Universidade Federal do Rio Grande Do Sul

Faculdade de Medicina

Graduação em Nutrição

Audrey Machado dos Reis

Custo-benefício da Imunonutrição Perioperatória em Cirurgia Oncológica do Trato Gastrointestinal: Uma Revisão Sistemática

Porto Alegre, 2014

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Trabalho de conclusão de curso de graduação apresentado como requisito parcial para obtenção do grau de Bacharel em Nutrição, à Universidade Federal do Rio Grande do Sul, Departamento de Nutrição.

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A Comissão Examinadora, abaixo assinada, aprova o Trabalho de Conclusão de Curso intitulado **"Custo-benefício da imunonutrição perioperatória em cirurgia oncológica do trato gastrointestinal"**, elaborado por Audrey Machado dos Reis, como requisito parcial para obtenção do grau de Bacharel em Nutrição.

Comissão Examinadora

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Orientador - Prof. Luis Fernando Moreira, MD - UFRGS

Dedico este trabalho ao meu avô, Molisson Machado, que bravamente lutou contra o câncer (*in memoriam).*

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RESUMO

Introdução: Custos, tempo de hospitalização e morbidade estão frequentemente aumentados na presença de infecções e outras complicações decorrentes do câncer de cabeça, pescoço e trato gastrointestinal. Recentemente, a melhora de mecanismos de defesa do hospedeiro tem se tornado um alvo de interesse. Nutrição adequada está fortemente relacionada com a melhora da imunidade e redução de infeções. Imunonutrição tem como objetivo a melhora da imunidade, principalmente para manutenção de linfócitos-T e outras defesas. **Objetivo:** Revisar imunonutrição em pacientes oncológicos submetidos a cirurgias de trato gastrointestinal e avaliar o custo-benefício desta suplementação. **Métodos:** Este estudo consiste em uma revisão sistemática da literatura baseada em referências encontradas em base de dados, como PubMed, *LILACS* e SCIELO. Para análise de custos, moedas locais usadas nos artigos foram convertidas em Dólar Americano. **Resultados e Discussão:** Seis estudos randomizados prospectivos foram incluídos nesta Revisão. Todos os artigos encontraram redução de complicações entre grupos controles e os grupos suplementados. Duas mortes ocorreram em um grupo suplementado devido à Síndrome da Resposta Inflamatória Sistêmica. Todos os estudos que analisaram internação hospitalar demonstraram que pacientes do grupo intervenção permaneceram por um tempo mais curto no hospital. O tempo de hospitalização e a redução de complicações podem causar uma diminuição no custo total gerado pelo paciente. Em relação às análises econômicas, algumas limitações podem influenciar na reprodutibilidade: alguns artigos antigos estavam economicamente ultrapassados, e, além disso, alguns artigos não informavam a data em que a pesquisa foi realizada. Ainda, parâmetros econômicos podem ser diferentes entre países, devido ao tipo de sistema de saúde e taxas de reembolso que eles possuem. **Conclusão:** O custo-benefício foi positivo na maioria dos estudos, sugerindo que este tipo de dieta pode ser rentável. Contudo, os resultados não podem ser ampliados para outras regiões devido a particularidades existentes.

Palavras-chave: Imunonutrição, cirurgia oncológica gastrointestinal, custo-benefício.

ABSTRACT

Introduction: Costs, length hospital staying and morbidity are frequently and significantly increased as a result of infections and other complications following gastrointestinal tract and head and neck cancer. Recently, improving host defence mechanisms have become a target of interest. Immunonutrition aiming to improve immunity, most likely providing key nutrients that maintain T-lymphocyte and other host defence. **Objective:** The aim of this study is to review immunonutrition for oncologic patients who are undergoing surgery for gastrointestinal tract and to evaluate the cost-effectiveness of this supplementation. **Methods:** The study consisted of a systematic review of the literature based on reference analyses found in current databases such as PubMed, *LILACS* e SCIELO. For cost analyses, currencies used in the papers needed to be converting to American dollar in order to uniform and facilitate comparison. **Results and Discussion**: Six prospective randomized studies were included in this review. Overall, the articles found a reduction of complications between control group and groups that received some type of immunonutrient. Two deaths occurred in a treatment group because of systemic inflammatory response syndrome. All the studies that analysed length hospital staying found that treated patient groups had a shorter hospital admission. The length hospital staying and complication reduction can cause a less value of total patient expense. For economic analyses, some limitations may influence the reproducibility, since old articles can be economically outdate, and especially considering that some articles have not the research date informed. Besides that, economic parameters used may differ from country to country based on the type of health care system and reimbursement rates they have. **Conclusion:** The cost-effectiveness was positive in most of studies, leading that this diet type can be profitable. However, results cannot be extended to any region due to the particularities existents.

Keywords: Immunonutrition, oncologic gastrointestinal surgery, cost-effectiveness.

LISTA DE ABREVIATURAS

INCA – Instituto Nacional do Câncer

OMS – Organização Mundial da Saúde

VA TPN COOPERATIVE STUDY GROUP - Veterans Affairs Total Parenteral Nutrition Cooperative Study Group

ω-3 – Ácidos Graxos Ômega-3

ω-6 – Ácidos Graxos Ômega-6

SUMÁRIO

1. REFERENCIAL TEÓRICO

1.1 EPIDEMIOLOGIA DO CÂNCER

Câncer é um termo genérico para um grande grupo de doenças que podem afetar qualquer parte do corpo. Uma característica que define o câncer é a rápida proliferação de células anormais que crescem além dos limites normais. O câncer surge de uma única célula, cuja transformação envolve um processo com múltiplos estágios responsáveis pela progressão de uma lesão pré-cancerosa para tumores malignos. Esta progressão é resultado da interação entre fatores genéticos individuais e agentes externos, como - carcinógenos físicos (radiação ultravioleta e ionizante, por exemplo), químicos (arsênico, asbesto e aflatoxinas) e biológicos (infecções decorrentes de vírus, bactérias e parasitos) (OMS, 2014).

O câncer é uma das principais causas de morte em todo mundo (INCA, 2014). Em 2012, houve 14.1 milhões de novos casos de câncer no mundo, 8.2 milhões de mortes e 32.6 milhões de pessoas com diagnóstico de câncer (diagnóstico de no mínimo cinco anos). Nos países menos desenvolvidos, observaram-se oito milhões de novos casos, 5.3 milhões de mortes por câncer e 15.6 milhões de pessoas com cinco anos ou mais de diagnóstico (GLOBOCAN, 2012).

