

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

**AVALIAÇÃO DA CAPACIDADE PROGNÓSTICA DA INFLAMAÇÃO
SISTÊMICA, FUNCIONALIDADE E ESTADO NUTRICIONAL EM
PACIENTES COM CÂNCER AVANÇADO**

BRUNA MARIA MALAGOLI ROCHA SANTOS

UBERLÂNDIA

2023

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SISTÊMICA, FUNCIONALIDADE E ESTADO NUTRICIONAL EM
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Tese apresentada ao Programa de Pós-graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do Título de Doutor em Ciências da Saúde.

Área de concentração: Ciências da Saúde

Orientadora: Profa. Dra. Yara Cristina de Paiva Maia

Coorientador: Prof. Dr. Carlos Eduardo Paiva

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*Aos pacientes com câncer avançado
que diariamente se enchem de esperança por dias melhores.*

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“O sofrimento humano só é intolerável quando ninguém cuida.”

Cicely Saunders

RESUMO

Introdução: No contexto do câncer avançado, a eficácia do tratamento e o planejamento adequado do cuidado dependem de uma predição acurada da sobrevida do paciente. As ferramentas prognósticas clássicas, amplamente utilizadas na prática clínica, têm apresentado limitações em termos de acurácia devido à sua complexidade e subjetividade, resultando em estimativas prognósticas imprecisas. Diante disso, surge a necessidade de desenvolver novas estruturas de avaliação prognóstica que incorporem fatores validados, objetivos e de fácil aplicação prática. **Objetivos:** Comparar fatores prognósticos validados (capacidade funcional, resposta inflamatória sistêmica e índice de massa corporal [IMC]), em duas coortes internacionais de pacientes com câncer avançado; estabelecer uma estrutura de avaliação prognóstica para pacientes com câncer avançado; avaliar o valor prognóstico do critério *The Global Leadership Initiative on Malnutrition* (GLIM), incluindo IMC, perda de peso e resposta inflamatória sistêmica em pacientes com câncer avançado. **Material e métodos:** No primeiro artigo que compõe esta tese, os seguintes fatores prognósticos foram analisados em dois bancos internacionais de pacientes com câncer avançado (n=1.518): capacidade funcional (*Eastern Cooperative Oncology Group Performance Status* [ECOG-PS]), IMC e resposta inflamatória sistêmica (*modified Glasgow Prognostic Score* [mGPS]). A relação entre esses fatores e a sobrevida dos pacientes foi avaliada pelos métodos Kaplan-Meier e Regressão de Cox. No segundo artigo, o valor prognóstico do critério GLIM foi avaliado em uma coorte brasileira e europeia combinada (n=1.303). A relação entre os fatores que compõe o critério e a sobrevida dos pacientes foi avaliada pelo método de Regressão de Cox. **Resultados:** No primeiro artigo, de acordo com a análise multivariada, observou-se que na coorte europeia os melhores fatores preditivos foram IMC<20 kg/m² (*hazard ratio* [HR] 1.644), IMC 20-21.9 kg/m² (HR 1.347), ECOG-PS (HR

1.597–11.992) e mGPS (HR 1.843–2.365). Na coorte brasileira, os melhores fatores preditivos foram ECOG-PS (HR 1.678–8.938) e mGPS (HR 2.103–2.837). Os dados permitem a sugestão de uma estrutura de avaliação prognóstica composta por ECOG-PS e mGPS (ECOG-PS/mGPS *framework*). No segundo artigo, a taxa de sobrevida dos pacientes em 3 (três) meses variou de acordo com o IMC, mGPS e perda de peso. De acordo com a análise multivariada, os melhores fatores preditivos foram IMC/perda de peso grau 3 (HR 1.454, $P=0.004$), IMC/perda de peso grau 4 (HR 2.285, $P<0.001$) e mGPS (HR 1.887–2.545, $P < 0.001$). Os dados permitem a sugestão de uma estrutura de avaliação prognóstica composta por mGPS e classificação IMC/perda de peso (classificação IMC/perda de peso/mGPS *framework*). **Conclusão:** Os fatores prognósticos comparados nas coortes brasileira e europeia apresentaram similar capacidade prognóstica em ambas. Elevados escores de ECOG-PS e mGPS, e uma elevada classificação IMC/perda de peso estão consistentemente associados à pior sobrevida de pacientes com câncer avançado. Ainda, as duas estruturas de avaliação prognóstica sugeridas nos artigos (ECOG-PS/mGPS e classificação IMC/perda de peso/mGPS) podem ser incorporadas na avaliação rotineira dos pacientes, devido à sua simplicidade e utilidade clínica.

Palavras-chave: Câncer avançado; inflamação sistêmica; capacidade funcional; composição corporal; prognóstico; análise de sobrevida.

Apoio: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

ABSTRACT

Introduction: In the context of advanced cancer, treatment effectiveness and adequate care planning depend on an accurate prediction of patient survival. Classic prognostic tools, widely used in clinical practice, have presented limitations in terms of accuracy due to their complexity and subjectivity, resulting in inaccurate prognostic estimates. Therefore, it is necessary to develop new structures for prognostic evaluation that incorporate validated and objective factors that are easy to apply in practice. **Objectives:** To compare established prognostic factors (performance status, systemic inflammatory response and body mass index [BMI]) in two international cohorts of patients with advanced cancer; to establish a prognostic framework for treatment in this cohort; to examine the prognostic value of The Global Leadership Initiative on Malnutrition (GLIM) criteria including BMI, weight loss and systemic inflammatory response in patients with advanced cancer. **Material and methods:** In the first article of this thesis, the following prognostic factors were analyzed in two international cohorts of patients with advanced cancer (n=1,518): performance status (Eastern Cooperative Oncology Group Performance Status [ECOG-PS]), BMI and systemic inflammatory response (modified Glasgow Prognostic Score [mGPS]). The relationship between these and survival was examined using Kaplan–Meier and Cox regression methods. In the second article, the prognostic value of the GLIM criteria was assessed in a combined Brazilian and European cohort (n=1303). The relationship between the factors and patient survival was assessed using Cox regression method. **Results:** In the first article, according to multivariate analysis, in the European cohort the most highly predictive factors were BMI <20 kg/m² (hazard ratio [HR] 1.644), BMI 20–21.9 kg/m² (HR 1.347), ECOG-PS (HR 1.597–11.992) and mGPS (HR 1.843–2.365). In the Brazilian cohort, the most highly predictive factors were ECOG-PS (HR 1.678–8.938) and mGPS (HR 2.103–2.837). A prognostic framework ECOG-PS/mGPS was

proposed. In the second article, the survival rate at 3 months varied according to BMI, mGPS, and weight loss (WL). According to multivariate analysis, the most highly predictive factors were BMI/WL grade 3 (HR 1.454, P=0.004), BMI/WL grade 4 (HR 2.285, P<0.001) and mGPS (HR 1.887–2.545, all P < 0.001). A prognostic framework BMI/WL grade/mGPS was proposed. **Conclusion:** Prognostic factors compared in the Brazilian and European cohorts showed similar prognostic capacity. A high ECOG-PS and mGPS scores, and a high BMI/weight loss score are consistently associated with poorer survival of patients with advanced cancer. Furthermore, the two prognostic frameworks suggested in the articles (ECOG-PS/mGPS and BMI/WL grade/mGPS) can be incorporated into the routine assessment of patients due to their simplicity and clinical utility.

Keywords: Advanced cancer; systemic inflammation; performance status; body composition; prognosis; survival analysis.

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LISTA DE ABREVIATURAS E SIGLAS

RESUMO E FUNDAMENTAÇÃO TEÓRICA

CC	Caquexia do câncer
ECOG-PS	<i>Eastern Cooperative Oncology Group – Performance status</i>
ECS	Estimativa clínica de sobrevida
EAPC	<i>European Association of Palliative Care</i>
ESMO	<i>European Society of Medical Oncology</i>
GLIM	<i>Global Leadership Initiative on Malnutrition</i>
IDH	Índice de Desenvolvimento Humano
IMC	Índice de massa corporal
IARC	<i>International Agency for Research on Cancer</i>
INCA	Instituto Nacional do Câncer
mGPS	<i>Modified Glasgow Prognostic Score</i>
NPB	Nomograma Prognóstico de Barretos
OMS	Organização Mundial da Saúde
PPS	<i>Palliative Performance Scale</i>
PPI	<i>Palliative Prognostic Index</i>
PaP	<i>Palliative Prognostic Score</i>
PCR	Proteína C-reativa
TNM	Tumor, linfonodo e metástase

ARTIGOS

BMI	<i>Body mass index</i>
CC	<i>Cancer cachexia</i>

CCR	<i>Colorectal cancer</i>
CI	<i>Confidence intervals</i>
CRP	<i>C-reactive protein</i>
ECOG-PS	<i>Eastern Cooperative Oncology Group – Performance status</i>
GLIM	<i>Global Leadership Initiative on Malnutrition</i>
HR	<i>Hazard Ratio</i>
HD	<i>Hormone-dependent</i>
HI	<i>Hormone-independent</i>
IQR	<i>Interquartile range</i>
KPS	<i>Karnofsky</i>
mGPS	<i>Modified Glasgow Prognostic Score</i>
NLR	<i>Neutrophil lymphocyte ratio</i>
PS	<i>Performance status</i>
SE	<i>Survival rate</i>
SIR	<i>Systemic inflammatory response</i>
UK	<i>United Kingdom</i>
WL	<i>Weight loss</i>

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1. INTRODUÇÃO

O câncer representa um grave problema de saúde pública, sendo a segunda principal causa de morte por doenças no Brasil e no mundo (INCA, 2022). De acordo com a *International Agency for Research on Cancer* (IARC), estima-se um total de 28,4 milhões de casos de câncer no mundo em 2040, um aumento de 47% em relação ao ano de 2020. As neoplasias de mama feminina, pulmão, colorretal, próstata e estômago são as mais incidentes no mundo (SUNG et al., 2021).

O câncer é classificado como avançado quando apresenta metástase e/ou recorrência loco-regional inoperável e que não é passível de cura. Nesse contexto, a *European Society of Medical Oncology* (ESMO) reconhece a importância da integração de cuidados de suporte e paliativos centrados no paciente desde o diagnóstico inicial e ao longo de toda a trajetória da doença. Ainda, o cuidado ao paciente não deve ter como único objetivo oferecer o tratamento oncológico mais qualificado, mas deve também considerar os impactos do diagnóstico da doença e do seu tratamento na vida de cada paciente (JORDAN et al., 2018; DALY et al., 2020).

Sabe-se que o manejo adequado do tratamento da doença e o planejamento do cuidado dependem da predição acurada da sobrevida do paciente (HUI et al., 2014). Dentro desta temática, destacam-se os fatores prognósticos, que são achados clínicos, patológicos e biológicos do paciente e do tumor, utilizados para predizer o comportamento clínico do paciente, sua sobrevida ou a possibilidade de recorrência da doença (PICCART-GEBHART et al. 2005).

Embora a estimativa clínica de sobrevida seja a abordagem mais utilizada para a formulação de um prognóstico, ela geralmente apresenta baixa acurácia e tende a superestimar a sobrevida em pacientes com câncer avançado (HUI, 2015). Além disso, apesar de serem comumente utilizados na prática clínica, fatores como estadiamento tumoral, grau histológico e fatores genéticos aparentemente

não têm impacto no prognóstico de pacientes com câncer avançado não passíveis de cura (KRISHNAN et al., 2013).

Dessa forma, diversos fatores prognósticos têm sido considerados no desenvolvimento de modelos prognósticos para pacientes com câncer avançado, incluindo a deterioração da capacidade funcional, dispneia, delírio, comprometimento cognitivo, síndrome anorexia-caquexia e anormalidades bioquímicas. Exemplos dessas ferramentas incluem a *Palliative Performance Scale* (PPS), *Palliative Prognostic Index* (PPI), *Palliative Prognostic Score* (PaP) e Nomograma Prognóstico de Barretos (NPB). Embora esses modelos sejam bem descritos na literatura, é necessário simplificá-los para a aplicação na prática clínica e buscar novos marcadores prognósticos objetivos (HUI, 2015). Devido à sua natureza subjetiva e complexa, muitas vezes essas ferramentas tornam-se menos acuradas e, conseqüentemente, menos utilizadas de forma rotineira.

Sendo assim, este estudo justifica-se pela necessidade de aprimorar a acurácia da predição de sobrevida de pacientes com câncer avançado, por meio da implementação de novas estratégias, como a criação de estruturas de avaliação prognóstica que incorporem fatores validados, objetivos, factíveis e de fácil aplicação prática.

