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ORIGINAL RESEARCH

Evaluation of the inflammation-based modified Glasgow Prognostic Score (mGPS) as a prognostic and predictive biomarker in patients with metastatic colorectal cancer receiving first-line chemotherapy: a *post hoc* analysis of the randomized phase III XELAVIRI trial (AIO KRK0110)

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Background: The inflammation-based modified Glasgow Prognostic Score (mGPS) combines serum levels of C-reactive protein and albumin and was shown to predict survival in advanced cancer. We aimed to elucidate the prognostic impact of mGPS on survival as well as its predictive value when combined with gender in unselected metastatic colorectal cancer (mCRC) patients receiving first-line chemotherapy in the randomized phase III XELAVIRI trial.

Patients and methods: In XELAVIRI, mCRC patients were treated with either fluoropyrimidine/bevacizumab followed by additional irinotecan at first progression (sequential treatment arm; Arm A) or upfront combination of fluoropyrimidine/bevacizumab/irinotecan (intensive treatment arm; Arm B). In the present *post hoc* analysis, survival was evaluated with respect to the assorted mGPS categories 0, 1 or 2. Interaction between mGPS and gender was analyzed.

Results: Out of 421 mCRC patients treated in XELAVIRI, 362 [119 women (32.9%) and 243 men (67.1%)] were assessable. For the entire study population a significant association between mGPS and overall survival (OS) was observed [mGPS = 0: median 28.9 months, 95% confidence interval (CI) 25.9-33.6 months; mGPS = 1: median 21.4 months, 95% CI 17.6-26.1 months; mGPS = 2: median 16.8 months, 95% CI 14.3-21.2 months; $P < 0.00001$]. Similar results were found when comparing progression-free survival between groups. The effect of mGPS on survival did not depend on the applied treatment regimen ($P = 0.21$). In female patients, a trend towards longer OS was observed in Arm A versus Arm B, with this effect being clearly more pronounced in the mGPS cohort 0 (41.6 versus 25.5 months; $P = 0.056$). By contrast, median OS was longer in male patients with an mGPS of 1-2 treated in Arm B versus Arm A (20.8 versus 17.4 months; $P = 0.022$).

Conclusion: We demonstrate the role of mGPS as an independent predictor of OS regardless of the treatment regimen in mCRC patients receiving first-line treatment. mGPS may help identify gender-specific subgroups that benefit more or less from upfront intensive therapy.

Key words: modified Glasgow Prognostic Score, mGPS, metastatic colorectal cancer, gender, XELAVIRI trial

INTRODUCTION

The modified Glasgow Prognostic Score (mGPS) represents an inflammation-based prognostic score and was shown to predict cancer survival in a variety of advanced solid tumors.[1,2] Serum levels of only two biomarkers, the acute-phase protein C-reactive protein (CRP) and albumin, are applied for risk stratification and allocation of patients to

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one of three categories quoted as mGPS 0, 1 or 2.[2] An elevated mGPS is associated with reduced cancer-specific survival independent of tumor site, tumor stage, performance status and treatment (active or palliative).[3] Also, in patients with colorectal cancer (CRC) and operable[4,5] or relapsed/refractory[6-8] disease, mGPS was described as an independent prognostic factor for survival.

However, few studies have been published that focus on the value of mGPS in metastatic colorectal cancer (mCRC) receiving first-line therapy.[9] Most analyses refer to non-randomized trials and retrospectively collected datasets from further or last-line (salvage-line) treatment settings.[10-12] Also, most data are derived from Asian patient populations and transferability to Caucasian patients has to be at least questioned. One single meta-analysis reports on nine studies with a total of 2227 CRC patients of all stages, where an mGPS $\geq$1 was independently associated with overall survival (OS) with a hazard ratio (HR) of 1.69 [95% confidence interval (CI) 1.4-2.04, $P < 0.00001$].[13] Six studies including a total of 1751 patients reported that a high mGPS was associated with cancer-specific survival [HR 1.84; 95% CI 1.43-2.37, $P < 0.00001$].[13]