A taxa global de incidência de câncer é quase 25% maior em homens (205 por 100.000 habitantes) que em mulheres (165 por 100.00 habitantes). As taxas de incidência no sexo masculino podem variar quase cinco vezes entre as diferentes regiões do mundo, como é o caso da África Ocidental (79 para 100.000 habitantes) e Austrália/Nova Zelândia (365 para 100.000 habitantes). Em relação às mulheres, se percebe uma menor variação (quase três vezes), com taxas variando de 103 por 100.00 habitantes na África Ocidental e 295 por 100.000 habitantes na América do Norte.

Em 2030 estima-se que o total de novos casos de câncer será de 21.4 milhões, além de 13.2 milhões de mortes pela doença devido ao crescimento e envelhecimento da população, assim como houve redução de mortalidade infantil e redução de mortes por doenças infeciosas em países desenvolvidos (GLOBOCAN, 2012).

No Brasil, o número estimado de novos casos de câncer para 2013/2014 é de aproximadamente 576 mil, incluindo os casos de pele não melanoma, que é o tipo mais incidente para ambos os sexos, seguido de próstata, mama feminina, cólon e reto, pulmão, estômago e colo do útero (INCA, 2014).

1.2 CÂNCER GASTROINTESTINAL

O câncer colorretal é o terceiro tipo mais comum em homens (746.000 casos, representando 10% do total) e o segundo mais comum em mulheres (614.000 casos, representando 9.2% do total). A mortalidade é baixa (694.000 mortes, 8,5% do total), sendo maior número de mortes (52%) em regiões menos desenvolvidas do mundo, refletindo a pior sobrevivência nestas regiões (GLOBOCAN, 2012).

Já o câncer esofágico é o terceiro mais comum no mundo. O câncer de esôfago apresenta baixa taxa de sobrevivência (risco absoluto de mortalidade para incidência de 0,88). Observa-se que a mortalidade acompanha os padrões geográficos de incidência, com as maiores taxas de mortalidade ocorrendo no leste da Ásia e do sul da África em homens e na África Oriental e Austral em mulheres (GLOBOCAN, 2012).

Câncer de estômago lidera a terceira causa de morte em ambos os sexos em todo mundo (723.000 mortes, 8,8% do total). As maiores taxas de mortalidade estimadas são na Ásia Oriental e, a mais baixa, na América do Norte. Porém, altas taxas de mortalidade também estão presentes em ambos os sexos, na Europa Central e Oriental, e na América do Sul e Central (GLOBOCAN, 2012).

No Brasil, estima-se que o câncer colorretal é o quarto câncer com o maior índice em 2014, com 32.600 novos casos. Os tumores gástricos aparecem em terceiro lugar para o sexo masculino e quinto lugar para o sexo feminino. Em relação ao câncer esofágico, este é sexto mais incidente entre os homens e apenas o 15º entre as mulheres, excluindo o câncer não melanoma da análise (INCA, 2014).

1.3 CIRURGIA DE CÂNCER GASTROINTESTINAL

Câncer, quando em estágios iniciais, pode ser controlado e/ou curado através de tratamento cirúrgico, quando este for o tratamento indicado.

O tratamento cirúrgico pode ser utilizado para um propósito curativo ou paliativo. A cirurgia curativa é considerada indicada em casos de tumores mais sólidos. Trata-se de um tratamento radical, não apenas o tumor primário é removido, mas também é removida a margem de segurança e, se indicado, também podem ser removidos linfonodos de cadeias de drenagem linfática do órgão que abriga o tumor primário. A cirurgia utilizada como tratamento paliativo tem como objetivo reduzir a população de células tumorosas ou controlar os sintomas que ameacem a vida ou comprometam sua qualidade (INCA, 2014).

As taxas de complicações no pós-operatório de cirurgias para câncer gastrointestinal podem variar de 15% a 54% (WAITZBERG *et al*., 2006; MARIMUTHU *et al.*, 2012), com complicações infecciosas sendo as mais frequentes: infecções de feridas, abcesso abdominal, pneumonia, deiscência de anastomose, infecção de trato urinário e sepse (STEINER; ELIXHAUSER; SCHNAIER, 2002). Podem ocorrer outros tipos de complicações, como: fístulas, insuficiência renal aguda e eventos cardiovasculares (BRAGA *et al*, 2005; PROCTER *et al*, 2010).

As complicações decorrentes deste tipo de cirurgia são ainda uma importante questão, pois apresentam um impacto significativo na recuperação dos pacientes, tempos de hospitalização e custos (BRAGA *et al*, 2005; PROCTER *et al*, 2010).

Recentemente, estudos estão sendo voltados para prevenção de complicações relacionadas com cirurgia, bem como pesquisas contínuas para tratamentos rentáveis têm sido fortemente recomendável (DAVEY; NATHWANI, 1998; BURNIE, 1999; BADIA; BROSA; TELLADO, 1999).

Políticas para prevenção e redução destas complicações geralmente focam na erradicação do patógeno; por exemplo, profilaxia com uso de antibióticos perioperatórios, a redução do trauma cirúrgico e contaminação intraoperatória, assim como a melhoria no ambiente hospitalar (STEINER *et al*., 2002).

Apesar da melhora de técnicas utilizadas em cirurgias, a morbidade pós-operatória e os custos do tratamento médico continuam a ser um alto custo para qualquer sistema de saúde. (FAIST; WICHMANN; KIM, 1997; SENKAL *et al*., 1995; GIANOTTI *et al.*, 1997; DALY *et a*l, 1992; BRAGA *et al*., 1996; GIANOTTI *et al.*, 1999).

1.4 IMUNONUTRIÇÃO

O campo da terapia de suporte nutricional tem passado por transformações desde sua concepção. Originalmente, suplementação era recomendada para fornecimento de energia, proteínas e micronutrientes essenciais para compensar a perda de massa magra e prevenir depleção imune induzida por inanição. Posteriormente, vários componentes da dieta têm sido utilizados na tentativa de modular a função imune. Para este fim, aminoácidos específicos, ácidos graxos de cadeia-longa e nucleotídeos têm sido estudados. Embora a composição da terapia nutricional possa influenciar a defesa do hospedeiro, a literatura ainda divide-se na efetividade de suporte nutricional manipulado por fórmulas para atingir desfechos clínicos importantes (VA TPN COOPERATIVE STUDY GROUP, 1991).