1.1. Considerações iniciais

A formatação desta tese seguiu o modelo alternativo estabelecido pelo Programa de Pós-graduação em Ciências Saúde da Faculdade de Medicina na Universidade Federal de Uberlândia. Este modelo determina que os resultados sejam apresentados em formato de artigos científicos.

A organização da tese contempla as seguintes seções: **Fundamentação Teórica**, a qual será apresentada como forma de revisão da literatura sobre os temas abordados na tese; **Objetivos**, na qual são descritos os propósitos do estudo; **Resultados**, que apresenta os dois artigos elaborados; **Conclusão**, que sintetiza

os principais resultados do estudo; **Perspectivas**, que descreve expectativas para futuros estudos; **Pós-texto**, que inclui referências bibliográficas, anexos e apêndices.

O primeiro artigo intitulado “*Inflammation and Performance Status: The Cornerstones of Prognosis in Advanced Cancer*”, teve como objetivos comparar fatores prognósticos estabelecidos, como capacidade funcional, resposta inflamatória sistêmica e índice de massa corporal, em duas coortes internacionais de pacientes com câncer avançado; e estabelecer uma estrutura de avaliação prognóstica para estes pacientes. Esse artigo foi publicado em 6 de dezembro de 2022 no periódico *Journal of Pain and Symptom Management* (Fator de impacto = 5.576). Referência: ROCHA B.M.M., et al. Inflammation and Performance Status: The Cornerstones of Prognosis in Advanced Cancer. **J Pain Symptom Manage**. 2022 doi: <https://doi.org/10.1016/j.jpainsymman.2022.11.021>

O segundo artigo intitulado “*Prognostic value of GLIM criteria including systemic inflammation in patients with advanced cancer*”, teve como objetivo avaliar o valor prognóstico do critério GLIM incluindo índice de massa corporal (IMC), perda de peso e resposta inflamatória sistêmica em pacientes com câncer avançado. Este artigo está sob revisão no periódico *Cancers, Special Issue "Palliative Care in Cancer: Recent Advances and Upcoming Trends"* (Fator de impacto = 5.2).

2. FUNDAMENTAÇÃO TEÓRICA

A seguir, serão abordados aspectos relacionados à epidemiologia do câncer, à avaliação prognóstica clássica em pacientes oncológicos e aos principais fatores prognósticos utilizados na prática clínica, os quais foram avaliados e discutidos nos artigos elaborados nesta tese.

2.1. Epidemiologia do câncer

As estatísticas mundiais, segundo o *Global Cancer Statistics* em 2020, estimaram 19,3 milhões de novos casos de câncer e 10 milhões de óbitos anualmente, enquadrando a doença como a segunda causa de morte no mundo. Considerando esse total de casos, os cânceres mais comumente diagnosticados em todo o mundo foram mama feminina (2,3 milhões de casos, 11,7%), pulmão (11,4%), colorretal (10%), próstata (7,3%) e estômago (5,6%). Dados sobre mortalidade indicam que as principais causas de óbito foram câncer de pulmão (1,8 milhão de mortes, 18% do total de mortes por câncer), colorretal (9,4%), fígado (8,3%), estômago (7,7%) e câncer de mama (6,9%) (SUNG et. al., 2021).

Considerando o crescimento demográfico e o envelhecimento populacional, especialmente nas regiões menos desenvolvidas, as estimativas para o ano de 2030 indicam a ocorrência de 26 milhões de novos casos de câncer e cerca de 17 milhões de mortes. De acordo com a OMS, aproximadamente 57% dos casos e 70% dos óbitos por câncer ocorrem em países subdesenvolvidos (SUNG et. al., 2021).

Para cada ano do triênio 2023-2025, o Instituto Nacional do Câncer (INCA) estima que haverá 704 mil casos novos de câncer no Brasil, com destaque para as regiões Sul e Sudeste, que concentram cerca de 70% da incidência. O tipo de tumor maligno mais incidente no Brasil é o de pele não melanoma (31,3% do total de casos), seguido pelos de mama feminina (10,5%), próstata (10,2%), cólon e reto (6,5%), pulmão (4,6%) e estômago (3,1%) (INCA, 2022).

Totalizando 72 mil casos novos estimados a cada ano do próximo triênio, o câncer de próstata é predominante em todas as regiões, sendo superado apenas pelo câncer de pele não melanoma em homens. Os tumores malignos de cólon e reto ocupam a segunda ou a terceira posição nas regiões de maior Índice de Desenvolvimento Humano (IDH). Nas regiões de menor IDH, o câncer de

estômago é o segundo ou o terceiro mais frequente entre a população masculina (INCA, 2022).

Considerando a população feminina, depois do câncer de pele não melanoma, o de mama é o mais incidente, com 74 mil casos novos previstos por ano até 2025. Nas regiões de maior IDH, o câncer de mama é sucedido pelo câncer colorretal e, nas regiões menos desenvolvidas, o câncer de mama é sucedido pelo câncer do colo do útero (INCA, 2022).

Dentre os tipos de câncer mencionados anteriormente, observa-se que aproximadamente 6% (mama) a 60% (pulmão) dos casos já apresentam doença metastática ao diagnóstico, indicando que o tratamento curativo não é mais factível. Isso resulta em taxa de sobrevida estimada em cinco anos, variando de aproximadamente 29% (próstata) a 1% (pulmão) (SUNG et. al., 2021).

2.2 Prognóstico de pacientes com câncer avançado

Estimar o prognóstico de pacientes com câncer avançado é um componente fundamental do tratamento por diversas razões. Primeiramente, estimar o prognóstico de forma acurada é útil na avaliação dos benefícios do tratamento antineoplásico (ANSHUSHAUG et al., 2015; NAPPA et al., 2011). Ainda, a ansiedade do paciente e de seus familiares associada a um prognóstico incerto pode ser reduzida (SMITH et al., 2013). Por fim, um prognóstico acurado pode auxiliar no planejamento dos cuidados no final da vida, incluindo a determinação do local de atendimento (LAIRD et al., 2013).

No entanto, em pacientes com câncer avançado, os sistemas de classificação TNM (tumor, linfonodo e metástase), as características patológicas do tumor e os critérios clínicos de natureza subjetiva, como o status de desempenho (*performance status*), a experiência ou o conhecimento profissional, podem resultar em estimativas prognósticas imprecisas e potencialmente enganosas. Consequentemente, isso pode ensejar tratamentos ineficazes para o

paciente, tornando-o mais vulnerável a ser tratado inadequadamente (NAPPA et al., 2011).

Como dito, a estimativa clínica de sobrevida (ECS) é amplamente empregada na prática clínica para avaliar a expectativa de vida de pacientes oncológicos. No entanto, essa abordagem baseada na experiência e conhecimento do profissional de saúde apresenta limitações importantes. Estudos têm demonstrado consistentemente que os profissionais tendem a superestimar a sobrevida dos pacientes, comprometendo a precisão da ECS. A acurácia da ECS varia consideravelmente, estimando-se que esteja entre 20% e 30% (CHRISTAKIS et al., 2000; PEREZ-CRUZ et al., 2014).

Com o objetivo de aprimorar a acurácia prognóstica, a *European Association of Palliative Care* (EAPC) publicou, em 2005, diretrizes sobre a utilização de marcadores prognósticos em pacientes com câncer avançado. Essas recomendações foram baseadas em oito estudos distintos que avaliaram ferramentas prognósticas utilizadas na prática clínica entre os anos de 1993 e 2003. Entre as ferramentas recomendadas, destacam-se o *Terminal Cancer Prognostic Score*, a *Palliative Performance Scale*, o *Palliative Prognostic Index* e o *Palliative Prognostic Score* (MALTONI et al., 2005).

A partir dessas recomendações, estudos foram feitos no mundo todo, buscando desenvolver e validar novas ferramentas prognósticas, assim como avaliar a utilização dos instrumentos clássicos (GLARE et al., 2008).

Uma revisão sistemática recente da literatura, que comparou diferentes métodos de avaliação prognóstica, constatou que a maioria das ferramentas recomendadas depende em grande parte da avaliação do estado funcional como um componente central. Portanto, seu uso na prática clínica torna-se limitado, uma vez que é necessário realizar a avaliação funcional preliminarmente, por meio de um outro instrumento, para que posteriormente a ferramenta prognóstica possa ser plenamente aplicada. Além disso, os sistemas de pontuação

relativamente complexos também podem prejudicar a aplicabilidade dessas ferramentas (SIMMONS et al., 2017).

Um estudo prospectivo, que avaliou a acurácia da estimativa clínica de sobrevida (ECS) em 216 pacientes com câncer avançado, demonstrou que ferramentas compostas por parâmetros objetivos ou escalas numéricas são mais precisas do que a ECS. Ademais, a combinação da ECS com ferramentas objetivas resultou em uma redução da acurácia do modelo. Esse estudo destaca as limitações de ferramentas predominantemente subjetivas, ou seja, aquelas baseadas na observação e interpretação do profissional responsável. Essa subjetividade pode interferir diretamente na acurácia da estimativa prognóstica (HUI et al., 2016).

Apesar dos modelos prognósticos auxiliarem os profissionais de saúde na predição da sobrevida do paciente, cálculos com entendimento complexo ou com interpretação ambígua podem limitar sua utilidade clínica. Nesse sentido, é necessário realizar a tradução do conhecimento científico para a prática clínica, a fim de garantir a sua aplicabilidade efetiva (HUI et al., 2019).

Portanto, é inegável a relevância de se estabelecer um prognóstico acurado do paciente com câncer avançado. Apesar dos inúmeros desafios, a comunidade científica mundial tem se dedicado para criar estruturas de avaliação prognóstica mais acuradas, que integrem tanto fatores clássicos, como capacidade funcional, quanto fatores objetivos, como resposta inflamatória sistêmica e estado nutricional.

2.2.1 Capacidade funcional

A avaliação da capacidade funcional é, atualmente, o padrão-ouro e o parâmetro mais amplamente utilizado no prognóstico do câncer avançado. Essa avaliação é baseada nas informações fornecidas pelos pacientes oncológicos ou seus cuidadores sobre o desempenho de suas atividades diárias (LAIRD et al.,

2013). Os profissionais de saúde utilizam instrumentos específicos para mensurar essas informações e, conseqüentemente, classificar os pacientes de acordo com a sua capacidade física.

Considerando que o relato dos pacientes e/ou cuidadores pode não ser totalmente preciso e que a interpretação pode variar entre os profissionais de saúde, as ferramentas de avaliação da capacidade funcional são frequentemente consideradas subjetivas e, conseqüentemente, questionadas quanto à sua reprodutibilidade (LAIRD et al., 2013).

Dentre os diversos instrumentos para avaliação da capacidade funcional, o *Eastern Cooperative Oncology Group – Performance status* (ECOG-PS) é uma das escalas de funcionalidade mais conhecidas e utilizadas no mundo. Essa escala avalia o impacto da doença nas habilidades de vida diária do indivíduo, atribuindo uma pontuação que varia de zero a quatro pontos. O paciente pode ser classificado com escore 0 (completamente ativo, sem restrição), 1 (restrição a atividades físicas rigorosas, porém, é capaz de realizar trabalhos leves e de natureza leve ou sedentária), 2 (completamente capaz para o autocuidado, mas incapaz de realizar qualquer atividade de trabalho; permanece em pé aproximadamente 50% do tempo em que está acordado), 3 (capaz de realizar autocuidados limitados; restrito ao leito ou à cadeira mais de 50% do tempo em que está acordado), 4 (completamente incapaz de realizar autocuidados básicos; totalmente restrito ao leito ou à cadeira) (Quadro 1) (OKEN et al., 1982; PEREIRA; SANTOS; SARGES, 2014).

Quadro 1. Avaliação da capacidade funcional pelo *Eastern Cooperative Oncology Group – Performance status* (ECOG-PS)

Escore	Capacidade funcional
0	Completamente ativo, sem restrição
1	Restrição a atividades físicas rigorosas, porém, é capaz de realizar trabalhos leves e de natureza leve ou sedentária
2	Completamente capaz para o autocuidado, mas incapaz de realizar qualquer atividade de trabalho; permanece em pé aproximadamente 50% do tempo em que está acordado
3	Capaz de realizar autocuidados limitados; restrito ao leito ou à cadeira mais de 50% do tempo em que está acordado
4	Completamente incapaz de realizar autocuidados básicos; totalmente restrito ao leito ou à cadeira

Um estudo multicêntrico que avaliou pacientes com câncer avançado demonstrou que a capacidade funcional, avaliada por meio do ECOG-PS, foi capaz de prever, de forma independente, a sobrevida dos pacientes (LAIRD et al., 2013). Além disso, outro estudo prospectivo multicêntrico que avaliou 730 pacientes oncológicos concluiu que um escore elevado no ECOG-PS estava consistentemente associado à pior sobrevida dos pacientes (DOLAN et al., 2020). Esses estudos também demonstraram que a capacidade preditiva do ECOG-PS é aumentada quando essa ferramenta é associada a fatores prognósticos objetivos, como os relacionados à resposta inflamatória sistêmica (LAIRD et al., 2013; DOLAN et al., 2020).

