differences between groups (p<0,01)
10M: 10 g MCT
5M5L: 5 g MCT and 5 g LCT
10L: 10 g LCT
ALA-DAG: Alpha Linolenic Acid-enriched Diacylglycerol
BMI: Body Mass Index
BMR: Basal Metabolic Rate
CH: Carbohydrates
cm: Centimeters
CT: Control
CVP: Conventional Peanuts
d: days
DHA: Docosahexaenoic acid
DIT: Diet-Induced Thermogenesis
EE: Energy expenditure
EVOO: Extra Virgin Olive Oil
EPA: Eicosapentaenoic Acid
fl oz: Fluid ounces
g: Grams
HOP: High oleic Peanuts
h: Hours
HWC: High Waist Circumference
kJ: Kilojoules
kg: Kilograms
LCFA: Long Chain Fatty Acids
LCT: Long-Chain Triacylglycerols
LPS: Lipids
M: Men
m: Meter
min: minute
ml: Milliliters
MCFA: Medium Chain Fatty Acids
MCT: Medium Chain Triacylglycerols
MUFA: Monounsaturated Fatty Acids
NS: Non-Significant
NE: Not specified
PEE: Postprandial Energy Expenditure
P/S: Polyunsaturated/Saturated
PS: Proteins;
PUFA: Polyunsaturated Fatty Acids
SCFA: Short Chain Fatty Acids
SFA: Saturated fatty acids
TAG: triacylglycerol
TEE: Total energy expenditure
VS: versus
w: weeks
W: Women
WM: Weight maintenance

say saturated (from butter, palm and coconut oils), monounsaturated (canola and olive oils) or polyunsaturated (sunflower and linen oils). The food was composed of chocolate flavored Ensure®, soy lecithin, Nesquick®, and the treatment fat, in a crossover with three sessions of one day each.[2,10] Two studies compared only two fatty acid types: saturated and monounsaturated.[8,13] In the first, the test breakfast was high in saturated fat and consisted of 92 g of muesli, 57 g of cream and 275 g of skimmed milk, while the high-monounsaturated fat treatment consisted of 285 g of skimmed milk and 96 g of baked muesli with 20 g of extra virgin olive oil in two intervention sessions.[8] In the other study, the first group's breakfast consisted of 65 g of muesli, 40 grams of cream and 188 g of skimmed milk, while the other contained 66 and 195 g of muesli and skim milk respectively and 15 g of extra virgin olive oil.[13] There was another study that followed this same type of intervention, in which the effects of two diets with different proportions of polyunsaturated/saturated fatty acids, 1.67 and 0.19 respectively, were compared.[9] This research did not specify the composition of the two-week crossover treatments and only mentions that the meal previous to the postprandial energy expenditure determination had the same fatty acid composition as the diet, and the energy came 46% from fat, 37% from carbohydrates and 17% from proteins without further details.[9]

Finally, we also found a pilot study[7] in which two grams of polyunsaturated omega-3 fatty acids (Eicosapentaenoic acid, EPA; and docosahexaenoic acid, DHA) were added daily to the participant's usual diet, for two weeks.