Os nutrientes imunomoduladores mais utilizados incluem ácidos graxos ômega-3 (ω-3), nucleotídeos e arginina. Ainda não está claro qual constituinte é mais responsável pela imunomodulação porque normalmente os componentes não são independentemente testados em grandes estudos (KEMEN *et al*., 1995; WU; ZHANG; WU, 2001).

Imunonutrição tem sido estudada em múltiplos ensaios clínicos, os quais demonstraram redução de complicações infecciosas pós-cirúrgicas. Alguns estudos mostraram redução de complicações não infecciosas em pacientes submetidos à cirurgia eletiva, incluindo pacientes que sofreram ressecções de tumores de trato gastrintestinal. Meta-análises demonstraram uma redução de risco de 38-62% de infecções e outras complicações. (MARIK; ZALOGA, 2010; CENTAROLA *et al*., 2011; DROVER *et al*., 2011; HEYLAND *et al*, 2001, WAITZEBERG *et al*., 2006, ZHANG *et al*., 2012; MARIMUTHU *et al*., 2012).

1.4.1 Arginina

Arginina é um aminoácido condicionalmente essencial. Sua síntese endógena pode estar limitada durante doenças, e por isto constitui o maior componente na grande maioria das fórmulas nutricionais de imunonutrição (DALY *et al*., 1998).

Este aminoácido está envolvido com a síntese de proteína, ureia, nucleotídeos e geração de ATP. É precursor de óxido nítrico – um potente regulador imunitário e mediador do fluxo sanguíneo. Precursor da síntese de poliaminas, as quais apresentam um papel-chave na replicação de DNA, regulação do ciclo celular e divisão celular.

Experimentos em animais diminuíram involução do timo associado com trauma, promoveram celularidade no timo, proliferação de linfócitos, atividade de células *natural killer*, e a citotoxicidade de macrófagos, bem como melhorou hipersensibilidade retardada e resistência para infecções bacterianas. Em humanos saudáveis sua suplementação aumentou a proliferação de linfócitos no sangue em resposta a mitógenos e promoveu melhora da cicatrização de feridas (CALDER; YAGOOB, 2004, p. 305; POPOVIC; ZEH; OCHOA, 2007).

1.4.2 Nucleotídeos

Os nucleotídeos estão envolvidos com a estrutura do DNA e RNA, metabolismo para geração de energia e regulação da atividade enzimática. A ativação de linfócitos causa um rápido aumento da demanda de nucleotídeos devido ao aumento da necessidade energética e, depois, para síntese de RNA para produção de proteínas e divisão celular de DNA.

Experimentos em animais mostraram que nucleotídeos melhoraram a função de células-T, respostas de anticorpos, hipersensibilidade retardada e resistência a patógenos (CARVER *et al*., 1991; GIL, 2002). Nucleotídeos estão presentes em abundância no leite materno, talvez por isto, justifique a grande função imunomodulatória em crianças (FANSLOW *et al*., 1988).

1.4.3 Ácidos Graxos Ômega-3

Estes ácidos graxos são precursores de eicosanoides, incluindo prostaglandinas, prostaciclinas, tromboexanos e leucotrienos.

A dieta ocidental moderna é relativamente rica em ácidos graxos ômega-6 (ω-6), levando ao grande quantidade deste ácido graxo em membranas celulares. O ômega-6 origina o ácido araquidônico, através da conversão de ácidos linoleicos em ácido araquidônico. Sendo assim, o ω-6 é potencialmente pró-inflamatório, levando um aumento de produção de interleucina-1, fator de necrose tumoral alfa e interleucina-6 (WACHTLER *et al*., 1997). Adicionando ω-3 à dieta há inibição de conversão de ácido linoleico em ácido araquidônico. Além disso, ω-3 substitui o ω-6 presente em excesso na membrana, aumentando, desta forma, a produção de prostaglandinas e leucotrienos – potenciais redutores da pró-inflamação (KENLER *et al*., 1996).

Curiosamente, em pessoas saudáveis, ω-3 parece ter feitos limitados na produção de eicosanoides, sendo fortemente considerado o nutriente-chave para imunomodulação, sendo crucial para evitar qualquer efeito pró-inflamatório ocasionado pela arginina na suplementação (KENLER *et al*., 1996).

1.5 IMUNONUTRIÇÃO EM PACIENTES CIRÚRGICOS COM CÂNCER GASTROINTESTINAL

Os pacientes com câncer gastrintestinal sempre apresentam um risco aumentado de desnutrição por diversos fatores: obstrução mecânica, limitação da ingestão de alimentos, caquexia induzida pelo tumor, obstrução pancreática-biliar, má-absorção e perda de sangue. Desnutrição deprime imunidade celular e humoral. Além disso, procedimento cirúrgico complexo pode ocasionar em depleção da imunidade. (SAX, 2005; TARTTER; MARTINELI; STEINBERG, 1986) Portanto, estes pacientes são mais suscetíveis para contração de complicações infecciosas (MULLER *et al*., 1982)..

Nutrição parenteral total uma semana antes da cirurgia em pacientes com perda de peso mostrou reduzir infecções pós-operatória (MULLER *et al*., 1982). Braga *et al*. (2000) demonstraram em um estudo randomizado com pacientes com perda de peso maior que 10%, que o grupo que recebeu imunonutrição antes e após a cirurgia teve menos complicações que o grupo que foi suplementado apenas no pós-operatório.

Riso *et al*. (2000) também encontrou em seu estudo, com pacientes desnutridos que apresentavam câncer de cabeça e esôfago, benefícios da imunonutrição em relação à infecção e complicações da ferida. Pacientes que não apresentavam desnutrição significativa também foram analisados. Encontrou-se benefício significativo no uso de suplementação de imunomoduladores em pacientes oncológicos de trato gastrintestinal siperior, em relação ao número de complicações e tempo de hospitalização (GIANOTTI *et al*., 2002).