2.1.2 Resposta inflamatória sistêmica

Sabe-se que o desenvolvimento do câncer ocasiona respostas inflamatórias sistêmicas capazes de alterar o metabolismo neuroendócrino, hematopoiético e proteico. O fígado desempenha um papel central na elaboração da resposta inflamatória sistêmica, uma vez que os hepatócitos sintetizam e liberam várias proteínas de fase aguda, como a proteína C-reativa (PCR), que desempenha um papel crucial no início e manutenção do processo inflamatório sistêmico (GABAY et al., 1999; THOMPSON, 1995).

Em pacientes com câncer, existem evidências claras do aumento da PCR e da diminuição da albumina como características de resposta inflamatória sistêmica. Ainda, essa relação é observada de forma semelhante em diferentes tipos de tumores (MCMILLAN et al., 2001).

Devido à sua sensibilidade, especificidade e fácil reprodutibilidade, a PCR é comumente utilizada para avaliar a magnitude da resposta inflamatória (GABAY et al., 1999; VERMEIRE et al., 2005). De fato, o aumento das concentrações dessa proteína tem sido associado à pior sobrevida em pacientes com câncer, especialmente em pacientes com doença avançada (MALTONI et al., 2005).

Em um estudo desenvolvido com 106 pacientes diagnosticados com câncer de pulmão não pequenas células, foi observado que o aumento da PCR foi associado à perda de peso ($> 5\%$), pior capacidade funcional e fadiga. Além disso, níveis elevados de PCR e baixa concentração de albumina foram associadas a uma pior sobrevida dos pacientes, independente do estadiamento tumoral (SCOTT et al., 2002).

Baseando-se nessas evidências, McMillan (2008) desenvolveu e validou o *Modified Glasgow Prognostic Score* (mGPS), uma ferramenta para avaliar a resposta inflamatória sistêmica baseada na combinação de níveis séricos de PCR (mg/L) e albumina (g/L). O mGPS atribui uma pontuação de 0 para pacientes que

apresentam PCR ≤ 10 , uma pontuação de 1 para pacientes que apresentam PCR >10 , e uma pontuação de 2 para pacientes que apresentam PCR >10 e albumina <35 (Quadro 2) (MCMILLAN, 2008). O mGPS é valorizado por ser uma escala de fácil e rápida utilização, além de ser composta exclusivamente por fatores objetivos (SIMMONS et al., 2017).

Quadro 2. Avaliação da resposta inflamatória sistêmica pelo *Modified Glasgow Prognostic Score* (mGPS)

Escore	PCR (mg/L)	Albumina (g/L)
0	≤ 10	--
1	>10	--
2	> 10	< 35

O valor prognóstico do mGPS foi avaliado em diversos estudos que envolveram grandes coortes de pacientes com diferentes cânceres avançados, como pulmão, mama, gastroesofágico, pancreático, renal e colorretal. Esses estudos demonstraram que o valor prognóstico do mGPS não está relacionado com o estadiamento tumoral, com o sistema de classificação TNM, com a capacidade funcional e nem com a alteração de leucócitos e linfócitos (CHOU et al., 2015).

Recentemente, um estudo que incluiu 650 pacientes com câncer colorretal demonstrou que a resposta inflamatória sistêmica, avaliada pelo mGPS, estava associada à sobrevida dos pacientes (DOLAN et al., 2019). Outro estudo, que envolveu 1.825 pacientes com câncer avançado e diversos tipos tumorais, também demonstrou uma associação consistente entre o mGPS e a sobrevida dos pacientes (LAIRD et al., 2013).

Especialmente por se tratar de uma ferramenta objetiva, a associação entre o mGPS e o ECOG-PS (uma ferramenta subjetiva), potencializa a capacidade

preditiva da ferramenta de avaliação funcional, conforme demonstrado nos estudos desenvolvidos por Dolan e colaboradores (DOLAN et al., 2019; DOLAN et al., 2020)

Dessa forma, as evidências literárias demonstram de forma robusta a capacidade preditiva do mGPS como ferramenta de avaliação da resposta inflamatória sistêmica. Ainda, quando associado a outras ferramentas subjetivas, a sua capacidade preditiva torna-se ainda mais acurada.

2.1.3 Estado nutricional

No câncer em particular, o tumor produz citocinas inflamatórias que alteram o metabolismo de carboidratos, proteínas e lipídeos. Essas citocinas podem impactar no controle neuroendócrino do apetite, causar perda de massa muscular e de tecido adiposo (MOLFINO et al., 2015), além de aumentar as necessidades energéticas e proteicas (RYAN et al., 2016). Esses fatores contribuem para o desenvolvimento da caquexia e sarcopenia em pacientes com câncer, os quais estão associados a uma pior qualidade de vida, maior toxicidade do tratamento e maior risco de mortalidade (RYAN et al., 2016).

Nesse contexto, o estado nutricional tem sido considerado um fator prognóstico importante para pacientes com câncer avançado. Estudos envolvendo pacientes oncológicos têm demonstrado que a progressão da doença está relacionada a uma deterioração gradual do estado nutricional e funcional, resultando em uma pior resposta ao tratamento e pior sobrevida. A perda de peso e o índice de massa corporal (IMC) são utilizados como indicadores dessa deterioração (DOLAN et al., 2019).

Estudos evidenciam que a perda desproporcional de tecido muscular esquelético é um fator prognóstico independente de sobrevida dos pacientes com câncer colorretal. Especificamente, a perda de massa muscular foi associada a

uma pior tolerância e resposta ao tratamento (AUTOUN et al., 2010) e pior qualidade de vida (BOZZETTI et al., 2017). Ainda, Malietzis e colaboradores (2016) reportaram que há associação significativa entre baixa densidade musculoesquelética e pior sobrevida de pacientes com câncer colorretal.

A caquexia do câncer (CC), por sua vez, é considerada uma síndrome multifatorial complexa caracterizada por perda contínua de massa muscular esquelética, com ou sem perda de massa gorda (FEARON et al., 2011). Pode afetar até metade dos pacientes com câncer avançado, e evidências recentes sugerem que a CC é responsável por aproximadamente 20% das mortes relacionadas ao câncer (ARENDS et al., 2021). Além disso, ela está negativamente associada à resposta ao tratamento (BACHMANN et al., 2008), função física, sobrevida e qualidade de vida de pacientes com câncer avançado (ARENDS et al., 2017; KAASA et al., 2008). Assim, por muito tempo, a caquexia foi reconhecida como um efeito adverso do câncer e seu manejo clínico é limitado e complexo (ARENDS et al., 2017; KAASA et al., 2008).

O consenso da *Global Leadership Initiative on Malnutrition* (GLIM) definiu caquexia como desnutrição relacionada à doença crônica com inflamação. Foi acordado que o diagnóstico da caquexia requer um dos três critérios fenotípicos reconhecidos (baixo IMC, perda de peso não voluntária e redução da massa muscular) e um critério etiológico (redução da ingestão alimentar e inflamação secundária à doença aguda ou crônica) (CEDERHOLM et al., 2019). No entanto, as estruturas para a aplicação clínica dos critérios GLIM ainda requerem validação.

Um estudo desenvolvido por Martin e colaboradores (2014) sugeriu a criação de um sistema de classificação de perda de peso ajustado ao IMC (classificação IMC/perda de peso). Esse sistema foi capaz de prever a sobrevida de pacientes com câncer avançado, independentemente da localização e estadiamento tumoral. O estudo observou que quanto maior o grau de classificação do paciente no sistema criado (classificação IMC/perda de peso),

menor a sua sobrevida. Ainda no mesmo estudo, os autores descreveram uma categorização de IMC capaz de discriminar melhor os pacientes oncológicos em 5 grupos: <20.0 ; 20.0 a 21.9 ; 22.0 a 24.9 ; 25.0 a 27.9 ; e ≥ 28.0 kg/m^2 (Quadro 3) (MARTIN et al., 2014).

Quadro 3. Categorização de IMC segundo Martin e colaboradores (2014).

Categorização de IMC
<20.0 kg/m^2
20.0 a 21.9 kg/m^2
22.0 a 24.9 kg/m^2
25.0 a 27.9 kg/m^2
≥ 28.0 kg/m^2

Em outro estudo do mesmo grupo, que analisou uma coorte de quase 5.000 pacientes, os pesquisadores demonstraram que a perda de peso é amplamente determinada pela ingestão alimentar e pela inflamação sistêmica (MARTIN et al., 2021). Os autores concluíram que a avaliação do padrão alimentar e da resposta inflamatória sistêmica podem melhorar o diagnóstico e a classificação da caquexia do câncer (MARTIN et al., 2021).

Diante do exposto, é evidente que o estado nutricional, assim como a capacidade funcional e a resposta inflamatória sistêmica, têm sido descritos como fatores prognósticos para pacientes com câncer avançado. No entanto, a acurácia desses fatores pode ser ampliada por meio da associação com outros indicadores, tornando importante a criação de novas estruturas para a avaliação prognóstica.

3. OBJETIVOS

3.1 Objetivo geral

Esta tese teve como objetivo geral avaliar a capacidade prognóstica de fatores subjetivos (funcionalidade) e objetivos (inflamação sistêmica e estado nutricional) em pacientes com câncer avançado.

3.2 Objetivos específicos

- Comparar a capacidade funcional, resposta inflamatória sistêmica e índice de massa corporal em duas coortes internacionais de pacientes com câncer avançado, visando a identificar diferenças significativas e associações prognósticas;
- Desenvolver e estabelecer uma estrutura de avaliação prognóstica precisa e confiável para pacientes com câncer avançado, integrando múltiplos fatores, como capacidade funcional, resposta inflamatória e índice de massa corporal;
- Avaliar o valor prognóstico do critério GLIM, incluindo índice de massa corporal (IMC), perda de peso e resposta inflamatória sistêmica, em pacientes com câncer avançado, a fim de determinar a sua eficácia na predição de desfechos clínicos relevantes.

4. RESULTADOS

4.1 Artigo 1

Intitulado “*Inflammation and Performance Status: The Cornerstones of Prognosis in Advanced Cancer*”, foi publicado em 6 de dezembro de 2022 no periódico *Journal of Pain and Symptom Management* (Fator de impacto = 5.576). Referência: ROCHA B.M.M., et al. Inflammation and Performance Status: The Cornerstones of Prognosis in Advanced Cancer. **J Pain Symptom Manage.** 2022 doi: <https://doi.org/10.1016/j.jpainsymman.2022.11.021>

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Original Article

Inflammation and Performance Status: The Cornerstones of Prognosis in Advanced Cancer

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Title: Inflammation and performance status: the cornerstones of prognosis in advanced cancer

Running title: Prognosis' cornerstones in advanced cancer

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Abstract

Background: In advanced cancer, although performance status (PS), systemic inflammatory response and nutritional status are known to have prognostic value, geographical variations and sociodemographic indexes may also impact survival. This study compares validated prognostic factors in two international cohorts and establishes a prognostic framework for treatment.

Methods: Two international biobanks of patients (n=1.518) with advanced cancer were analyzed. Prognostic factors (Eastern Cooperative Oncology Group Performance Status [ECOG-PS], body mass index [BMI] and modified Glasgow Prognostic Score [mGPS]) were assessed. The relationship between these and survival was examined using Kaplan–Meier and Cox regression methods.

Results: According to multivariate analysis, in the European cohort the most highly predictive factors were BMI <20 kg/m² (hazard ratio [HR] 1.644), BMI 20–21.9 kg/m² (HR 1.347), ECOG-PS (HR 1.597–11.992) and mGPS (HR 1.843–2.365). In the Brazilian cohort, the most highly predictive factors were ECOG-PS (HR 1.678–8.938) and mGPS (HR 2.103–2.837). Considering gastrointestinal cancers in particular (n=551), the survival rate at 3 months in both cohorts together ranged from 93% (mGPS 0, PS 0–1) to 0% (mGPS 2, PS 4), and from 81% (mGPS 0, BMI >28 kg/m²) to 44% (mGPS 2, BMI <20 kg/m²).

Conclusion: The established prognostic factors that were compared had similar prognostic capacity in both cohorts. A high ECOG-PS and a high mGPS as outlined in the ECOG-PS/mGPS framework were consistently associated with poorer survival of patients with advanced cancer in the prospective European and Brazilian cohorts.