In four publications,[12,14-16] treatments were described according to the provided fatty acid chains length, comparing the effects of short-, (SCFA) medium- (MCFA) or long-chain (LCFA) fatty acids. Specifically, there was one that presented two experiments[15]; in the first they analyzed the effects of providing three different treatments: 10 g of LCFA, 10 g of MCFA or a mixture of 5 g of MCFA and 5 g of LCFA, in a liquid food with an average of 246 kcal coming from 21% proteins, 36% fats and 43% carbohydrates. In the second experiment, the effects of providing 5 g of MCFA or 5 g of LCFA using a clear soup and a sandwich with mayonnaise or margarine as food, were compared. Mayonnaise contained vegetable oils, vinegar, starch, mustard, sucrose and no eggs. The margarine contained hydrogenated fats, powder skimmed milk and salt. The sandwich included bread, lettuce and tomato. The meal's energy with 5 g of LCFA and 5 g of MCFA was 253 and 249 kcal/test respectively, for mayonnaise, 244 and 240 kcal/test for margarine with the energy coming 10% from protein, 40% from fats and 50% from carbohydrates for both. In turn, a liquid food was used[16] with 500 kcal obtained 14.8% from protein, 25.2% from fat and 60% from carbohydrate, which included 14 g of LCFA from rapeseed oil, or the same amount of a combination of LCFA and MCFA. Another investigation[12] compared the effects of two MCFA and LCFA proportions, in maintenance diets whose energy came from 15% protein, 45% carbohydrate and 40% fat, 80% of which was the treatment's fat, which included 26% MCFA and 74% LCFA in one treatment, or 2% MCFA and 98% LCFA in the other. Finally, one research[14] compared the effects of isoenergetic diets in which 40% of the energy came from fats, 80% of which was the test's fat, represented by medium-chain triacylglycerols (MCTs) in one treatment, or long-chain triacylglycerols (LCTs) in the other. These fats came from butter and coconut oil, or beef tallow respectively, in a crossover with two intervention periods of two weeks each.

In addition, two of the investigations studied the effect of specific foods.[5,11] In the first one, the effect of three foods was compared: 56 g of conventional peanuts, 56 g of peanuts with high oleic content, and biscuits as control.[5] In the second, the effect of adding 1,440 kJ of raw unsalted almonds to the participant's usual diet was evaluated in a crossover with two 10 weeks interventions.[11] Lastly, three studies evaluated the effects of providing specific oils.[1,4,6] The first, compared the effects of providing 5 g of alpha-linolenic acid-enriched diacylglycerol, ALA-DAG, or 5 g of triacylglycerol, TAG, from rapeseed oil ingested daily for two weeks.[1] In the second one,[4] the effect of a conventional fat composed of rapeseed oil and three modified fats was studied in four sessions: lipase structured fat, chemically structured fat, and physically mixed fat. Fats were provided at a pre-measurement breakfast containing 4,698 ± 174 kJ, 34% from carbohydrate, 60% fat, 91% of which were the experimental fat, and 6% protein. The test meal consisted of bread, ham, two slices of orange and a chocolate drink containing the test fat; in this investigation, the diet on the previous day was controlled.[4] The third study[6] analyzed the effect of a breakfast with 60% (50.4 g on average) of the

energy from 3 sources of fat: oleic acid-rich olive oil (18: 1n-9), linoleic acid-rich sunflower oil (18: 2n-6), and linolenic acid-rich rapeseed oil (18: 3n-3).

The differences between the treatments were found to be statistically significant only in nine of the 15 publications analyzed.[1,2,4-7,9,15,16] When analyzing these differences in depth according to the type of fatty acids provided, three of the publications described a DIT increment with the use of polyunsaturated fatty acids.[2,7,9] The first[2] described greater DIT with a liquid food with PUFA added in comparison with the MUFA or SFA addition; in these, the fatty acids contributed approximately 200 kcal. The second[7] described an increase in the Thermic Effect of Foods (TEF) after two weeks of adding 2.0 g a day of PUFA n-3 (EPA and DHA) to the participant's usual diet, compared to the values before the intervention. The third[9] reported an increase in the basal metabolic rate and DIT as an effect of two weeks with a diet high in a polyunsaturated/saturated ratio.

Considering the classification of fatty acids according to chain length, we found two publications that reported a greater DIT as a result of the use of MCFA.[15,16] One[15] reported a greater DIT with the use of foods with 10 g of added MCFA or with a combination of 5 g of MCFA and 5 g of LCFA, compared to the use of 10 g of LCFA. Additionally, in their second experiment, they reported a higher DIT with the use of mayonnaise or margarine containing 5 g of MCFA compared to the addition of 5 g of LCFA.[15] The other investigation[16] described a higher DIT with the use of medium- and long-chain triacylglycerols (MLCT) when compared to the use of long-chain triacylglycerols (LCT).