2. JUSTIFICATIVA

Suspeita-se que pacientes possam ser beneficiados através da suplementação de imunonutrição. Pacientes com câncer submetidos a cirurgias de trato gastrintestinal por neoplasia podem ser beneficiados devido ao risco elevado de apresentar complicações pós-cirúrgicas. Estas complicações ocasionam em um aumento de custo para os hospitais, pois além da necessidade de obter todos os recursos para cura da complicação, alguns pacientes podem ser encaminhados para Centro de Unidade Intensiva ou para uma nova cirurgia. Contudo, se sabe que os suplementos com nutrientes imunomoduladores são de elevado custo para os hospitais. Portanto, torna-se necessário avaliar a rentabilidade da aplicação deste tipo de suplemento nestes pacientes e, assim, definir se este tipo de suplementação realmente apresenta um custo-benefício satisfatório para receber investimentos de hospitais.

3. OBJETIVO

O objetivo desta Revisão Sistemática é avaliar o custo-benefício da suplementação com imunomoduladores em pacientes com neoplasia do trato gastrointestinal submetidos à ressecção cirúrgica.

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4. ARTIGO DE REVISÃO

Cost-effectiveness of Perioperative Immunonutrition in Gastrointestinal Oncologic Surgery: A Systematic Review

Custo-benefício da Imunonutrição Perioperatória em Cirurgia Oncológica do Trato Gastrointestinal: Uma Revisão Sistemática

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RESUMO

Introdução: Custos, tempo de hospitalização e morbidade estão frequentemente aumentados na presença de infeções e outras complicações decorrentes do câncer gastrointestinal. Recentemente, a melhora de mecanismos de defesa do hospedeiro tem se tornado um alvo de interesse. Nutrição adequada está fortemente relacionada com competência imune e redução de infeções. Imunonutrição objetiva a melhora da imunidade, principalmente para manutenção de linfócitos-T e outras defesas. **Métodos:** Este estudo consiste em uma revisão sistemática da literatura baseada em referência encontradas em bases de dados, como PubMed, *LILACS* e SCIELO. A busca foi realizada com combinação de termos em inglês relacionados ao tema da revisão: [*immunonutrition, arginine, omega-3, nucleotides*] combinado com [*costs, cost-effective, cost-effectiveness*] e [*gastrointestinal cancer surgery, oesophageal, gastric or pancreatic surgery*]. Para análise de custos, moedas usadas nos artigos foram convertidas em Dólar Americano. Seis estudos randomizados prospectivos foram incluídos nesta Revisão. **Conclusão:** O custo-benefício foi positivo na maioria dos estudos, sugerindo que este tipo de dieta pode ser rentável. Contudo, os resultados não podem ser ampliados para outras regiões devido a particularidades existentes.

Palavras-chave: Imunonutrição, cirurgia oncológica gastrointestinal, custo-benefício.

ABSTRACT

Background: Costs, length hospital staying and morbidity are frequently and significantly increased as a result of infections and other complications following gastrointestinal tract cancer. Recently, improving host defence mechanisms have become a target of interest. Immunonutrition aiming to improve immunity, most likely providing key nutrients that maintain T-lymphocyte and other host defence. **Methods:** The study consisted of a systematic review of the literature based on reference analyses found in current databases such as PubMed, *LILACS* e SCIELO. The search strategy was defined by terms related [immunonutrition, arginine, omega-3 and nucleotides] in combination with [costs, cost-effective and cost-effectiveness] as well as [gastrointestinal cancer surgery, oesophageal, gastric or pancreatic surgery]. For cost analyses, currencies used in the papers needed to be converting to American dollar (USD) in order to uniform and facilitate comparison. Six prospective randomized studies were included in this review. **Conclusion:** The cost-effectiveness was positive in most of studies, leading that this diet type can be profitable. However, results cannot be extended to any region due to the particularities existents.

Keywords: Immunonutrition, oncologic gastrointestinal surgery, cost-effectiveness.

Introduction

Recently, the relation between infection rates and length of hospital staying (LHS) has been increasing. Surgical procedures involving visceral organs are at a particular high-risk to the patient. Immunity is compromised due to reperfusion and tissue ischemia from stress associated with blood transfusion and haemorrhage [1].

Costs, LHS and morbidity are frequently and significantly increased as a result of infections and other complications following gastrointestinal tract (GIT) and head and neck cancer [2,3]. Wound infection, abdominal abscess, pneumonia, urinary tract infections are considered postoperative infection complications. Other important complications include: anastomotic leaks, acute renal failure and cardiovascular events [2]. Usually, the policies used to reduce and prevent postoperative complications emphasises on the pathogen eradication as perioperative antibiotic prophylaxis, surgical trauma reduction, intraoperative contamination and improvement in the hospital environment [4].

Only recently, improving host defence mechanisms have become a target of interest. Adequate nutrition is strongly linked with immune competence and risk reduction for infections [5, 6]. Immunonutrition is composed by omega-3 fatty acids (ω-3), arginine and nucleotides aiming to improve immunity, most likely providing key nutrients that maintain T-lymphocyte and other host defence [7, 8].

The aim of this systematic review was to review immunonutrition for oncologic patients who are undergoing surgery for GIT tract and to evaluate the cost-effectiveness of this supplementation.

Methods

The study consisted of a systematic review of the literature based on reference analyses found in current databases such as PubMed (*National Library of Medicine and National Institute of Health* – USA), *LILACS* e SCIELO.

The search strategy was defined by terms related to immunonutrition [immunonutrition, arginine, omega-3 and nucleotides] in combination with terms of hospital costs [costs, cost-effective and cost-effectiveness] as well as oncological patients undergoing GIT surgery [gastrointestinal cancer surgery, oesophageal, gastric or pancreatic surgery]. The research occurred in September to October 2014.

SCIELO e LILACS did not provide any article. A total of 59 articles were found in a first round. Studies included in the search were those carried out in adults and of English or Portuguese language. No Portuguese articles were found. Reviews, meta-analysis, short/brief communications articles or those that did not have full text available and either methods or subject of the study clearly proposed were also excluded.

Of the 59 articles, 43 (73%) articles were replicated and because of duplicity were excluded from analyses. Additionally, four (7%) articles were reviews, three (5%) were meta-analysis, one study was performed in children (2%), one had

confused methods of cost assessment (1.7%), and one (1.7%) have the proposed subject out of our scope, and were also excluded.

For cost analyses, currencies used in the papers needed to be convert to American dollar (USD) in order to uniform and facilitate comparison; for this purpose we considered the first day of the month and the year that the paper was submitted or published as stated accordingly. Also all currencies have cost values updated by 1st Nov. 2014 at a European Central Bank website [9]. Two papers had Deutsche Mark (DM) as currency [14, 15], one had Chinese Yuan Renminbi (RMB) [11] and the other ones used Euro (EUR)**.** It was not possible convert the currency from one article because of the old date [14]. More details in **Table 1**.