Hence, we aimed to evaluate mGPS in a large cohort of mCRC patients treated in the first line in the prospective randomized controlled phase III XELAVIRI trial. The XELAVIRI study aimed to demonstrate non-inferiority of first-line fluoropyrimidine (either infusional 5-fluorouracil/folinic acid or oral capecitabine) plus bevacizumab followed by the addition of irinotecan at first progression (sequential intensification of treatment, Arm A) versus upfront intensive combination chemotherapy with fluoropyrimidine, irinotecan and bevacizumab (Arm B) in untreated and unselected mCRC patients.[14,15]

Although XELAVIRI failed to show non-inferiority, results showed no clear benefit from one or the other treatment arm in terms of time to failure of strategy (Arm A versus B: 10.0 versus 10.2 months; HR 0.93; 90% CI 0.79-1.10, $P = 0.482$) and OS (Arm A versus B: 21.9 versus 23.5 months; HR 0.85; 95% CI 0.69-1.05, $P = 0.131$). Objective response rates in Arm A versus Arm B reached 37.7% versus 56.0% (odds ratio 2.10; 95% CI 1.42-3.10, $P < 0.001$). Interestingly, *post hoc* analyses revealed notable findings with regard to gender-specific treatment efficacy. While male patients clearly benefited from intensive upfront combination therapy (fluoropyrimidine/irinotecan/bevacizumab) with regard to OS, women drew a comparable benefit from less-intensive sequential treatment and thus might not necessarily need to be exposed to upfront combination chemotherapy to achieve longest survival times.[16]

In the present *post hoc* analysis, we aimed to evaluate the prognostic and gender-specific predictive role of mGPS in mCRC patients treated within the XELAVIRI trial. To our knowledge, this is the first study investigating this subject in a cohort of untreated mCRC patients based on data from a prospective randomized phase III trial.

PATIENTS AND METHODS

Study design

The XELAVIRI trial (AIO KRK0110; ClinicalTrials.gov, number NCT01249638) was an open-label randomized prospective multicenter phase III trial that compared the effectiveness of sequentially escalated chemotherapy versus upfront combination therapy with fluoropyrimidine, bevacizumab and irinotecan in unselected patients with untreated mCRC.

In brief, patients were randomly assigned 1 : 1 to start first-line treatment with either fluoropyrimidine/bevacizumab that was followed by additional irinotecan at the time of first progression (sequential treatment arm; Arm A) or to receive upfront combination chemotherapy with fluoropyrimidine/bevacizumab/irinotecan (intensive treatment arm; Arm B). In Arm B, the three-drug regimen could be de-escalated to fluoropyrimidine/bevacizumab in case of response or stabilization of disease after a minimum of 6 months and was to be re-escalated to fluoropyrimidine/bevacizumab/ irinotecan when disease progressed during the de-escalation period. Fluoropyrimidine could be administered orally (capecitabine) or intravenously (5-fluorouracil/folinic acid). Treatment was continued until progression of disease under the three-drug regimen, occurrence of unacceptable toxicity, complete response or until patients' and/or physicians' decision to change or discontinue therapy.[14]

The full study population, treatment schedules, ethics committee approval and Declaration of Helsinki accordance as well as outcome results have been published by our study group and are reported elsewhere. [14-17]

The trial was conducted in compliance with the Declaration of Helsinki. The protocol was approved by the ethics committees of all centers (Supplementary Material list of recruiting study centers, available at https://doi.org/10.1016/j.esmoop.2024.103374). All patients provided written informed consent before trial entry.