Keywords: Advanced cancer, Inflammation, Performance status, Prognosis, Survival analysis.

Key message: This article compared prognostic factors in international cohorts of patients with advanced cancer and established a prognostic framework for treatment. A high ECOG-PS and mGPS were consistently associated with poorer survival and the ECOG-PS/mGPS framework proposed can be incorporated into the routine assessment due to its simplicity and clinical utility.

Introduction

The management of patients with advanced cancer should include a prognostic assessment as a fundamental component to guide appropriate care and optimal therapies to improve quality of life and survival [1, 2].

In this context, performance status (PS) in patients with advanced cancer is established using routine prognostic tools such as Karnofsky (KPS) or Eastern Cooperative Oncology Group (ECOG) [2]. However, PS is a subjective assessment as it is primarily based on daily living activities, and this depends on the information giving by the patient and carers [2].

Simmons and colleagues, following a systematic review [1], carried out a prospective comparison of validated prognostic factors and identified that, in addition to PS, the modified Glasgow Prognostic Score (mGPS), a method used to measure systemic inflammation that uses a combination of C-reactive protein (CRP) and albumin, had independent prognostic value [3,4].

Another study showed that the mGPS predicts survival in advanced cancer independently and performs well compared with PS in terms of prognostic power. Yet, these findings highlighted that the combination of mGPS (objective measure) and PS (subjective measure), synergistically, effectively predicted survival [2].

A multi-center observational study with prospective follow-up of 414 incurable cachectic cancer patients showed that mGPS, PS and tumor spread were significantly associated with 3 and 6-month survival [5]. Recently, two systematic reviews provided consistent evidence that the presence of a systemic inflammatory response as evidenced by the mGPS is associated with the loss of lean tissue, anorexia, weakness and fatigue and poor survival in patients with advanced cancer [6, 7].

Given the above, it is important to extend these data to different populations and in different geographic locations. Knowing that several external factors, such as geographical variations and sociodemographic indexes may impact the survival of patients with advanced cancer [8,9], one hypothesis of this study is that even in international and multicentric samples, physical function, systemic inflammation, and nutrition remain strong prognostic factors.

In this way, the present study had two aims: Firstly, to compare established prognostic factors, such as performance status, systemic inflammatory response, and body mass index in two international cohorts of patients with advanced cancer. Secondly, to establish a prognostic framework for treatment in this cohort.

Materials and Methods

Study population

Analysis was undertaken on two international biobanks of adult cancer patients: the European cohort and the Brazilian cohort.

The European cohort was a prospective data collection of patients across sites in the United Kingdom and Ireland between 2011 and 2016 [10, 11] whereas the Brazilian cohort included patients from Brazil (Barretos Cancer Hospital, Barretos-SP) over three years (2011–

2014). In both cohorts, eligible adult patients with advanced cancer (defined as locally advanced or with histological, cytological, or radiological evidence of metastasis), across all cancer subtypes, who provided a venous blood sample and with a recorded ECOG-PS were assessed for inclusion. In the European cohort, patients who were undergoing active anticancer therapy or not, in either an inpatient or outpatient setting were included. In the Brazilian cohort, patients who attended the Palliative Care Outpatient Clinic for their first consultation, regardless of whether or not they were undergoing palliative antineoplastic treatment, were included.

All patients provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (West of Scotland Ethics Committee UK: 18/WS/0001 [18/01/2018]; Cork Research Ethics Committee Ireland: ECM 4 [g] [03/03/2015]; Ethics Committee of the Barretos Cancer Hospital [HCB433/2011 and HCB783/2014]). The study also conformed to the STROBE guidelines for cohort studies [12].

Procedure and assessment

General demographic data and clinicopathological characteristics were recorded for each patient. Primary cancer site was grouped as lung, breast, gynecological, gastrointestinal, urological, hematological, skin and soft tissue, neurological, head and neck, unknown primary, and other. Then, these groups of mentioned tumor sites were categorized into hormone-dependent (breast, gynecologic and urological) and hormone-independent (lung, gastrointestinal, hematological, skin and soft tissue, neurological, head and neck, unknown primary, and others). ECOG-PS was determined by a clinician or clinical researcher at the institute the patient was receiving treatment. Patients were categorized according to their ECOG-PS into five grades (grades 0–4) and then grouped as 0-1/2/3/4, as previously described

[10]. Patients were categorized according to BMI as previously described (<20.0, 20.0 to 21.9, 22.0 to 24.9, 25.0 to 27.9, and ≥ 28.0 kg/m²) [13]. The systemic inflammatory response was analyzed using CRP and albumin. The biomarkers were taken by venous blood sampling at entry points in both studies and all samples were analyzed at a central laboratory. The mGPS was calculated and grouped as follows [14]: mGPS 0 (CRP $\leq$ 10mg/L), mGPS 1 (CRP > 10mg/L) and mGPS 2 (CRP > 10mg/L and albumin < 35 g/L) [14].

Statistical analysis

The survival time, defined as the number of months from study entry until death, or censored if alive at the follow-up date, was calculated. Survival curves were plotted using Kaplan–Meier methods and the log-rank test was applied. Survival analysis was carried out using Cox proportional hazards model, and hazard ratios (HR) were calculated. Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding P value had to be >0.10. The Chi-square test was used for comparisons of categorical variables. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Two-sided P-values less than 0.05 were considered significant. All analyzes were conducted in SPSS Version 20 (SPSS Inc).

Results

European cohort

The clinicopathological characteristics from 1,027 European cohort patients are shown in Table 1. The median age was 65.87 years (interquartile range [IQR] 56.93–73.57) and 524 patients were male (51%). The majority of patients had either BMI ≥ 28 kg/m² (29%, n=279) or BMI 22–24.9 kg/m² (24%, n=223). The majority of patients had either gastrointestinal (40%, n=411) or lung (26%, n=266) tumors as primary cancer sites. The median ECOG-PS was 1 (IQR 1–2). 43% of the patients had mGPS 0 and 40% of the patients had mGPS 2. At the time of cessation of data collection, 317 patients were alive (31%) and 710 (69%) had died. The median survival was 7.3 months (IQR 3.3 – 16.7).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular (n=411), their clinicopathological characteristics are shown in Table 2. The median age was 66.44 years (IQR 57.02–74.41) and 253 patients were male (62%). The majority of patients had either BMI ≥ 28 kg/m² (27%, n=102) or BMI 22–24.9 kg/m² (27%, n=105). The median ECOG-PS was 1 (IQR 1–2). 46% of the patients had mGPS 0 and 41% of the patients had mGPS 2. At the time of cessation of data collection, 96 patients were alive (23%) and 315 (77%) had died. The median survival was 7.7 months (IQR 3.4 – 16.8).

The relationship between clinicopathological characteristics and survival in patients with advanced cancer is shown in Table 3. On univariate survival analysis, age >74 ($P = 0.048$), BMI 20–21.9 kg/m² ($P = 0.006$), primary tumor site ($P < 0.001$), ECOG-PS (all $P < 0.001$) and mGPS ($P < 0.001$) were significantly associated with survival. Age (65–74) and sex were not associated with survival. On multivariate survival analysis, the most highly predictive factors

were BMI $<20 \text{ kg/m}^2$ (HR 1.644, $P=0.001$), BMI $20\text{--}21.9 \text{ kg/m}^2$ (HR 1.347, $P=0.044$), ECOG-PS (HR 1.597–11.992, all $P < 0.001$) and mGPS (HR 1.843–2.365, all $P < 0.001$).

When further stratification of the sample was carried out for gastrointestinal cancers in particular, the relationship between their clinicopathological characteristics and survival is shown in Table 4. On univariate survival analysis, ECOG-PS (all $P < 0.001$) and mGPS 1 and 2 ($P=0.004$ and $P < 0.001$, respectively) were significantly associated with survival. Age, sex and BMI were not associated with survival. On multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 1.911–19.518, all $P < 0.001$) and mGPS 1 and 2 (HR 1.736–2.270, $P = 0.004$ and $P < 0.001$, respectively).

Brazilian cohort

The clinicopathological characteristics of 491 patients in the Brazilian cohort are shown in Table 1. The median age was 60 years (IQR 52–69) and 271 patients were female (55%). The majority of patients had either BMI $\geq 28 \text{ kg/m}^2$ (25%, $n=120$) or BMI $< 20 \text{ kg/m}^2$ (24%, $n=114$). The majority of patients had either gastrointestinal (29%, $n=140$) or breast (21%, $n=102$) tumors as primary cancer sites. The median ECOG-PS was 2 (IQR 1–2). 80% of the patients had mGPS 0 and 13% of the patients had mGPS 2. At the time of cessation of data collection, 38 (8%) patients were alive and 453 (92%) had died. The median survival was 4.6 months (IQR 2 – 10.7).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular ($n=140$), their clinicopathological characteristics are shown in Table 2. The median age was 63 years (IQR 57.2–68.9) and 80 patients were male (57%). The majority of patients had either BMI $< 20 \text{ kg/m}^2$ (36%, $n=49$) or BMI $20\text{--}21.9 \text{ kg/m}^2$ (19%, $n=26$). The median ECOG-PS was 2 (IQR 1–2). 76% of the patients had mGPS 0 and 15% of the patients had

mGPS 2. At the time of cessation of data collection, 10 patients were alive (7%) and 130 (93%) had died. The median survival was 4.15 months (IQR 2.0 – 9.2).

The relationship between clinicopathological characteristics and survival in patients with advanced cancer is shown in Table 3. According to univariate survival analysis, sex ($P = 0.001$), BMI $<20 \text{ kg/m}^2$ ($P = 0.001$), BMI 22-24.9 kg/m^2 ($P = 0.006$), primary tumor site ($P = 0.002$), ECOG-PS (all $P < 0.01$) and mGPS ($P < 0.001$) were significantly associated with survival. Age was not associated with survival. According to multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 1.678–8.938, all $P < 0.001$) and mGPS (HR 2.103–2.837, all $P < 0.001$).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular, the relationship between their clinicopathological characteristics and survival is shown in Table 4. According to univariate survival analysis, ECOG-PS (all $P < 0.001$) and mGPS 2 ($P < 0.001$) were significantly associated with survival. Age, sex and BMI were not associated with survival. According to multivariate survival analysis, the most highly predictive factors were ECOG-PS (HR 2.380–14.081, all $P < 0.001$) and mGPS (HR 2.147–2.208, $P = 0.015$ and $P = 0.003$, respectively).

Considering the relationship between mGPS, performance status, BMI and survival in the European cohort, increasing mGPS was significantly associated with poorer survival ($P < 0.001$). Also, worsening performance status and BMI 20-21.9 kg/m^2 were associated with poorer survival ($P < 0.001$ and $P = 0.02$, respectively) (Figure 1). These findings were similar in the Brazilian cohort (Figure 2). Increasing mGPS, worsening performance status and BMI $<20 \text{ kg/m}^2$ were significantly associated with poorer survival ($P < 0.001$, $P < 0.001$ and $P = 0.006$, respectively).

When further stratification of the sample was carried out for gastrointestinal cancers, in particular, the relationship between mGPS, performance status, BMI and survival rate at 3

months in both cohorts together is shown in Table 5. When mGPS and ECOG-PS were used in combination, survival at 3 months ranged from 93% (mGPS 0, ECOG-PS 0–1) to 0% (mGPS 2, ECOG-PS 4). When mGPS and BMI were used in combination, survival at 3 months ranged from 81% (mGPS 0, BMI >28 kg/m²) to 44% (mGPS 2, BMI < 20 kg/m²).

Discussion

The results of the present study show that performance status and mGPS, which independently predicted survival, were the strongest predictors of survival in the European and Brazilian cohorts. Furthermore, although there was considerable variation in case mix between the cohorts, these prognostic factors had similar Hazard Ratios across both datasets (in particular mGPS). Although an objective marker of nutritional status, BMI did not show consistent prognostic value.

The results of the present study are consistent with the observations of Dolan and co-workers who found that ECOG-PS and mGPS remained independently associated with overall survival in 730 patients with advanced cancer [11]. In addition, Simmons and colleagues showed that ECOG-PS, mGPS, and neutrophil count were independent predictors of survival of 478 patients with advanced cancer at 1 and 3 months [3]. These results are consistent with a systematic review and meta-analysis of the systemic inflammatory response in predicting outcomes that showed a significant association between elevated mGPS and overall survival in thirty six studies of patients with advanced inoperable cancer [15].

When further stratification of the results was carried out for gastrointestinal cancers, in particular, similar results were obtained by univariate and multivariate analysis in both the European and Brazilian cohorts, suggesting that ECOG-PS and mGPS could be independent prognostic factors in different cancer types and remain strong when used in combination.