Table 1 – Conversion details.

Author; year	Currency	Article date considered	Rate
Senkal M *et al*., 1999	DM	December, 1999.	1 EUR = 1.95583 DM 1 EUR = 1.0091 USD
Gianotti L *et al*., 2000	EUR	September, 2000.	1 EUR = 0.8902 USD
Kłek S *et al*., 2005	EUR	April, 2005.	1 EUR = 1.2959 USD
Braga M *et al.,* 2005	EUR	July, 2004.	1 EUR = 1.2168 USD
Zhu M *et al*., 2012	RMB	January, 2012.	1 EUR = 8.1588 RMB 1 EUR = 1.2939 USD

DM = Deutsche Mark; EUR = Euro; RMB = Chinese Yuan Renminbi.

Results and Discussion

Six prospective randomized studies were included in this review and these articles are summarized in **Table 2**. The GIT cancer analysed were: GIT cancer in general (n=3), colon or rectal cancer (n=1), upper GIT cancer (n=1) and gastric cancer (n=1). In all articles ω-3 supplement use was described. Arginine and RNA were used as supplements in four studies and glutamine supplementation was used in only one study. GIT supplement via chosen in the studies were: parenteral supplementation (n=2), oral supplementation (n=3; in preoperative cases only) and enteral supplementation (n=4). **Table 3** describes the group characteristics of the studies more detailed – age, sex and sample size.

Nutritional Status is described in **Table 4.** Albumin, pre-albumin and weight-loss were chosen in three studies to define nutritional status. Body mass index (BMI) and Nutritional Risk Index both were observed in two articles to define nutritional status. One study selected just well-nourished patients [10]. The other studies have not restricted nutritional status. Zhu *et al*. (2012) selected only elderlies (65 to 85 years old) that had 18.5 – 25.0 kg/m² BMI. Klek *et al*. (2005) classified your patients in “well-nourished” and “minor grade malnutrition”, and then equally distributed the sample into the three groups.

Table 2- Articles Description.

Author, year, Country;	Journal, Study;	Sample, cancer type;	Diet	Diet administration	Supplementation via
Senkal M *et al*., 1997. Germany.	Crit Care Med Prospective, randomized, double-blind study and a retrospective cost-comparison analysis.	154 patients. Upper gastrointestinal cancer.	Treatment group: diet supplemented with arginine, omega 3 and RNA Control group: isonitrogenous and isocaloric liquid diet.	The feeding was started in the first postoperative day.	Enteral Nutrition.
Senkal M *et al*., 1999. Germany.	Arch Surg. Prospective, randomized, double-bind study.	154 patients. Gastrointestinal tract cancer.	Treatment group: diet supplemented with arginine, omega 3 and RNA Control group: isocaloric liquid diet.	They are fed at least 5 d before surgery and at least 5 d after surgery.	Preoperative: oral Postoperative: enteral.
Gianotti L *et al*., 2000. Italy	SHOCK Prospective, randomized, double-bind study.	206 patients. Gastrointestinal tract cancer.	Treatment group: diet supplemented with arginine, omega 3 and RNA Control group: isonitrogenous and isocaloric liquid diet.	The groups received the diet for 7 d before and 7 d after the surgery.	Preoperative: oral Postoperative: enteral.
Kłek S *et al*., 2005 Cracow.	Acta Chir Belg Prospective, randomized study	90 patients. Gastric carcinoma.	Group Control: standard diet; Group B: diet supplemented with glutamine Group C: diet supplemented with omega-3.	The diet was started 24 hours after surgery and continued for at least 7 d, until enteral diet covering at least 60% of protein and energy requirements was administered.	Parenteral Nutrition.
Braga M *et al*., 2005. Italy.	Nutrition Prospective, randomized study and a retrospective cost-comparison analysis	305 well-nourished patients. Gastrointestinal tract cancer.	Diet specialized supplemented with arginine, RNA and omega-3.	Preoperative group - received a specialized diet for 5 d before surgery. Perioperative group - received the same preoperative treatment plus specialized diet for 7 d after surgery. Conventional group – no supplementation.	Preoperative: oral supplementation Postoperative: enteral supplementation
Zhu M *et al*., 2012. Chine.	Chin Med J. Prospective, randomized, double-blind study	57 Elderly patients with a body mass index (BMI) of 18.5–25.0 kg/m². Colon or rectal cancer.	Treatment group: 0,2 g/kg fish oil and 1,0 g/kg soybean oil. Control group: 1,2 g/kg soybean oil	Both groups had diet started on the first day after surgery and ended on the morning of the eighth day.	Parenteral Nutrition.

Table 3 – Detailed group characteristics.

Author, year;	Sample Size		Age (y)		Male:Female	
	Control Group	Treat. Group	Control Group	Treat. Group	Control Group	Treat. Group
Braga *M et al*., 2005	102	102*	68.1 (11.7 SD)	69.4 (10.1 SD)*	56:46	50:52*
Zhu M *et al*., 2012	28	29	70.8 (6.4 SD)	69.8 (10.5 SD)	17:11	16:13
Senkal M *et al*., 1999	76	78	67 (9 SD)	64 (11 SD)	48:30	52:24
Gianotti L *et al*., 2000	104	102	61.1 (9.5 SD)	60.8 (11.5 SD)	42:62	39:63
Senkal M *et al*., 1997	77	77	66.3 (1.8 SD)	65.1 (1.5 SD)	Not available	
Kłek S *et al*., 2005	30	Group B: 31 Group C: 29	Total Sample: 61.9		Total Sample: 51:39	

Group A = control group; Group B = glutamine supplemented group; Group C = omega-3 supplemented group; Treat. = Treatment; Preoperative group only*. SD = Standard Deviation.

Table 4 - Patients Nutritional Status.