Patient population

For inclusion into the XELAVIRI trial, patients had to be $\geq$18 years of age and medically fit [Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1]. They had to be diagnosed with stage IV, unresectable CRC and have at least one measurable tumor lesion based on the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. All patients had histologically proven adenocarcinoma of colorectal origin and had not received any chemotherapy for metastatic disease before central randomization in the XELAVIRI trial. Precise description of inclusion and exclusion criteria were published earlier.[17] For the present analysis, patients with available data on baseline CRP and albumin levels as well as information on gender were eligible. Gender was self-reported by patients. No karyotype analysis was carried out. Baseline patient demographics and tumor characteristics as well as OS times of the entire study

population have been reported earlier by our study group.[14,15]

The modified Glasgow Prognostic Score (mGPS)

According to McMillan and co-workers who invented and validated the mGPS as a useful prognostic tool reflecting the systemic inflammatory response in solid tumors,[3,4] CRP and albumin serum levels were analyzed in all assessable XELAVIRI study patients at baseline (within 14 days before treatment start). Biomarker testing was carried out decentrally at the individual site's laboratory. Patients were assigned to one of the three mGPS categories: 0 when CRP was $\leq$1.0 mg/dl, 1 when CRP was $>$1.0 mg/dl and albumin $\geq$3.5 g/dl, or 2 when CRP was $>$1.0 mg/dl and albumin $<$3.5 g/dl.

Statistical analysis

In XELAVIRI, the primary study objective was to investigate the 'time to failure of strategy' in a statistical non-inferiority design.[14] For the present analysis, progression-free survival (PFS) and OS, which were both secondary endpoints in the XELAVIRI trial, served as efficacy endpoints. PFS was defined as time to progression or death, whichever occurred first. OS was defined as time to death of any cause.

Survival probabilities were estimated using the Kaplan—Meier method and differences in survival were calculated using the log-rank test at a significance level of 0.05 (two-sided). Continuous variables were described as medians and compared using the Mann—Whitney *U* test. Differences were assessed using a log-rank test. A Cox regression model was applied to estimate HRs and the corresponding 95% CIs. Interactions between treatment arms and mGPS category and/or gender were assessed through Cox model for OS and PFS.

For comparison of categorical variables, Pearson's chi-square test (two-sided) and Fisher's exact test (two-sided) were used. To further describe the relationship between CRP and/or albumin and survival, fractional polynomials were applied.

Uni- and multivariate Cox proportional hazards models were used to explore the effect of independent variables on survival and the relevance of confounding factors. For this model, the HR, its 95% CI and the *P* value (two-sided) resulting from the Wald test are reported. Results are illustrated by forest plots and Kaplan—Meier survival curves.

To analyze CRP and albumin as continuous parameters, they were integrated as log-transformed variables in logistic regressions, where indicated. To evaluate independent prognostic factors for survival, multivariate Cox proportional hazard models were fitted to estimate the effect of log-transformed CRP and albumin on PFS and OS adjusted for possibly prognostic baseline parameters. To examine how CRP and albumin cut-off thresholds would influence survival, HR and median OS times for both treatment arms were plotted for subgroups of patients with CRP and albumin levels below or equal to varying thresholds.

For all statistical tests, the level of significance was set at $P \leq 0.05$. Statistical analyses were implemented in R version 3.2.2. The packages survival, Forest plot and mfp (fractional polynomial) were used.

RESULTS

Trial population

Overall, 362 out of 421 mCRC patients treated in the full analysis set of the XELAVIRI trial had a defined mGPS at baseline and available survival data and thus were assessable for the present analysis. Of those, 174 (48.1%) were treated in Arm A and 188 (51.9%) in Arm B. With regard to gender, 119 assessable patients were female (32.9%) and 243 male (67.1%). Baseline patient demographics and tumor characteristics of the analyzed patient cohort are listed in Table 1.