Therefore, the present study highlights the ECOG-PS/mGPS prognostic framework for patients with advanced cancer in both cohorts and its use should be considered as part of routine assessment.

The present study shows that BMI had a modest impact on the survival prediction of patients in both cohorts. Similarly, Fearon and co-workers found that weight loss alone did not identify the full effect of cachexia on physical function and was not a prognostic variable. In this way, the authors proposed a three-factor profile assessment to identify patients at risk of adverse outcomes: weight loss, reduced food intake and systemic inflammation [16]. Also, a prospective study concluded that some extra factors gain importance in the survival prediction of patients with cancer cachexia, such as chronic inflammation, anemia, protein depletion, reduced food intake, fatigue, decreased muscle strength and lean tissue depletion [17]. It is important to consider that Cederholm and co-workers proposed the Global Leadership Initiative on Malnutrition (GLIM) criteria that defined cancer cachexia as a chronic disease related to malnutrition and inflammation. The three phenotypic criteria identified were involuntary weight loss, low BMI and low muscle mass, and the tumor etiologic criteria were reduced food intake or assimilation and inflammation or disease burden [18]. Given this, an international and multi-cohort analysis of almost 13,000 patients reported that weight loss is largely determined by dietary intake and systemic inflammation measured by CRP [19]. Also, in the context of GLIM phenotypic criteria, a consistent association between the systemic inflammatory response and low muscle mass has been reported in a recent systematic review [6].

In daily practice, oncologists often have to decide whether to maintain or stop anticancer treatments for patients with advanced cancers. In this complex task, they need to take into account the risks and potential benefits of anticancer therapy and the beliefs, desires and treatment goals of the patients [20]. Moreover, estimating the prognosis is a cornerstone in this decision-making process. The performance status assessment, usually performed by the ECOG-

PS, is essential for the oncologist to map the patient's clinical conditions while estimating at the same time the treatment risks and the patient's prognosis. We believe that the addition of mGPS to the ECOG-PS should improve the ability to assess the patient in these situations. The patient with ECOG-PS 2, for example, is in a borderline condition to continue with chemotherapy. In these cases, if the mGPS is 2, the prescription of chemotherapy is very unfavorable. Further studies need to prospectively evaluate the impact of the ECOG-PS/mGPS framework in the real-world decision-making process.

The present study had limitations. It is subject to sample bias and the majority of patients were undergoing palliative care and it may be assumed that there was a high symptom burden which has been an indicator of a shorter prognosis. Also, there was heterogeneity in the primary cancer types. However, the prognostic value was consistent across tumor types. Finally, in the present study, weight loss (WL) data was not reliably recorded in most patients and therefore the BMI/WL grade was not assessed. Nevertheless, these data may be readily tested in other prospective datasets.

In summary, the established prognostic factors compared had similar prognostic capacity in both cohorts. A high ECOG-PS and a high mGPS, as outlined in the ECOG-PS/mGPS framework, were consistently associated with poorer survival of patients with advanced cancer in the prospective European and Brazilian cohorts. It can be readily incorporated into the routine assessment of patients due to its simplicity and clinical utility.

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Authors' contributions

Conceptualization, design and methodology (B.M.M.R., R.D.D., C.E.P., J.M., D.C.M, Y.C.P.M., B.J.L.), data curation (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P, D.C.M, Y.C.P.M., B.J.L.), formal analysis (B.M.M.R., R.D.D., C.E.P., J.M., D.C.M, Y.C.P.M., B.J.L.), funding acquisition (B.M.M.R., R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), project administration (B.M.M.R., R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), supervision (R.D.D., C.E.P., D.C.M, Y.C.P.M., B.J.L.), writing: original draft (B.M.M.R., C.E.P., D.C.M, Y.C.P.M., B.J.L.), review and editing (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P, D.C.M, Y.C.P.M., B.J.L.).

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

All patients provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018); Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015); Ethics Committee of the Barretos Cancer Hospital (HCB433/2011 and HCB783/2014))

Data availability

The datasets that formed the basis of this article are contained in the University of Glasgow's MVLS institute (Scotland) and Barretos Cancer Hospital (Brazil). They contain patient sensitive information and therefore cannot be made available on a public repository.

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Table 1. Clinicopathological characteristics of patients with advanced cancer – European cohort (n=1027) and Brazilian cohort (n=491).

Parameter	European cohort (n = 1027)	Brazilian Cohort (n = 491)	P - value ^a
	n (%)	n (%)	
Age			<0.001
<65 years	483 (47)	301 (61)	
65-74 years	300 (29)	116 (24)	
74 years	244 (24)	74 (15)	
Sex			0.023
Male	524 (51)	220 (45)	
Female	503 (49)	271 (55)	
BMI ^b			<0.001
< 20.0 kg/m ²	122 (13)	114 (24)	
20 - 21.9 kg/m ²	123 (13)	64 (13)	
22 - 24.9 kg/m ²	223 (24)	95 (20)	
25 - 27.9 kg/m ²	202 (21)	85 (18)	
>= 28.0 kg/m ²	279 (29)	120 (25)	
Primary cancer site			<0.001
Lung	266 (26)	68 (14)	
Breast	91 (9)	102 (21)	
Gynecological	64 (6)	49 (10)	
Gastrointestinal	411 (40)	140 (29)	
Urological	69 (7)	55 (11)	
Hematological	43 (4)	0 (0)	
Skin and soft tissue	40 (4)	20 (4)	
Neurological	10 (1)	4 (1)	
Head and neck	0 (0)	40 (8)	
Unknown primary	12 (1)	11 (2)	
Others	21 (2)	2 (0)	
ECOG ^c			<0.001
0/1	575 (59)	186 (38)	
2	292 (30)	188 (38)	
3	96 (10)	93 (19)	
4	16 (1)	23 (5)	
mGPS ^d			<0.001
0	353 (43)	367 (80)	
1	139 (17)	31 (7)	
2	329 (40)	59 (13)	
Status			<0.001
Alive	317 (31)	38 (8)	
Dead	710 (69)	453 (92)	

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

^a P value from χ^2 analysis.

^bBMI available on 949 patients in the European cohort and 478 patients in the Brazilian cohort.

^cECOG available on 979 patients in the European cohort and 490 patients in the Brazilian cohort.

^dmGPS available on 821 patients in the European cohort and 457 patients in the Brazilian cohort.

Table 2. Clinicopathological characteristics of patients with gastrointestinal cancers – European cohort (n=411) and Brazilian cohort (n=140).

Parameter	European cohort (n = 411) n (%)	Brazilian Cohort (n = 140) n (%)	P - value^a
Age			0.023
<65 years	187 (45)	78 (56)	
65-74 years	118 (29)	41 (29)	
74 years	106 (26)	21 (15)	
Sex			0,356
Male	253 (62)	80 (57)	
Female	158 (38)	60 (43)	
BMI ^b			<0.001
< 20.0 kg/m ²	46 (12)	49 (36)	
20 - 21.9 kg/m ²	51 (13)	26 (19)	
22 - 24.9 kg/m ²	105 (27)	21 (15)	
25 - 27.9 kg/m ²	79 (21)	18 (13)	
>= 28.0 kg/m ²	102 (27)	24 (17)	
ECOG ^c			<0.001
0/1	246 (61)	57 (41)	
2	111 (28)	53 (38)	
3	36 (9)	26 (19)	
4	8 (2)	4 (3)	
mGPS ^d			<0.001
0	159 (46)	101 (76)	
1	45 (13)	12 (9)	
2	145 (41)	20 (15)	
Status			<0.001
Alive	96 (23)	10 (7)	
Dead	315 (77)	130 (93)	

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

^a P value from χ^2 analysis.

^b BMI available on 383 patients in the European cohort and 138 patients in the Brazilian cohort.

^c ECOG available on 401 patients in the European cohort.

^d mGPS available on 349 patients in the European cohort and 133 patients in the Brazilian cohort.

Table 3. The relationship between clinicopathological factors and survival in patients with advanced cancer – European cohort (n=1027) and Brazilian cohort (n=491).

		European cohort					Brazilian cohort					
		Univariate ^a		Multivariate ^a		Patients <i>N</i>	Univariate ^a		Multivariate ^a			
	Patients <i>N</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>		
Age												
<65	483	1.000 (Ref.)				301	1.000 (Ref.)					
65-74	300	1.100 (0.926-1.307)		0.276		116	1.181 (0.946-1.475)		0.143			
>74	244	1.209 (1.002-1.459)		0.048		74	1.138 (0.872-1.486)		0.340			
Sex												
Female	503	1.000 (Ref.)				271	1.000 (Ref.)					
Male	524	1.135 (0.980-1.315)		0.092		220	1.357 (1.126-1.635)		0.001			
BMI												
<20.0	122	1.287 (0.994 – 1.667)		0.055	1.644 (1.219 – 2.216)	0.001	114	1.585 (1.209 – 2.078)		0.001	1.253 (0.926 – 1.697)	0.144
20.0 – 21.9	123	1.411 (1.104 – 1.802)		0.006	1.347 (1.007 – 1.802)	0.044	64	1.306 (0.951 – 1.794)		0.099	1.159 (0.823 – 1.632)	0.398
22.0 – 24.9	223	0.993 (0.802 – 1.230)		0.948	1.142 (0.890 – 1.466)	0.296	95	1.483 (1.120 – 1.962)		0.006	1.282 (0.955 – 1.722)	0.099
25.0 – 27.9	202	0.873 (0.698 – 1.093)		0.873	1.059 (0.814 – 1.377)	0.671	85	1.130 (0.842 – 1.518)		0.416	1.224 (0.897 – 1.670)	0.203
≥28	279	1.000 (Ref.)			1.000 (Ref.)		120	1.000 (Ref.)			1.000 (Ref.)	
Primary tumor site												
HD	224	1.000 (Ref.)				206	1.000 (Ref.)					
HI	803	1.421 (1.181 – 1.708)		<0.001	1.187 (0.921 – 1.530)	0.184	285	1.354 (1.121 – 1.635)		0.002	1.216 (0.976 – 1.514)	0.081
Performance status												
ECOG 0/1	575	1.000 (Ref.)			1.000 (Ref.)		186	1.000 (Ref.)			1.000 (Ref.)	
ECOG 2	292	2.015 (1.696-2.395)		<0.001	1.597 (1.308 – 1.950)	<0.001	188	1.756 (1.416-2.176)		<0.001	1.678 (1.337 – 2.105)	<0.001
ECOG 3	96	3.830 (3.001-4.887)		<0.001	2.469 (1.804 – 3.312)	<0.001	93	2.826 (2.171-3.678)		<0.001	2.449 (1.822 – 3.292)	<0.001
ECOG 4	16	22.699 (13.471-38.247)		<0.001	11.992 (6.346 – 22.663)	<0.001	23	10.344 (6.545-16.348)		<0.001	8.938 (5.426–14.722)	<0.001
mGPS												
mGPS 0	353	1.000 (Ref.)			1.000 (Ref.)		367	1.000 (Ref.)			1.000 (Ref.)	
mGPS 1	139	2.014 (1.577-2.573)		<0.001	1.843 (1.403 – 2.422)	<0.001	31	1.987 (1.370-2.880)		<0.001	2.103 (1.437 – 3.078)	<0.001
mGPS 2	329	2.849 (2.362-3.435)		<0.001	2.365 (1.928 – 2.900)	<0.001	59	3.761 (2.819-5.017)		<0.001	2.837 (2.083 – 3.864)	<0.001

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; HD, hormone-dependent; HI, hormone-independent.

^aHR expressed as per 10 unit change.

Table 4. The relationship between clinicopathological factors and survival in patients with gastrointestinal cancers – European cohort (n=411) and Brazilian cohort (n=140).