Author, year;	Sample Nutritional Status	Albumin (g/ml)		Pre-albumin (mg/dL)		Weight Loss (%)		BMI		Nutrition Risk Index	
		Control Group	Treat. Group	Control Group	Treat. Group	Control Group	Treat. Group	Control Group	Treat. Group	Control Group	Treat. Group
Braga M *et al.,* 2005	Well-nourished patients.	40 (6.5 SD)	40 (5.6 SD)*	0.2 (0.07 SD)	0.3 (0.08 SD)*	2 (2.7 SD)	2 (2.6 SD)*	NA		NA	
Zhu M *et al*., 2012	Different nutritional status	NA		NA		NA		23.2 (3.6 SD)	22.9 (3.1 SD)	NA	
Kłek S *et al*., 2005	Different nutritional status	NA		NA		NA		NA		NA	
Senkal M *et al.,* 1999	Different nutritional status	NA		NA		NA		23.2 (3.6 SD)	22.9 (3.1 SD)	91 (15 SD)	97 (12 SD)
Gianotti L *et al.,* 2000	Different nutritional status	39 (11 SD)	38 (10 SD)	NA		5 (4.1 SD)	6 (4.2 SD)	NA		NA	
Senkal M *et al*., 1997	Different nutritional status	NA		NA		NA		NA		98 (1.7 SD)	99.5 (1.9 SD)

Treat. = treatment; BMI = Body Mass Index; NA = Not Available; Preoperative group only*. SD = Standard Deviation.

Reduction of complications

Overall, the articles found a reduction of complications in the group that received some type of immunonutrient. Five of them, demonstrated a statistically significant difference on complications [10, 11, 13-15]. On the other hand, considering Intensive Care Unit (ICU) admissions, two studies did not present any protection by supplementation [10,13].

Braga *et al*. (2005) supplementing with arginine, RNA and ω-3 showed a significant decrease in the number of patients who developed postoperative infections in both treatment groups received immune-enhancing diets as compared to controls. Though, complications were not isolated analysed by groups; they were classified as major (infections complications) and minor (non-infections complications). Both complications were reduced in the groups with patients receiving immunonutrition. There were 42 major complication episodes (18 in the conventional group, 10 preoperative and 14 perioperative group) and 157 minor complications (67 in the conventional group, 44 in the preoperative, and 46 in the perioperative). Eight patients were transferred to the ICU (four in the perioperative group, three in the conventional, and only one in the preoperative).

Gianotti *et al*. (2000) supplemented arginine, RNA and ω-3 in GIT cancer patients as well. They found that the number of complications was significant lower (except for peritonitis) in the treatment group; where less anastomotic leak and pneumonia occurred. Two and three treated and non-treated patients were sent to ICU, respectively. Same immunonutrients were analysed in another randomised study, including 18% of the patients with GIT cancer showing postoperative complications. After postoperative day 3, the number of patients who developed complications was significantly lower in the treatment group than in the control group. Moreover, the number of patients who had late complications was suggestively lower in the treatment group compared to control group [14].

Upper GIT cancer patients were observed in a study using arginine, RNA and ω-3. A total of five deaths occurred, three in the group receiving the studied diet and two controls receiving standard formula. The causes of death in the treatment group were systemic inflammatory response syndrome (SIRS; n = 2) and myocardial infarction (n = 1). Two eligible patients who received control diet died because of cardiopulmonary complications. The number of patients with complications clearly decreases as for postoperative day 4 under immunonutrition, considering the number of patients with complications in control group remained at a constant level until postoperative day seven. Among 77 eligible patients, 17 and 24 in the supplemented diet and non-supplemented groups experienced postoperative complications, respectively. Also, late complications were much more observed in controls than in treatment group (5 vs. 13 cases; $p<0.05$). However, prevalence of complicating events was not significantly lower in the supplemented diet group complications as compared with controls (30 *vs.* 32 cases) [15].

Elderlies with colon or rectal cancer were analysed by Zhu *et al*. (2012). Eight patients in the control group (five respiratory tract infections, one urological and two wound infection) as compared to four (three respiratory tract infections and one wound infection) in the treatment group that received fish oil (*P* >0.05) had postoperative complications. Besides that, fish oil significantly reduced the incidence of SIRS (*P* <0.05). Omega-3 fatty acids were observed too in the study of Kłek *et al*. (2005) and pneumonia was observed more frequently in the control group, but no significant differences were seen between immunomodulation and standard groups.

Two deaths occurred in a treatment group because of SIRS [15] while another study observed prevention [11]. However, in that study where deaths occurred, ω-3 was offered associated to arginine, while in the second study [11] that found protection to SIRS isolated omega-3 fatty acids was offered. Studies done with critical patients pointed that the use of arginine in sepsis patients was associated with higher mortality rates [16,17], suggesting that arginine, by increasing pro-inflammatory cytokines and nitric oxide, increased the inflammatory response due to toxic effects, bigger in patients with sepsis, SIRS or severe infection [18]. Omega-3 fatty acids reduced in a significantly way the incidence of SIRS in another studies too [19, 20, 21].

LHS

All the studies that analysed LHS found that treated patient groups had a shorter hospital admission.

Zhu et al. (2012) showed that mean (SD) LHS in treatment group significantly decreased compared to control group; 12(4) days and 15(6) days, respectively (*p* <0.05). Senkal *et al*. (1997) and Klek *et al*. (2005) did not find significantly differences between control and treatment group.

Patients receiving ω-3 supplementation resulted in shorter number of mean (SD) days in hospital – 14 (4) days – when compared to those receiving glutamine supplementation – 14 (8) days – and to controls – 16 (4) days. The range was also bigger for controls (9 to 45 days) when compared to ω-3 (9 to 42 days) and glutamine (8 to 41 days) supplementation [12]. Senkal et al. (1997) supplementing patients with ω-3, arginine and RNA diet found that these patients had a mean (SD) LHS of 5.1 (1.2) days in the ICU *vs*. 6.8 (1.4) days for the controls. Total (SD) LHS was 27 (2.3) days in the supplemented diet group *vs.* 30.6 (3.1) days for controls. The same immunonutrient combination was given by Braga *et al.* (2005) who separately analysed LHS by cancer type in patients without complications. Mean (SD) LHS values for patients who underwent gastro-oesophageal resection were 10.7 (3.9) days in the control group and 9.9 (4.2) in the preoperative group. Mean (SD) LHS values for patients who underwent pancreatic resection were 13.8 (6.1) days in the standard diet group and 12.7 (5.8) days in the preoperative group. The

mean (SD) LHS values for patients who underwent colorectal resection were 8.8 (4.0) days in the control group and 8.4 (3.7) days in the preoperatively treated group.

Cost-effectiveness

As expected, the supplemented diet costs were higher than standard diet in all studies. Overall supplemented diet costs ranged from 14 USD to 101 USD per-patient while standard diet costs ranged from 22 USD per-patient to 348 USD per-patient. These costs are shown in **Table 5**.