Impact of mGPS on survival of mCRC patients

A significant association between mGPS and survival was observed in the entire study population. Median OS significantly differed between patients with an mGPS of 0 (28.9 months; 95% CI 25.9-33.6 months), 1 (21.4 months; 95% CI 17.6-26.1 months) and 2 (16.8 months; 95% CI 14.3-21.2 months) (log-rank test $P < 0.00001$) (Figure 1). In pairwise comparisons, patients with an mGPS of 1 or 2 had significantly shorter OS than patients with an mGPS of 0 (HR 1.55; 95% CI 1.18, 2.04, $P = 0.0046$; and HR 2.02; 95% CI 1.5, 2.72, $P = 0.00002$, respectively). No significant survival difference was observed between patients with mGPS 1 and 2 (HR 1.3; 95% CI 0.97, 1.75, $P = 0.18$). The effect of mGPS on OS was independent of the applied treatment regimen ($P = 0.21$) (Figure 2A-C).

Similar results were observed when comparing PFS between groups assigned to the mGPS category 0 (10.2 months; 95% CI 9.5-10.9 months), 1 (8.8 months; 95% CI 7.4-11.9 months) and 2 (8.2 months; 95% CI 7.1-9.4 months) (log-rank test $P = 0.018$) (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103374). In a head-to-head comparison, significant PFS difference was only detected between patients with an mGPS of 0 versus 2 (HR 1.53; 95% CI 1.14-2.04, $P = 0.012$), but not patients with an mGPS of 0 versus 1 (HR 1.17; 95% CI 0.90-1.53, $P = 0.46$) and 1 versus 2 (HR 1.30; 95% CI 0.97-1.74, $P = 0.18$). The observed association of mGPS with PFS was independent of the applied treatment regimen ($P = 0.65$) (Supplementary Figure S2A-C, available at https://doi.org/10.1016/j.esmoop.2024.103374).

Uni- and multivariate analysis demonstrated the role of mGPS as an independent predictor for OS (Figure 3) and PFS (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.103374). In uni- and multivariate analysis, the known impact of *RAS*/*BRAF* mutational status as well as primary sidedness (right versus left) on outcome was confirmed (Figure 3, Supplementary

Table 1. Baseline patient demographics and tumor characteristics of the analyzed study patient cohort

Total patient number $N = 362$	mGPS = 0	mGPS = 1	mGPS = 2	*P*
Arm, *n* (%)				
Capecitabine/FUFA + Bev.	71 (48.3%)	56 (44.4%)	47 (52.8%)	0.49
XELIRI/FOLFIRI + Bev.	76 (51.7%)	70 (55.6%)	42 (47.2%)	
Age (years)				
Median (range)	71 (42-86)	69.5 (42-87)	71 (43-88)	0.5
Gender, *n* (%)				
Male	97 (66%)	83 (65.9%)	63 (70.8%)	0.7
Female	50 (34%)	43 (34.1%)	26 (29.2%)	
ECOG performance status, *n* (%)				
0	101 (72.1%)	75 (61.5%)	38 (44.2%)	**0.00016**
1	39 (27.9%)	47 (38.5%)	48 (55.8%)	
NA	7 (4.8%)	4 (3.2%)	3 (3.4%)	
Primary tumor site, *n* (%)				
Colon	84 (58.7%)	69 (56.1%)	61 (70.1%)	0.33
Rectum	54 (37.8%)	49 (39.8%)	24 (27.6%)	
Colon + rectum	5 (3.5%)	5 (4.1%)	2 (2.3%)	
NA	4 (2.7%)	3 (2.4%)	2 (2.2%)	
Sidedness of primary, *n* (%)				
Left colon	96 (68.6%)	83 (68.6%)	53 (60.9%)	0.44
Right colon	44 (31.4%)	38 (31.4%)	34 (39.1%)	
NA	7 (4.8%)	5 (4%)	2 (2.2%)	
Number of organs with metastasis, *n* (%)				
0 or 1	63 (42.9%)	43 (34.1%)	26 (29.2%)	**0.00015**
2	66 (44.9%)	48 (38.1%)	29 (32.6%)	
3 or 4	18 (12.2%)	35 (27.8%)	34 (38.2%)	
CRP				
Median (range)	0.46 (0.02-1)	3 (1.01-82)	5.78 (1.08-110.3)	**<0.00001**
Missing, *n* (%)	0 (0%)	0 (0%)	0 (0%)	
Albumin				
Median (range)	4.09 (2.41-4.8)	3.9 (3.5-5.48)	3.14 (1.81-3.49)	**<0.00001**
Missing, *n* (%)	10 (6.8%)	0 (0%)	0 (0%)	
RAS/BRAF status, *n* (%)				
RAS/BRAF wild-type	53 (36.1%)	44 (34.9%)	30 (33.7%)	0.94
RAS mutated	73 (49.7%)	62 (49.2%)[a]	39 (43.8%)	
BRAFV600E mutated	7 (4.8%)	6 (4.8%)[a]	6 (6.7%)	
Missing	14 (9.5%)	15 (11.9%)	14 (15.7%)	
Body mass index, *n* (%)				
<18.5	3 (2.0%)	1 (0.8%)	4 (4.5%)	0.21
≥18.5	138 (93.9%)	118 (93.7%)	84 (94.4%)	
Missing	6 (4.1%)	7 (5.6%)	1 (1.1%)	