	European cohort					Brazilian cohort				
	Patients <i>N</i>	Univariate ^a		Multivariate ^a		Patients <i>N</i>	Univariate ^a		Multivariate ^a	
		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age										
<65	187	1.000 (Ref.)				78	1.000 (Ref.)			
65-74	118	0.953 (0.732-1.240)	0.720			41	1.261 (0.849-1.874)	0.250		
>74	106	1.198 (0.909-1.579)	0.200			21	0.879 (0.530-1.460)	0.619		
Sex										
Female	158	1.000 (Ref.)				60	1.000 (Ref.)			
Male	253	0.936 (0.747-1.174)	0.570			80	1.123 (0.792-1.591)	0.515		
BMI										
<20.0	46	1.104 (0.732 – 1.667)	0.637			49	1.153 (0.701 – 1.896)	0.575		
20.0 – 21.9	51	1.107 (0.753 – 1.626)	0.606			26	0.760 (0.430 – 1.343)	0.344		
22.0 – 24.9	105	0.959 (0.702 – 1.309)	0.790			21	1.036 (0.571 – 1.880)	0.907		
25.0 – 27.9	79	0.922 (0.661 – 1.287)	0.632			18	0.781 (0.413 – 1.479)	0.449		
>=28	102	1.000 (Ref.)				24	1.000 (Ref.)			
Performance status										
ECOG 0/1	246	1.000 (Ref.)		1.000 (Ref.)		57	1.000 (Ref.)		1.000 (Ref.)	
ECOG 2	111	2.074 (1.603-2.682)	<0.001	1.911 (1.455 – 2.514)	<0.001	53	2.338 (1.538-3.554)	<0.001	2.380 (1.542 – 3.672)	<0.001
ECOG 3	36	2.734 (1.840-4.062)	<0.001	2.012 (1.326 – 3.052)	0.001	26	2.491 (1.530-4.054)	<0.001	2.568 (1.516 – 4.350)	<0.001
ECOG 4	8	32.567 (15.040-70.521)	<0.001	19.518 (8.914 – 42.735)	<0.001	4	14.983 (5.114-43.896)	<0.001	14.081 (4.654–42.604)	<0.001
mGPS										
mGPS 0	159	1.000 (Ref.)		1.000 (Ref.)		101	1.000 (Ref.)		1.000 (Ref.)	
mGPS 1	45	1.758 (1.204-2.569)	0.004	1.736 (1.187 – 2.538)	0.004	12	1.741 (0.950-3.192)	0.073	2.147 (1.158 – 3.980)	0.015
mGPS 2	145	2.529 (1.951-3.279)	<0.001	2.270 (1.737 – 2.968)	<0.001	20	2.611 (1.577-4.323)	<0.001	2.208 (1.300 – 3.749)	0.003

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

^a HR expressed as per 10 unit change.

Table 5 – The relationship between the mGPS, performance status and BMI and the survival rate at 3 months in patients with gastrointestinal cancers – European cohort and Brazilian cohort (n=551)

Performance status (ECOG grouping)	mGPS 0 (n=260)	mGPS 1 (n=57)	mGPS 2 (n=165)	<i>P-Value</i>	mGPS 0-2 (n=482)
0-1 (n = 303)	93% (n=147)	83% (n=25)	85% (n=56)	0.724	90% (n=228)
2 (n = 164)	74% (n=59)	62% (n=13)	46% (n=25)	<0.001	63% (n=97)
3 (n = 62)	65% (n=13)	(n=1)	31% (n=11)	<0.001	42% (n=25)
4 (n = 12)	(n=0)	(n=0)	(n=0)		(n=0)
<i>P-Value</i>	0.071	<0.001	<0.001		
0-4 (n = 541)	84% (n=219)	68% (n=39)	65% (n=92)		73% (n=350)
Body mass index (BMI grouping)	mGPS 0 (n=260)	mGPS 1 (n=57)	mGPS 2 (n=165)	<i>P-Value</i>	mGPS 0-2 (n=482)
≥28 (n=126)	81% (n=38)	93% (n=13)	63% (n=27)	0.002	75% (n=78)
25.0 – 27.9 (n=97)	89% (n=47)	(n=8)	79% (n=15)	<0.001	80% (n=70)
22.0 – 24.9 (n=126)	87% (n=47)	(n=7)	64% (n=29)	<0.001	75% (n=83)
20.0 – 21.9 (n=77)	90% (n=38)	(n=5)	(n=8)	<0.001	80% (n=51)
<20 (n=95)	77% (n=43)	(n=1)	44% (n=12)	<0.001	64% (n=56)
<i>P-Value</i>	0.753	0.023	<0.001		
<20 - ≥28 (n=521)	85% (n=213)	68% (n=34)	61% (n=91)		75% (n=338)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index.

NOTE: Survival rate (SE)% at 3 months, not calculated if n < 10.

Figure 1 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. European cohort (n = 1.027).

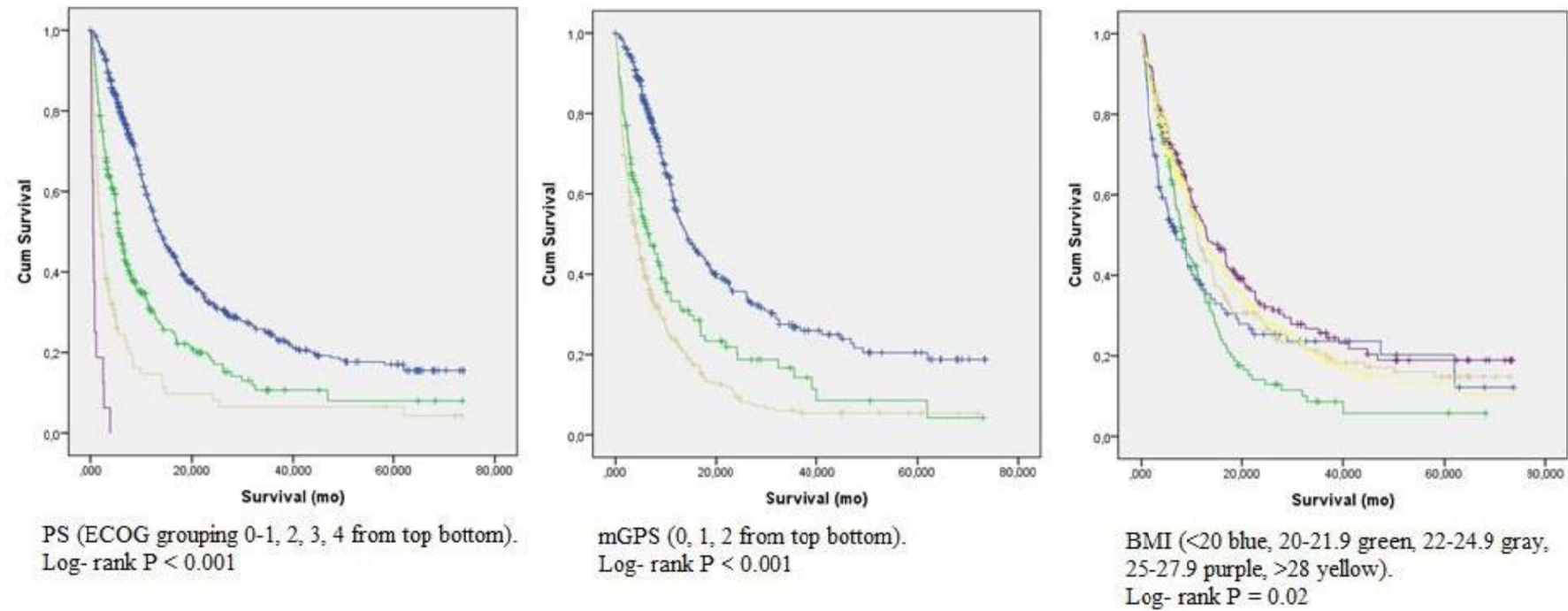
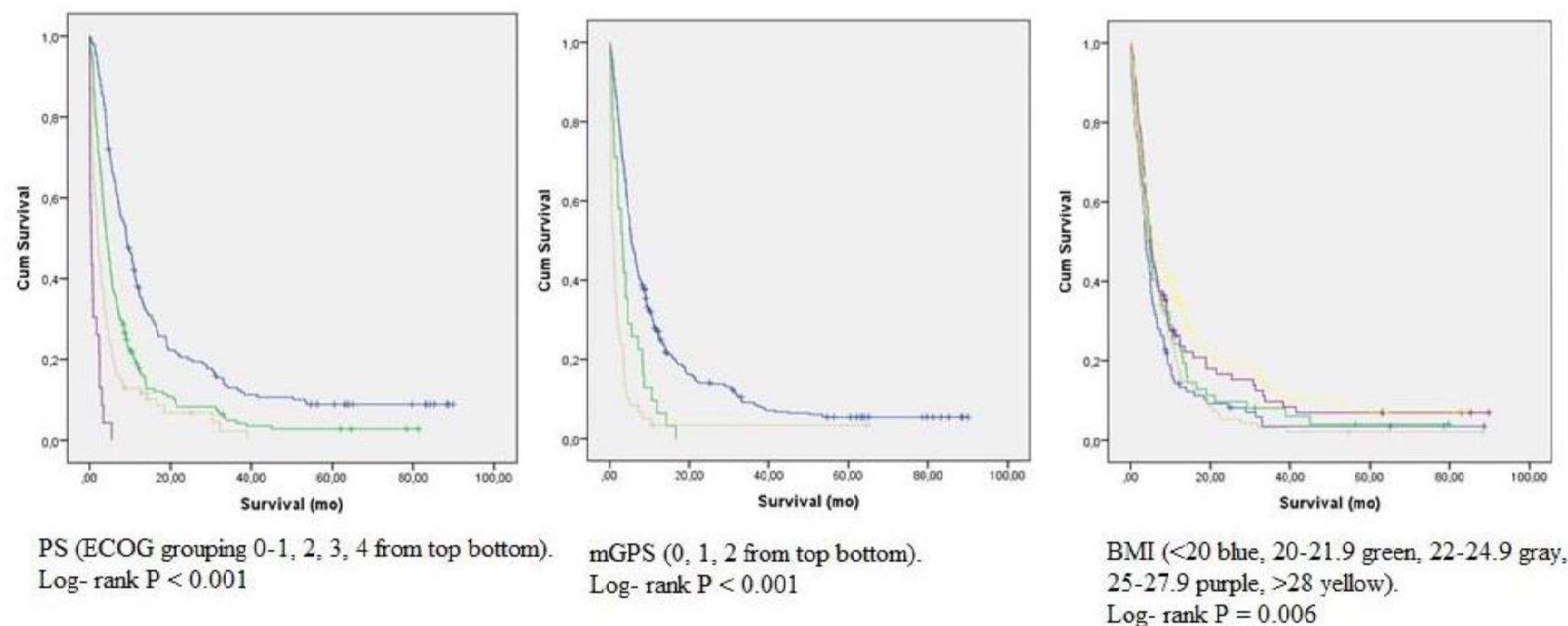


Figure 2 – Kaplan–Meier curves examining the relationship between performance status (ECOG grouping) and survival, mGPS and survival, and BMI and survival. Brazilian cohort (n = 491).



4.2 Artigo 2

Intitulado “*Prognostic value of GLIM criteria including systemic inflammation in patients with advanced cancer*”, está sob revisão no periódico *Cancers, Special Issue "Palliative Care in Cancer: Recent Advances and Upcoming Trends"* (Fator de impacto = 5.2).

Title: Prognostic value of GLIM criteria including systemic inflammation in patients with advanced cancer

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Abstract

An assessment of systemic inflammation and nutritional status may form the basis of a framework to examine the prognostic value of cachexia in patients with advanced cancer. The study examined the prognostic value of The Global Leadership Initiative on Malnutrition (GLIM) criteria in patients with advanced cancer (n=1.303). The relationship between these and survival was examined using Cox regression methods. Considering body mass index (BMI) and systemic inflammation (mGPS), the survival rate at 3 months varied from 74% (BMI>28 kg/m²) to 61% (BMI <20 kg/m²) and from 84% (mGPS 0) to 60% (mGPS 2). Considering weight loss (WL) and the mGPS, the survival rate varied from 81% (WL $\pm$ 2.4%) to 47% (WL $\geq$ 15%) and from 93% (mGPS 0) to 60% (mGPS 2). Considering BMI/WL grade and mGPS, the survival rate varied from 86% (BMI/WL grade 0) to 59% (BMI/WL grade 4) and from 93% (mGPS 0) to 63% (mGPS 2). On multivariate analysis, the most highly predictive factors were BMI/WL grade 3 (HR 1.454, P=0.004), BMI/WL grade 4 (HR 2.285, P<0.001) and mGPS (HR 1.887–2.545, all P < 0.001). A high BMI/WL grade and a high mGPS as outlined in the BMI/WL grade/mGPS framework were consistently associated with poorer survival.

Keywords: Advanced cancer; Palliative care; Systemic inflammatory response; Body composition; Malnutrition; Cachexia; Prognosis.

Simple Summary: Cachexia has been recognised for a long time as an adverse effect of cancer and its clinical management is currently both limited and complex. An assessment of systemic inflammation may form the basis of a framework to examine the prognostic value of cachexia in patients with advanced cancer. This article examined the prognostic value of The Global

Leadership Initiative on Malnutrition (GLIM) criteria, including body mass index (BMI), weight loss (WL) and systemic inflammation (mGPS), in patients with advanced cancer. A high BMI/WL grade and a high mGPS as outlined in the BMI/WL grade/mGPS framework were consistently associated with poorer survival of patients with advanced cancer. It can be readily incorporated into the routine assessment of patients due to its simplicity and clinical utility.