Finally, among the investigations that reported the use of specific foods or oils, four reported statistically significant differences.[1,4-6] They found greater postprandial fat oxidation and higher postprandial energy expenditure with the use of ALA-DAG compared to TAG.[1] Another research[4] reported higher postprandial oxidation and higher postprandial energy expenditure with the three modified fats, compared to the effect of conventional fat or rapeseed oil. Other study[6] found an increase in postprandial energy expenditure with the use of oleic acid-rich olive oil (18: 1n-9), when compared with linolenic acid-rich rapeseed oil, (18: 3n-3) or with linolenic acid rich sunflower oil (18: 2n-6). Finally, greater thermogenesis was observed induced by diet and higher postprandial energy expenditure with the consumption of 56 g of oleic rich peanuts, in comparison with the consumption of conventional peanuts.[5]

Although the rest of the investigations did not report significant differences between the treatments, two of them[8,14] found differences in subgroups, depending on specific characteristics of the participants or moments of the investigation. In one case,[8] significant differences were found when comparing treatments consisting of breakfast with MUFA or SFA, with a greater TEF with the MUFA in subjects with larger waist circumference (≥ 99 cm). In the other investigation,[14] they found significantly higher total energy expenditure and basal metabolic rate with the use of medium-chain triacylglycerols (MCT) compared to long-chain triacylglycerols at the midpoint of a 14-day treatment, on day seven, and although at the end of the treatment they also described a greater total energy expenditure, this was not significant.

Despite the fact that one of the studies found no significant differences between the groups,[11] these researchers emphasized that their treatment, the addition of 1,440 KJ of almonds to the participant's habitual diet, did not modify body weight after 10 weeks, suggesting that this food and dose does not represent a risk of weight gain.

Quantitative data from the TEF or DIT records are omitted because not all studies reported it as an absolute value. Some present figures in which the difference or change is represented, reporting the statistical significance of the finding without specifying the values.[6] Among the authors who present quantitative data, this is measured in different periods and expressed with different units, even as a percentage of change or difference. So, as an example, we have those who present their quantitative data of DIT as Cal/kg[15], kcal per minute[7], kcal * 5 h[10], kJ/5h[8] and kcal/6h[16]. Units like Kcal/day[12,13] and kJ/min[9,14] are also used. This means that the DIT numerical data is not comparable and representing it in the manuscript could represent a source of confusion.

DISCUSSION

The studies selected for this systematic review stand out for their differences. We found various fatty acids proportions, types, and even classifications. In addition, the conditions of the participants, the diets,

designs, and lengths also differ. More research is required, for longer periods and with greater control and number of participants in order to reproduce, quantify, and predict the effects of different fatty acids types and proportions in the diet.

It is noteworthy that while some studies show different effects in single-session tests with the treatment,[2,4,6,8,15,16] others show significant effects in periods of seven days, which then lose significance when prolonging treatment to 14 days,[14] while others show significant differences in treatments of 14 days.[1,7,9] Taking into account that the effect may diminish or be lost over time, it is advisable to carry out more research with intervention periods longer than two weeks.

Another aspect of great importance is the high percentage of energy that comes from fats in the test meals, which differs in the studies from 34%,[1] 36 and 40%,[15] 46%,[9] 60%[4,6] and up to 70%.[2,10] In other cases, it was not the test meal, but the diet that provided participants a percentage of energy from fats higher than recommended.[12,14]

Tendencies indicate an increase of the DIT with the use of polyunsaturated fatty acids in comparison with saturated or monounsaturated.[2,7,9] This effect was also observed with the use of MCFA, which can lead to greater postprandial energy expenditure than LCF.[15,16] Regarding the use of specific oils in an analogous way, it is worth mentioning the greater DIT caused by the consumption of foods containing olive oil, instead of sunflower oils, rapeseed, as well as the use of cream or saturated fatty acids foods.[6]

Regarding the selection bias, of the 15 studies selected, 12 were randomized, although the method used to generate the allocation sequence was not described. In the remaining publications, one was a pilot study[7] with only one intervention group, so there was no randomization. Another publication[15] included two experiments and described the random assignment in the first but did not mention this aspect in the second. The remaining study[16] does not mention this characteristic.