The table displays for each baseline variable the median (range) when the variable is continuous and number (percentage) when the variable is categorical. Statistically significant *P*-values are marked in bold.

[a]The tumor of one patient with mGPS 1 was both *RAS* and *BRAF V600E* mutated.

Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.103374). No interaction between mGPS and *RAS/BRAF* mutational status ($P = 0.94$, Table 1) and no interaction between mGPS and primary tumor site was observed ($P = 0.44$, Table 1).

Although the ECOG performance status showed significant association with OS in the univariate analysis, it lost its prognostic significance in the multivariate model, as ECOG and mGPS were not independent variables (Figure 3, Table 1). Similarly, the number of organs with metastasis, which varied significantly between the mGPS cohorts, was not an independent predictor of OS and PFS in the multivariate model (Figure 3, Table 1, Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.103374).

Gender-specific outcome according to mGPS and treatment arm

Female patients with an mGPS of 0 showed a clear tendency towards longer OS when treated with initial fluoropyrimidine/bevacizumab only (Arm A) compared to intensive combination therapy with fluoropyrimidine/bevacizumab/irinotecan (Arm B), with the effect almost reaching statistical significance (41.6 versus 25.5 months; $P = 0.056$). In female patients assigned to mGPS category 1 or 2, a numerical trend towards longer OS was also observed in Arm A compared to Arm B, however, with statistical testing not revealing a significant survival difference between treatment arms (24.6 versus 16.7 months; $P = 0.15$) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103374, Figure 4A and B).

In contrast, male patients with an mGPS of 1 or 2 did benefit significantly from intensive upfront treatment with fluoropyrimidine/bevacizumab/irinotecan compared to fluoropyrimidine/bevacizumab alone (OS: 20.8 versus 17.4 months; $P = 0.022$). However, male patients with an mGPS of 0 showed no survival difference between treatment arms [OS: 28.2 (Arm A) versus 29.8 (Arm B) months; $P = 0.64$] (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103374, Figure 4C and D).