Introduction

Cancer cachexia (CC) is considered a complex multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass, with or without loss of fat mass [1]. Considered to affect up to half of patients with advanced cancer, contemporary evidence suggests it is responsible for approximately 20% of cancer-related deaths [2]. Furthermore, it is negatively associated with response to anti-cancer therapy [3], physical function, survival and quality of life in patients with advanced cancer [4, 5]. Thus, cachexia has been recognised for a long time as an adverse effect of cancer and its clinical management is currently both limited and complex [4, 6].

The Global Leadership Initiative on Malnutrition (GLIM) consensus is that cachexia is chronic disease-related malnutrition with inflammation. It was agreed that diagnosis required one of three recognised phenotypic diagnostic criterion (low body mass index, non-volitional weight loss and reduced muscle mass) and one aetiologic criterion (reduced food intake/assimilation and disease burden/inflammation secondary to acute disease/injury or chronic disease) [7]. However, the frameworks for the clinical application of the GLIM criteria require validation.

Considering body mass index (BMI) and weight loss (WL), two phenotypic criterion proposed by GLIM, Martin and colleagues suggested that their BMI-adjusted WL grading

system was useful to predict survival as it was independent of cancer site, stage, and performance status and strongly discriminates survival differences [8]. In another study of the same group analyzing a cohort of almost 5.000 patients, they showed that weight loss is largely determined by dietary intake and systemic inflammation [9]. Of these two GLIM aetiologic criteria, the authors concluded that food intake impairment and C-reactive protein (CRP) may improve the diagnosis and classification of cancer-associated cachexia [9].

Based on present evidence, an assessment of systemic inflammation may form the basis of a framework to examine the prognostic value of cachexia in patients with advanced cancer. Indeed, previous inflammation-based frameworks, combining modified Glasgow Prognostic Score (mGPS) and performance status, have been shown to have complimentary prognostic value in patients with advanced cancer [10].

Therefore, the aim of the present study was to examine the prognostic value of the GLIM criteria including BMI, weight loss and systemic inflammation in patients with advanced cancer.

Material and Methods

Study population

Analysis was undertaken on a combined European and Brazilian cohort of adult patients with advanced cancer. The combined cohort was a prospective data collection of patients with advanced cancer across sites in the United Kingdom and Ireland between 2011 and 2016 [11, 12], and from Brazil (Barretos Cancer Hospital, Barretos-SP) between 2011 and 2014. Eligible adult patients with advanced cancer (defined as locally advanced or with histological, cytological or radiological evidence of metastasis), across all cancer subtypes, who provided a

venous blood sample were assessed for inclusion. Patients who were undergoing active anticancer therapy or not, in either an inpatient or outpatient setting were included. The study had ethics committee approval in the United Kingdom, Ireland and Brazil (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018), Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015) and Ethics Committee of the Barretos Cancer Hospital (HCB433/2011 and HCB783/2014)). All patients signed a consent-to-participate form in compliance with the Declaration of Helsinki [11, 12] and Resolution 466/12 of the Brazilian National Health Council. Furthermore, the study also conformed to the STROBE guidelines for cohort studies [13].

Procedure and assessment

General demographic data and clinicopathological characteristics were recorded for each patient. Tumor site was grouped as lung, breast, gynecological, gastrointestinal, urological, hematological, melanoma, neurological, unknown primary and other. The systemic inflammatory response was analyzed using CRP and albumin and the mGPS was calculated as previously described and grouped as 0/1/2 [14]. The biomarkers were taken by venous blood sampling at entry points and an autoanalyzer was used to measure CRP (mg/L) and albumin (g/L) concentrations according to routine clinical laboratory protocols.

Patients were also categorized according to BMI (<20.0, 20.0 to 21.9, 22.0 to 24.9, 25.0 to 27.9 and ≥ 28.0 kg/m²); WL (+- 2.4%, 2.5% to 5.9%, 6.0% to 10.9%, 11.0% to 14.9% and $\geq 15\%$) and BMI/WL grade (0, 1, 2, 3 and 4) as previously described by Martin and co-authors [8].

Statistical analysis

The survival time, defined as the number of months from study entry until death, or censored if alive at the follow-up date, was calculated. Survival analysis was carried out using Cox proportional hazards model, and HRs were calculated. Multivariate survival analysis was conducted using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding P value had to be >0.10 . The Chi-square test was used for comparisons of categorical variables. All statistical testing was conducted at the 5% level, and 95% confidence intervals (CI) are reported throughout. Two-sided P-values less than 0.05 were considered significant. All analyses were conducted in SPSS Version 20 (SPSS Inc).

Results

Data were available on 1303 patients in the combined European and Brazilian cohort. Patient's clinicopathological characteristics are shown in Table 1. The median age was 64.75 years (interquartile range (IQR) 55.54–72.70) and 667 patients were female (51%). The majority of patients had either gastrointestinal (37%, $n=487$) or lung (23%, $n=305$) tumors as a primary cancer site. The majority of patients had either $\text{BMI} \geq 28\text{kg/m}^2$ (29%, $n=353$) or $\text{BMI} 22 - 24.9\text{kg/m}^2$ (22%, $n=274$). 62% of the patients had weight stable and 35% had BMI/WL grade 0. 52% of the patients had mGPS 0 and 34% of the patients had mGPS 2. At the time of cessation of data collection, 344 patients were alive (26%) and 959 (74%) had died. The median survival was 6.6 months (IQR 3.0 – 14.6).

The relationship between BMI and the mGPS and survival rate at 3 months is shown in Table 2. Survival at 3 months varied from 74% ($\text{BMI} > 28\text{ kg/m}^2$) to 61% ($\text{BMI} < 20\text{ kg/m}^2$) and

from 84% (mGPS 0) to 60% (mGPS 2). When BMI and the mGPS were used in combination, survival at 3 months ranged from 82% (BMI>28 kg/m², mGPS 0) to 43% (BMI <20 kg/m², mGPS 2). Patients with a BMI>28 kg/m², the survival at 3 months ranged from 82% (mGPS 0) to 60% (mGPS 2) (P<0.001). Patients with a BMI 25.0 – 27.9 kg/m², the survival at 3 months ranged from 88% (mGPS 0) to 74% (mGPS 2) (P<0.001). In those patients with a BMI 22.0 – 24.9 kg/m², the survival at 3 months ranged from 83% (mGPS 0) to 67% (mGPS 2) (P<0.001). Patients with a BMI 20.0 – 21.9 kg/m², the survival at 3 months ranged from 90% (mGPS 0) to 54% (mGPS 2) (P<0.001). In those patients with a BMI<20 kg/m², the survival at 3 months ranged from 76% (mGPS 0) to 43% (mGPS 2) (P<0.001). Patients with the mGPS 0, the survival at 3 months ranged from 82% (BMI>28 kg/m²) to 76% (BMI<20 kg/m²) (P<0.001). Patients with the mGPS 2, the survival at 3 months ranged from 60% (BMI>28 kg/m²) to 43% (BMI<20 kg/m²) (P<0.001).

The relationship between WL and the mGPS and survival rate at 3 months is shown in Table 3. Survival at 3 months varied from 81% (WL +2.4%) to 47% (WL>=15%) and from 93% (mGPS 0) to 60% (mGPS 2). When WL and the mGPS were used in combination, survival at 3 months ranged from 95% (WL +2.4%, mGPS 0) to 28% (WL >=15%, mGPS 2). Patients with a WL $\pm$ 2.4%, the survival at 3 months ranged from 95% (mGPS 0) to 66% (mGPS 2) (P<0.001). Patients with a WL 2.5-5.9%, the survival at 3 months ranged from 95% (mGPS 0) to 65% (mGPS 2) (P<0.001). Patients with a WL 6.0-10.9%, the survival at 3 months ranged from 91% (mGPS 0) to 63% (mGPS 2) (P=0.002). Patients with the mGPS 0, the survival at 3 months ranged from 95% (WL +2.4%) to 87% (WL>=15%) (P<0.001). In those patients with the mGPS 2, the survival at 3 months ranged from 66% (WL +2.4%) to 28% (WL>=15%) (P<0.001).

The relationship between BMI/WL grade and mGPS and survival rate at 3 months is shown in Table 4. Survival at 3 months varied from 86% (BMI/WL grade 0) to 59% (BMI/WL

grade 4) and from 93% (mGPS 0) to 63% (mGPS 2). When BMI/WL grade and the mGPS were used in combination, survival at 3 months ranged from 93% (BMI/WL grade 0, mGPS 0) to 38% (BMI/WL grade 4, mGPS 2). In those patients with a BMI/WL grade 0, the survival at 3 months ranged from 93% (mGPS 0) to 78% (mGPS 2) ($P<0.001$). Patients with a BMI/WL grade 1, the survival at 3 months ranged from 97% (mGPS 0) to 73% (mGPS 2) ($P<0.001$). Patients with a BMI/WL grade 2, the survival at 3 months ranged from 93% (mGPS 0) to 61% (mGPS 2) ($P<0.001$). In those patients with a BMI/WL grade 3, the survival at 3 months ranged from 90% (mGPS 0) to 56% (mGPS 2) ($P<0.001$). Patients with a BMI/WL grade 4, the survival at 3 months ranged from 86% (mGPS 0) to 38% (mGPS 2) ($P=0.007$). Patients with the mGPS 0, the survival at 3 months ranged from 93% (BMI/WL grade 0) to 86% (BMI/WL grade 4) ($P<0.001$). Patients with the mGPS 2, the survival at 3 months ranged from 78% (BMI/WL grade 0) to 38% (BMI/WL grade 4) ($P<0.001$).

The relationship between objective clinicopathological factors and survival in patients with advanced cancer is shown in Table 5. On univariate survival analysis, lung, hematological and breast as primary cancer sites (HR 1.334 and $P=0.001$, HR 0.284 and $P<0.001$, HR 0.693 and $P=0.001$, respectively), mGPS (HR 1.543-2.175, all $P<0.001$) and BMI/WL grade 1, 2, 3 and 4 (HR 1.300 and $P=0.014$, HR 1.405 and $P=0.011$, HR 1.745 and $P<0.001$, HR 2.307 and $P<0.001$, respectively) were significantly associated with survival. Age and sex were not associated with survival. On multivariate survival analysis, the most highly predictive factors were BMI/WL grade 3 (HR 1.454, $P=0.004$), BMI/WL grade 4 (HR 2.285, $P<0.001$) and mGPS (HR 1.887–2.545, all $P<0.001$).

Discussion

The results of the present study show that BMI, WL and the mGPS, which are phenotypic and aetiologic criterion proposed by GLIM, were significantly and independently associated with survival in patients with advanced cancer (European and Brazilian cohorts combined). Furthermore, when these phenotypic and aetiologic criteria were combined they better predicted survival.

The results of the present study are consistent with the observations of Martin and co-workers who demonstrated that BMI and WL predicted survival independently of conventional prognostic factors and, when used in combination as a BMI/WL grading system, it provided a severity grade related to the risk of shortened survival [8]. Indeed, a prospective study with patients with advanced cancer showed that BMI/WL grade remained independently associated with overall survival and, in patients with a BMI/WL grade 0/1 both performance status and mGPS remained independently associated with overall survival [8].

Therefore, in this study the mGPS predict survival in those patients in which the GLIM criteria were considered normal. There are a number of implications of these results. In particular, that the systemic inflammatory response (SIR) precedes the development of malnutrition and that the SIR should form the basis of the application of GLIM criteria in clinical practice. A recent review published showed that the systemic inflammation has progressively moved to the forefront of the definition and diagnosis of cancer cachexia. The authors consider cancer cachexia as primarily a SIR syndrome and, in this way, there are a number of potential implications for daily clinical practice [15]. Even, a recent article compared prognostic factors of patients with advanced cancer and showed that a high score of performance status and mGPS were consistently associated with poorer survival [16].

Furthermore, contemporary evidence suggests that systemic inflammation is determinant of body composition, symptom burden, physical function and outcomes in patients with advanced cancer [9, 10, 13, 17, 18]. A phase III trial with advanced gastric and esophagogastric junction cancer patients showed that the mGPS was correlated with sarcopenia and dominated the prognostic role of baseline body composition parameters in these patients. The authors support a model where tumor-mediated inflammatory response, as measured by mGPS, represents a well-validated strong negative prognostic factor, which is related to sarcopenia. Whereas, a direct causal path from sarcopenia to survival is lacking [19].