Table 5 – Supplemented diet costs.

	Nutrition Cost	
Author, year;	**Control Group**	**Treat. Group**
Braga M et al., 2005	4,146 USD 41 USD per patient	17,922 USD 176 USD per patient
Zhu M et al., 2012	407 ±70 USD	638 ±49 (<0.01) USD
Senkal M et al., 1999	25 USD per patient	179 USD per patient
Gianotti L et al., 2000	91 USD per patient (intent-to-treat analysis) 101 USD per patient (core analysis)	309 USD per patient (intent-to-treat analysis) 348 USD per patient (core analysis)
Kłek S et al., 2005	Not available	8,668 USD (<0.5) 299 USD per patient *

Omega 3 supplemented group only*

Braga *et al*. (2005) showed the values of each complication based in LHS and resources used for major complications where the largest mean cost was sepsis (16,669 USD) occurring in three patients who had the most expensive resources used (15,173 USD). Abdominal abscess and anastomotic leak had the largest mean spending due to prolonged LHS. For minor complications, wound dehiscence that occurred in seven patients had the most expensive mean (7,740 USD), mainly because of prolonged LHS. Intestinal obstruction (n=2) had the largest mean cost (3,340 USD) due to resources used. There was only one episode of pulmonary embolism, but expenses (1,940 USD) were higher because of the resources used. No significant difference was found after comparing the mean cost of each complication across the three treatment (perioperative or preoperative supplementation vs. control) groups.

Senkal *et al.* (1999) analysing complications found that the most expensive early complication was pneumonia in supplemented group (6,008 USD), occurring in only one patient. In late complications the largest expenses were ICU admissions, pneumonia and sepsis (21,499 USD) in the supplemented (n=6) group, and pneumonia, anastomotic leak and pancreatitis (55,226 USD) for controls (n=17). Per-patient costs of treating postoperative complications were 497 USD in the group receiving immunonutrition and 1,387 USD in the control group. Gianotti *et al.* (2000) found that immunonutrition reduced the complications cost too. Mean total cost per complication was 3,874 USD in the treatment group and 6,385 USD in the control group, and in the intent-to-treat analysis and 2,660 USD in the treatment group versus 6,431 USD in the control group (core analysis; p= 0.05).

The total costs of treating postoperative complications amounted to 69,735 USD in the treatment group vs. 217,104 USD in the control group in the intent-to-treat analysis and 37,251 USD in the treatment group vs. 205,786 USD in the control group. The most expensive treatments to supplemented group were peritonitis (17,978 USD) in the intent-to-treat analysis – one instance – and anastomotic leak (mean cost 5,390 ±2,591 USD) – five instances. Anastomotic leak was the most expensive treatment in the control group as well (14,038 USD) in both analyses (n=10).

A basic analysis based in LHS found that immunonutrition cannot be profitable. Overall costs reached approximately 10,885 USD in control group; 11,075 USD in glutamine, and 13,672 USD in ω-3 diet supplementation. Authors did not evaluate, however, complications costs, compromising the profitability of immunonutrition [12].

The cost-effectiveness was positive in Gianotti *et al*. (2000) study. They found that the treatment with immunonutrition was overcompensated comparing to costs of postoperative infection treatment. It generated a significant net saving in the infection complications treatment of 1,186 USD in the intent-to-treat analyses and 1,484 USD in core analysis per complication-free patient. The total costs in a cost-effectiveness analysis produced a saving of 2,124 USD in intent-to-treat analysis and 2,416 USD in core analysis. Overall costs were 8,498 USD in the treatment group versus 12,060 USD in the control group, saving 3,562 USD in favour to immunonutrition.

The most recent study [11] did not find significant difference in the total medical care costs (nutritional plus non-nutritional) between the groups 6021 USD in control group and 6030 USD in treatment group. On the other hand, Senkal *et al* (1999) calculated immunonutrition supplementation was profitable, resulting a net saving of 1,439 USD per-patient in favour of immunonutrition. The total costs in the supplemented group were less than half 75,857 USD when compared to control group 206,099 USD. Senkal *et al*. (1997) did not find a statistically difference in the mean treatment costs per patient, but 32% were saved when total complications costs were analysed. Braga *et al*. (2005) related a net saving of total costs of 176,780 USD favourable to group that received immunonutrition in the postoperative period. Per patient, 2,280 USD was the cost-effectiveness in the preoperative group

(P=0.04) and 3,799 USD in the conventional group, saving 1,521 USD. When the analysis limited to infection complications the cost-effectiveness was 2,990 USD to conventional group and 956 USD to preoperative diet specialized group. The same did not happen to non-infection complications where no difference was found.

A randomized clinical trial out of this review concluded that for malnourished patients the use of nutritional approach seemed to be more clinically beneficial than only preoperative intervention [22]. Just one study included only well-nourished patients. They found that sole preoperative immunonutrition can be clinically and economically enough. This may explained, because malnourished patients have energy and nitrogen needs increased and immune response decreased. So, prolonged administration of immunonutrients on a diet can be indicated. [10]

The present systematic review showed that there were lots of advantages in the use of a diet with immunonutrients. The LHS and complication reduction can cause a less value of total patient expense. This review included a small number of studies what may difficult wider interpretations. For economic analyses, some limitations may influence the reproducibility, since old articles can be economically outdate, and especially considering that some articles have not the research date informed. Besides that, economic parameters used may differ from country to country based on the type of health care system and reimbursement rates they have [10], and more studies on cost-effectiveness needed to be carried out. In Brazil, there is no actual data about cost-effectiveness of immunonutrition [23].

Conclusion

Immunonutrition reduces complications and LHS, maybe excepting ICU admissions and death. The cost-effectiveness was positive in most of studies, leading that this diet type can be profitable. However, results cannot be extended to any region due to the difference between the health system and currency from country to country.

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ANEXO – Normas de Publicação da revista Arquivos Brasileiros de Cirurgia Digestiva

Scope and policy

ABCD – ARQUIVOS BRASILEIROS de CIRURGIA DIGESTIVA, the official publication of the Colégio Brasileiro de Cirurgia Digestiva – CBCD (Brazilian College of Digestive Surgery), is a quarterly Journal, published in a single volume per year, whose mission is the publication of articles of clinical and experimental studies that foster the advancement of the research, teaching and assistance in surgical, clinical, and endoscopic gastroenterology, and related areas. Its main sections are original articles, review or update articles, case reports, editorials (solicited) and letters to the Editor. Other sections may be included, depending on the interest of the Journal or the need to publish relevant subject matters not suitable for the categories above.