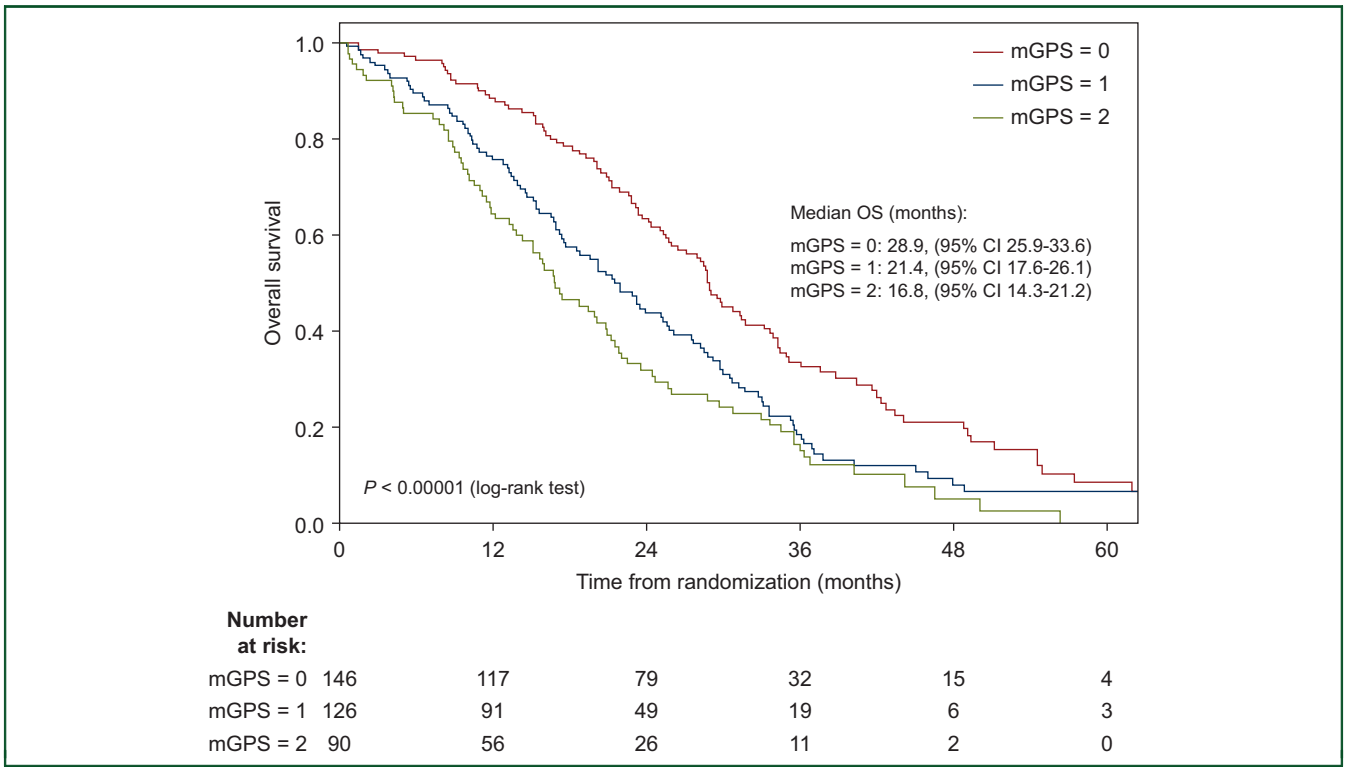

Figure 1. Overall survival according to mGPS in the entire study population.
CI, confidence interval; mGPS, modified Glasgow Prognostic Score; OS, overall survival.

Proof of principle—prognostic potential of the mGPS scoring system and comparison of models