Additionally, regarding the performance bias, it should be mentioned that in most studies[1,2,4-10,12-16] the participants had no knowledge of the assigned intervention, that is, the type or percentage of fatty acid in the meals, the exception was a study where almonds were provided to the participants as treatment.[11]

When analyzing the results of each study, regarding the detection bias, the totality does not specify whether the evaluators were aware of the intervention applied to each participant when carrying out energy expenditure measurements. However, these measurements were made in the participants of each study with the appropriate equipment, in the same conditions and for the same periods of time.[1,2,4-16]

CONCLUSIONS

Studies on the effect of different fatty acids in the diet have been varied, using different proportions, types, classifications, and doses. Additionally, the participant's characteristics, including their sex, age, health conditions, body weight, and others, have also been diverse. Although more research, in particular for longer periods, is still required regarding the effects of different types and percentages of fatty acids on the basal metabolic rate, thermogenesis induced by diet, and energy expenditure, some effects are starting to stand out, showing potential lines of research. Greater postprandial energy expenditure is described; specifically, greater diet-induced thermogenesis with the intake of polyunsaturated fatty acids in comparison with the saturated fatty acids. Greater DIT has also been documented with the use of MCFA compared to LCFA. Finally, the beneficial effect of extra virgin olive oil on the metabolism is highlighted, causing a higher DIT than other oils such as sunflower and rapeseed oil.

Authors Contribution

LCVC, AGMM, ALP, and ACEG contributed equally to the development of the systematic review protocol. LCVC and AGMM conducted the search and identified papers for inclusion, with ALP providing advice and expert opinion in this stage. LCVC and ACEG conducted the data extraction, with AGMM providing advice and expert opinion in this stage. This paper was translated by ACEG. LCVC, AGMM, ALP, and ACEG all contributed equally to the development of the manuscript.

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Conflict of Interest

The authors have no conflicts of interest to declare.

RESUMO

O desequilíbrio energético produzido pelo aumento da ingestão calórica e/ou diminuição do gasto energético provoca obesidade. Sem embargo, a composição de ácidos graxos da dieta pode afetar diferencialmente o metabolismo, tendo um papel no desenvolvimento da obesidade.

OBJETIVO: *Determinar os efeitos de diferentes tipos de ácidos graxos e sua composição na termogênese induzida por dieta e no gasto energético pós-prandial em humanos.*

MÉTODOS: *Uma busca nas bases de dados da PubMed e da Web of Science gerou um total de 269 artigos potenciais como primeiro resultado; 254 foram excluídos de acordo com os critérios.*

RESULTADOS: *Quinze artigos foram utilizados para esta revisão sistemática. Os estudos analisados informam os efeitos diferenciais dos ácidos graxos no tratamento da termogênese induzida pela dieta. As evidências indicam que o consumo dos ácidos graxos poli-insaturados ocasiona maior DIT que os ácidos graxos saturados. Além disso, demonstra-se que o consumo dos ácidos graxos da cadeia média, em comparação com os ácidos graxos da cadeia longa, aumenta o DIT. Do mesmo modo, o uso de certos azeites demonstra os efeitos positivos sobre o gasto de energia pós-prandial, como é o caso do azeite de oliva, em comparação com o azeite de colza.*

CONCLUSÃO: *O uso de tipos específicos de ácidos graxos na dieta habitual pode aumentar o gasto de energia pós-prandial nos seres humanos. Sem embargo, é necessária maior investigação no longo prazo.*

PALAVRAS-CHAVE: *Termogênese induzida pela dieta. Efeito térmico dos alimentos. Ácidos graxos. Gasto de energia. Gasto da energia pós-prandial.*

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Erratum

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