Considering that patients with advanced cancer who are systemically inflamed but with no evidence of weight loss are pre-cachexic [20], cancer cachexia may be considered a disease-related inflammation with malnutrition. For example, Wallengren and coworkers, reported that patients with advanced cancer and CRP > 10 mg/L had less muscle mass on study baseline and longitudinally [21]. In addition, Malietzis et al. reported that, in patient with operable CCR, an neutrophil lymphocyte ratio (NLR) > 3 was associated with lower muscle mass [22]. Another study with 650 operable colorectal cancer (CCR) patients showed that sarcopenia (SMI) and myosteatorsis (SMD) were associated with the presence of a systemic inflammatory (in particular the mGPS) and had independent prognostic value [18]. Given the above, the systemic inflammation assessment, in addition to nutritional status, should be considered an essential part of the routine clinical and nutritional evaluation.

The present study had limitations that should be considered. Given its cross sectional, heterogenous population and observational nature it is subject to sample bias. However, a large cohort of well characterised patients was examined and the prognostic value of GLIM criteria was consistent across tumor types.

Conclusion

In summary, a high BMI/WL grade and a high mGPS as outlined in the BMI/WL grade/mGPS framework were consistently associated with poorer survival of patients with advanced cancer in the prospective European and Brazilian combined cohort. It can be readily incorporated into the routine assessment of patients due to its simplicity and clinical utility.

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Authors' Contributions

Conceptualization, design and methodology (B.M.M.R., R.D.D., C.E.P., J.M., Y.C.P.M., B.J.L., D.C.M.), data curation (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P., Y.C.P.M., B.J.L., D.C.M.), formal analysis (B.M.M.R., R.D.D., C.E.P., J.M., Y.C.P.M., B.J.L., D.C.M.), funding acquisition (B.M.M.R., R.D.D., C.E.P., Y.C.P.M., B.J.L., D.C.M.), project administration (B.M.M.R., R.D.D., C.E.P., Y.C.P.M., B.J.L., D.C.M.), supervision (R.D.D., C.E.P., Y.C.P.M., B.J.L., D.C.M.), writing: original draft (B.M.M.R., C.E.P., Y.C.P.M., B.J.L., D.C.M.), review and editing (B.M.M.R., R.D.D., C.E.P., J.M., B.S.R.P., D.D.P., Y.C.P.M., B.J.L., D.C.M.).

Ethics Approval

The study complied with the Declaration of Helsinki and was approved by the Human Research Ethics Committee (West of Scotland Ethics Committee UK: 18/WS/0001 (18/01/2018); Cork Research Ethics Committee Ireland: ECM 4 (g) (03/03/2015); Ethics Committee of the Barretos Cancer Hospital (HCB433/2011 and HCB783/2014)).

Consent to Participate

Informed consent was obtained from all subjects involved in the study.

Data Availability

The datasets that formed the basis of this article are contained in the University of Glasgow's MVLS institute (Scotland) and Barretos Cancer Hospital (Brazil). They contain patient sensitive information and therefore cannot be made available on a public repository.

Conflict of Interest

The authors declare no potential conflicts of interest.

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Table 1. Clinicopathological characteristics of patients with advanced cancer – combined European and Brazilian cohort (n=1303)

Parameter	<i>n</i>	%
Age		
<65 years	658	50
65-74 years	362	28
74 years	283	22
Sex		
Male	636	49
Female	667	51
Primary cancer site		
Lung	305	23
Breast	156	12
Gynecological	91	7
Gastrointestinal	487	37
Urological	94	7
Haematological	43	3
Melanoma	50	4
Neurological	12	1
Unknown primary	19	2
Others	46	4
BMI ^a categories		
< 20.0 kg/m ²	188	15
20 - 21.9 kg/m ²	156	13
22 - 24.9 kg/m ²	274	23
25 - 27.9 kg/m ²	244	20
>= 28.0 kg/m ²	353	29
WL ^b categories		
±2.4% (weight stable)	617	62
2.5–5.9%	142	14
6.0–10.9%	119	12
11.0–14.9%	51	5
≥15.0%	68	7
BMI/WL grade ^c		
0	333	35
1	216	23
2	110	12
3	180	19
4	98	11
mGPS ^d		
0	564	52
1	153	14
2	372	34
Status		
Alive	344	26
Dead	959	74

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; WL, weight loss; BMI, body mass index.

^a BMI available on 1215 patients.

^b WL available on 997 patients.

^c BMI/WL grade available on 937 patients. BMI/WL grades calculated based on Martin *et al.*

^d mGPS available on 1089 patients.

Table 2 – The relationship between body mass index (BMI) and the mGPS and the survival rate at 3 months in patients with advanced cancer – European cohort and Brazilian cohort (n=1.303)

Body mass index ^a	mGPS 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i> ^b	mGPS 0-2 (n=1089)
>28 (n=353)	82% (n=122)	79% (n=34)	60% (n=56)	<0.001	74% (n=212)
25.0 – 27.9 (n=244)	88% (n=108)	56% (n=14)	74% (n=40)	<0.001	80% (n=162)
22.0 – 24.9 (n=274)	83% (n=93)	67% (n=22)	65% (n=55)	<0.001	74% (n=170)
20.0 – 21.9 (n=156)	90% (n=61)	93% (n=14)	54% (n=24)	<0.001	78% (n=99)
<20 (n=188)	76% (n=68)	(n=5)	43% (n=26)	<0.001	61% (n=99)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
<20 - >28 (n=1215)	84% (n=452)	69% (n=89)	60% (n=201)		74% (n=742)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score.

^a BMI grouping based on Martin *et al* [12]

^b P value from χ^2 analysis.

NOTE: Survival rate (SE)% at 3 months, not calculated if n < 10.

Table 3 – The relationship between weight lost (WL) and the mGPS and the survival rate at 3 months in patients with advanced cancer – European cohort and Brazilian cohort (n=1.303)

Weight loss ^a	mGPS 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i> ^b	mGPS 0-2 (n=1089)
±2.4%(weight stable)(n=617)	95% (n=218)	71% (n=58)	66% (n=111)	<0.001	81% (n=387)
2.5–5.9% (n=142)	95% (n=53)	61% (n=11)	65% (n=26)	<0.001	79% (n=90)
6.0–10.9% (n=119)	91% (n=30)	59% (n=10)	63% (n=31)	0.002	72% (n=71)
11.0–14.9% (n=51)	(n=9)	(n=5)	53% (n=10)	0.416	60% (n=24)
≥15.0% (n=68)	87% (n=13)	(n=6)	28% (n=12)	0.249	47% (n=31)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
±2.4% - ≥15.0% (n=997)	93% (n=323)	67% (n=90)	60% (n=190)		75% (n=603)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score.

^a WL grouping based on Martin *et al.*

^b P value from χ^2 analysis.

NOTE: Survival rate (SE)% at 3 months, not calculated if n < 10.

Table 4 – The relationship between BMI/WL grade and the mGPS and the survival rate at 3 months in patients with advanced cancer – combined European and Brazilian cohort (n=1.303)

BMI/WL grade ^a	mGPS ^b 0 (n=564)	mGPS 1 (n=153)	mGPS 2 (n=372)	<i>P-Value</i> ^b	mGPS 0-2 (n=1089)
0 (n=333)	93% (n=128)	73% (n=24)	78% (n=63)	<0.001	86% (n=215)
1 (n=216)	97% (n=72)	90% (n=26)	73% (n=44)	<0.001	87% (n=142)
2 (n=110)	93% (n=41)	(n=8)	61% (n=19)	<0.001	75% (n=68)
3 (n=180)	90% (n=45)	60% (n=15)	56% (n=43)	<0.001	68% (n=103)
4 (n=98)	86% (n=25)	(n=7)	38% (n=18)	0.007	59% (n=50)
<i>P-Value</i> ^b	<0.001	<0.001	<0.001		
0-4 (n=937)	93% (n=311)	71% (n=80)	63% (n=187)		78% (n=578)

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; BMI, body mass index; WL, weight loss.

^a BMI/WL grades calculated based on Martin *et al.*

^b P value from χ^2 analysis.

NOTE: Survival rate (SE)% at 3 months, not calculated if n < 10.

Table 5. The relationship between objective clinicopathological factors and survival in patients with advanced cancer – combined European and Brazilian cohort (n=1.303)

	Patients (N)	Univariate ^a		Multivariate ^a	
		HR (95% CI)	P	HR (95% CI)	P
Age					
<65	658	1.000 (Ref.)			
65-74	362	1.074 (0.926 – 1.246)	0.345		
>74	283	1.090 (0.923 – 1.287)	0.308		
Sex					
Male	636	1.000 (Ref.)			
Female	667	0.891 (0.785 – 1.012)	0.075		
Primary cancer site					
Gastrointestinal	487	1.000 (Ref.)		1.000 (Ref.)	
Lung	305	1.334 (1.130 – 1.574)	0.001	1.110 (0.896 – 1.376)	0.338
Neurological	12	1.010 (0.478 – 2.134)	0.979	2.472 (0.910 – 6.714)	0.076
Urological	94	0.932 (0.727 – 1.196)	0.580	0.823 (0.566 – 1.196)	0.307
Gynecological	91	0.846 (0.654 – 1.096)	0.205	1.376 (0.913 – 2.073)	0.127
Melanoma	50	0.838 (0.581 – 1.209)	0.345	0.814 (0.454 – 1.459)	0.490
Haematological	43	0.284 (0.175 – 0.463)	<0.001	0.267 (0.145 – 0.490)	<0.001
Breast	156	0.693 (0.557 – 0.864)	0.001	0.564 (0.344 – 0.926)	0.024
Unknown primary	19	1.530 (0.912 – 2.564)	0.107	1.668 (0.782 – 3.559)	0.186
Others	46	1.134 (0.806 – 1.596)	0.470	0.809 (0.415 – 1.579)	0.534
BMI/WL grade ^b					
0	333	1.000 (Ref.)		1.000 (Ref.)	
1	216	1.300 (1.055 – 1.601)	0.014	1.126 (0.880 – 1.441)	0.345
2	110	1.405 (1.082 – 1.824)	0.011	1.257 (0.930 – 1.698)	0.137
3	180	1.745 (1.398 – 2.177)	<0.001	1.454 (1.128 – 1.875)	0.004
4	98	2.307 (1.773 – 3.001)	<0.001	2.285 (1.703 – 3.067)	<0.001
mGPS					
mGPS 0	564	1.000 (Ref.)		1.000 (Ref.)	
mGPS 1	153	1.543 (1.249 – 1.906)	<0.001	1.887 (1.439 – 2.475)	<0.001
mGPS 2	372	2.175 (1.870 – 2.530)	<0.001	2.545 (2.084 – 3.109)	<0.001

Abbreviations: Legend: mGPS, modified Glasgow Prognostic Score; BMI, body mass index; WL, weight lost.

^a HR expressed as per 10 unit change.^b BMI/WL grades calculated based on Martin *et al* [12].

5. CONCLUSÃO

A partir dos resultados apresentados no primeiro artigo que compõe esta tese, foi possível concluir que os fatores prognósticos comparados nas coortes brasileira e europeia, como a funcionalidade e inflamação sistêmica, apresentaram capacidade prognóstica semelhante em ambas. Além disso, o estudo também permitiu concluir que escores elevados de ECOG-PS e mGPS estão consistentemente associados à pior sobrevida da população analisada.

A partir dos resultados apresentados no segundo artigo que compõe esta tese, foi possível concluir que uma elevada classificação IMC/perda de peso e um escore de mGPS elevado estão consistentemente associados à pior sobrevida da coorte combinada de pacientes brasileiros e europeus com câncer avançado.

Ainda, é recomendada a incorporação das duas estruturas de avaliação prognóstica propostas nos artigos (ECOG-PS/mGPS e classificação BMI/perda de peso/mGPS) na avaliação rotineira dos pacientes, devido à sua simplicidade e utilidade clínica.

6. PERSPECTIVAS

Pretende-se avaliar os fatores prognósticos em subtipos tumorais específicos, correlacionando-os também com as características tumorais e marcadores biológicos específicos de cada tumor. Considerando o câncer de mama, por exemplo, pretende-se avaliar estado nutricional, funcionalidade e resposta inflamatória sistêmica, correlacionando-os com a expressão de hormônios e genes específicos desse câncer.

Considerando o estado nutricional como importante fator prognóstico, outra perspectiva é avaliar o estado nutricional dos pacientes com câncer avançado por meio de outras técnicas e metodologias (bioimpedância elétrica, tomografia computadorizada, ultrassonografia) e associá-lo à funcionalidade e à resposta inflamatória sistêmica. Com isso, almeja-se uma nova estrutura de avaliação prognóstica que contemple fatores objetivos e precisos.

Ainda, utilizando os dois bancos de dados abordados nos artigos desta tese, outra perspectiva é avaliar a qualidade de vida dos pacientes com câncer avançado e comparar as duas coortes internacionais, com o objetivo de identificar diferenças significativas e associações prognósticas.

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