CRP and albumin as single markers. In the investigated study patient cohort, the median CRP was 1.6 mg/dl and median albumin was 3.8 g/dl (Supplementary Figure S4A and B, available at https://doi.org/10.1016/j.esmoop.2024.103374). There was no evidence that the effect of CRP depends on albumin and vice versa ($P = 0.43$ for log-transformed CRP/albumin as continuous variables; $P = 0.56$ for CRP/albumin as binary variables). When CRP was analyzed as a single marker, its absolute value (HR 1.009; 95% CI 1.004-1.014, $P = 0.0004$), the logarithmized value (HR 1.24; 95% CI 1.14-1.34, $P < 0.00001$) and the dichotomized marker with a cut-off at 1.0 mg/dl (HR 1.72; 95% CI 1.35-2.19, $P = 0.000013$) showed a significant association with OS (Supplementary Figure S5A, available at https://doi.org/10.1016/j.esmoop.2024.103374). In an analogous manner, albumin was also shown to be associated with OS as a single marker when evaluated as an absolute value (HR 0.65; 95% CI 0.52-0.81, $P = 0.00015$) and as a dichotomized marker with a cut-off at 3.5 g/dl (HR 0.59; 95% CI 0.45-0.77, $P < 0.00001$) (Supplementary Figure S5B, available at https://doi.org/10.1016/j.esmoop.2024.103374). However, the mGPS model incorporating both CRP and albumin was better than the model with albumin alone ($P = 0.000015$ for log-albumin as continuous variable; $P = 0.0005$ for binary variable) and tended to be better than the model with CRP alone ($P = 0.12$ for log-CRP as continuous variable; $P = 0.059$ for binary variable). With regard to PFS, similar effects for CRP and albumin as single markers were identified (data not shown).

Body mass index and impact of albumin as a non-inflammatory/nutrition marker. As albumin may not only be considered an inflammation marker but also a nutritional effect, a correlation analysis of body mass index (BMI) and albumin as a single marker was carried out. In the investigated patient cohort, albumin levels significantly depended on BMI and vice versa ($P = 0.0013$). An increase in BMI of 1 unit was associated in average with an increase in albumin level of 0.02 g/dl (95% CI 0.008-0.032). An increase in albumin level of 1 g/dl was associated in average with an increase in BMI of 1.52 (95% CI 0.59-2.44). Patients with albumin levels $\geq$3.5 g/dl had in average a BMI which was 1.57 (95% CI 0.39-2.74) times greater than the BMI of patients with an albumin level lower than 3.5 g/dl. The difference between groups was statistically significant ($P = 0.009$). Although BMI was associated with OS in univariate analysis, it was not an independent predictor of survival in multivariate analysis including albumin as a single marker or mGPS (Supplementary Figure S6A-C, available at https://doi.org/10.1016/j.esmoop.2024.103374).

DISCUSSION

In this *post hoc* analysis of the randomized phase III XELAVIRI trial, we evaluated the prognostic value of the inflammation-based mGPS as well as its predictive value when combined with gender in first-line mCRC patients. Our results confirmed mGPS as a valuable prognostic tool in this patient population and suggested its potential to refine the prediction of gender-specific treatment benefit from intensive versus less-intensive first-line therapy.