Form and preparation of manuscripts

MANUSCRIPTS

The manuscripts must be submitted for publication exclusively to the ABCD and report on original work; they cannot have been published previously in a similar format. Every subject matter involving human or animal research must have the previous approval of the Research Ethics Committee of the institution where the research was conducted or another local or regional institution if there is no such committee at the institution where it was conducted. In compliance with current guidelines for good practice in human research, the patients enrolled in the study must sign an informed consent form.

The ABCD supports the policies for the registration of clinical trials of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE), as it acknowledges the importance of such initiatives to the registration and international dissemination of information in publicly accessible clinical studies. As of 2007, articles reporting on randomized controlled trials and clinical trials will only be accepted for publication if they have been assigned an identification number in one of the Clinical Trials Registries validated by the criteria put forth by the WHO and ICMJE and whose URLs are available from the ICMJE website (www.icmje.org). The identification number should be included at the end of the abstract.

The manuscripts, in Portuguese or English, should be submitted in electronic form by email to abcd@evangelico.org.br (phone +55 0 xx 41 3240-5488). The author(s) will receive an email to acknowledge receipt of the manuscript and to notify that it was forwarded to editorial analysis. This confirmation is no guarantee of the publication of the manuscript. The writing of the manuscripts must conform to the format chosen by the author among the ABCD sections, which are detailed further on.

The manuscripts must be typewritten in 12-point Arial font, single-spaced throughout. The pages should be numbered consecutively beginning on the title page. The maximum length of the manuscript, including references, tables and figures, must not exceed 15 pages for original and review articles, five pages for case reports and editorials, and two pages for letters to the Editor (these should not contain tables and figures). Tables and figures should be placed immediately following their mention in the text, not at the end of the manuscript. The authors or advertisers are fully responsible for all concepts and scientific assertions expressed in the articles or printed advertisements. In order to standardize the usage of medical terminology, the authors should use the Terminologia Anatomica, São Paulo, Editora Manole, 1ªEd., 2001 for the anatomical terms. It is the ABCD's prerogative to do so if the author(s) have not complied.

Every manuscript submitted for publication, written concisely and in the third-person singular or plural throughout, must consist of the frontmatter/backmatter and the body of the text.

FRONTMATTER/BACKMATTER

These must comprise: 1) the title of the manuscript in Portuguese and English; 2) the full name(s) of the author(s); 3) the location(s) where the study was conducted, clearly stating the institution(s) involved, city, state and country; 4) the name and e-mail address of the corresponding author; 5) the acknowledgements after the conclusions, if applicable; 6) an abstract in Portuguese, which should not contain abbreviations, acronyms or references nor exceed 300 words, organized in a single paragraph and structured thus: *original article* – rationale, aim, method(s), results and conclusion(s); *case report* – introduction, aim (optional), case report and conclusion(s);*review article* – introduction, aim (optional), methods (which should mention how many articles were selected, the descriptors used and which databases were searched) with a summary of the text subheadings and a conclusion; 7) an abstract in English, containing the same headings and scientific data and in the same style as the Portuguese version, structured as follows: original article – background, aim, method(s), results, conclusion; case report – background, aim (optional), case report, conclusion; review article – background, objective (optional), method, conclusion; 8) headings in Portuguese, listing up to five key words included in the *Descritores de Ciências da Saúde* – DeCS at http://decs.bvs.br/ or from the MESH website at www.nlm.nih.gov/mesh/meshhome.html (please note: **key words not included in the DeCS/MESH will not be accepted**); 9) headings (key words in English) as they appear in the DeCS or MESH.

BODY OF THE MANUSCRIPT

Abbreviations are discouraged, and should be used only for technical terms repeated more than ten times throughout the text. They should come in parentheses at first mention, and thereafter only the abbreviations should be used. The structure of the text must conform to the following guidelines:

original articles – introduction (the last paragraph of which will be the objective), methods, results, discussion, conclusion(s) (if the article has no conclusions, the final recommendation can be stated in the last paragraph of the discussion section) and references;

review articles – introduction, methods (cite the key words and databases searched and the span of time covered), review of the literature (the review can be divided into sub-topics in order to group the findings together; the authors' experience can be included), conclusion(s) (summary of the current trends) and references;

editorials – these should be written by invitation of the Editorial Board;

case reports – introduction, case report, discussion (with a review of the literature, if there is any), conclusion and references;

letters to the Editor – clear writing on the commentary intended for publication in no more than three pages, which may or may not include references;

references – must conform to the Vancouver guidelines (Ann Inter Med 1997; 126:36-47 or at www.icmje.org - items IV.A.9 and V). Up to 30 reference entries will be accepted for original and review articles, and no more than 15 for case reports. List the references alphabetically by the first author's last name and number them in consecutive Arabic numerals. In text citation, use the superscript reference number. The Journal titles must be referenced in their abbreviated form according to the List of Journals Indexed in Index Medicus.

The text of the manuscript should be self-explanatory, i.e., it should provide clear interpretation and synthesis of the data without the need for the reader to refer to the graphs, tables, charts or figures. Results must be both presented in the tables and described in the text. Tables, graphs, charts and figures should also be self-explanatory, i.e., if readers wish to proceed with the reading of the article only by following them, in the end they should be able to interpret the results in the same way as they would if they had read only the text.

GRAPHS, CHARTS, TABLES AND FIGURES

In addition to the text, graphs, charts, tables and figures can be submitted, and should be referred to at the point where they are needed in the manuscript – either parenthetically or in the body of the text –, and should be placed immediately following their mention in the text and not at the end of the paper. Special care should be taken to avoid duplication, e.g., a graph showing the same information as a table. In that case, the reviewer of the article will suggest to the Editor the exclusion of whichever is found redundant.

Graphs and charts should be submitted in black and white, numbered in Arabic numerals. Titles and legends should be placed in the footnote.

Tables should be numbered in Arabic numerals, with the title above the table and the explanations for the symbols and abbreviations in the footnote.

Figures, numbered in Arabic numerals, are photographs or line art (maximum of six), and should be submitted with a minimum resolution of 300 dpi in black and white (color figures are paid for by the authors). The title and legends should be placed in the footnote. Figures that have been previously published must be cited with the author's permission