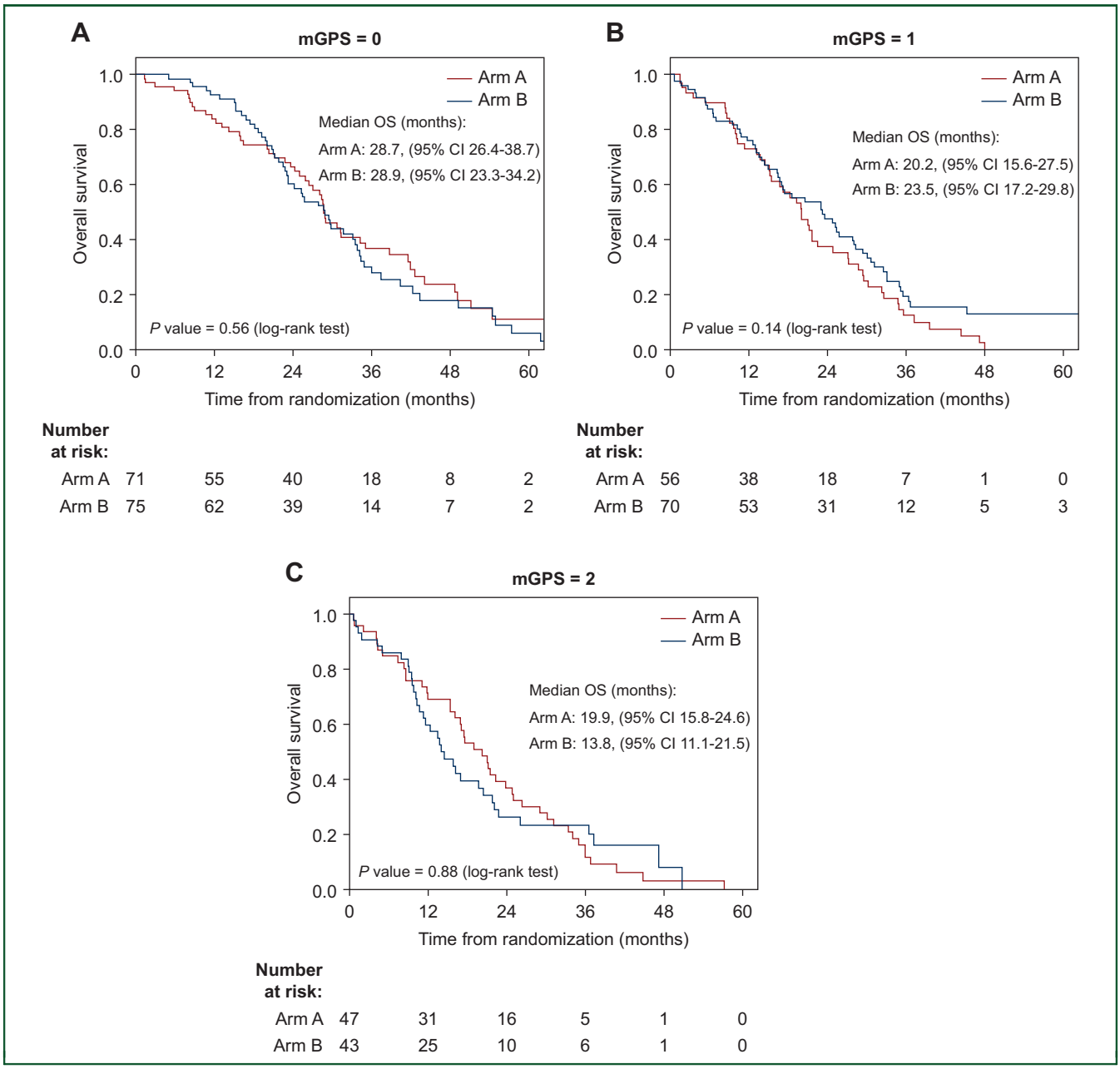

Figure 2. (A-C) Overall survival in each mGPS category comparing the two treatment arms.
CI, confidence interval; mGPS, modified Glasgow Prognostic Score; OS, overall survival.

The mGPS, an inflammatory-based score that combines serum CRP and albumin levels before treatment start, was shown to predict cancer survival in a variety of advanced solid tumors independent of tumor site, tumor stage, performance status and treatment.[2,3] Moreover, mGPS was shown to be a more powerful prognostic factor than other biochemical parameters and biomarkers such as liver function tests or cellular components of the systemic inflammatory response in CRC.[3,18] Advantages of the mGPS when compared to other established prognostic biomarkers in mCRC include absolute objectivity (unlike other factors like ECOG performance status) as well as wide accessibility and very simple measurement in any laboratory and in any clinical setting (in contrast to other biomarkers like molecular characteristics that require more complicated assessment techniques). Hence, mGPS may complement other well-defined clinicopathological characteristics as an easily measurable and widely accessible prognostic biomarker in mCRC patients.

In the present study, results reveal that mGPS was significantly associated with PFS and OS regardless of the applied treatment regimen (Figures 1 and 2A-C, Supplementary Figures 1 and 2A-C). This effect remained significant also in a multivariate model including *RAS/BRAF* mutational status and primary tumor sidedness. Therefore, we can confirm the strong prognostic impact of mGPS on long-term outcome in first-line mCRC patients. In the entire study population, mCRC patients with an mGPS of 1 had a

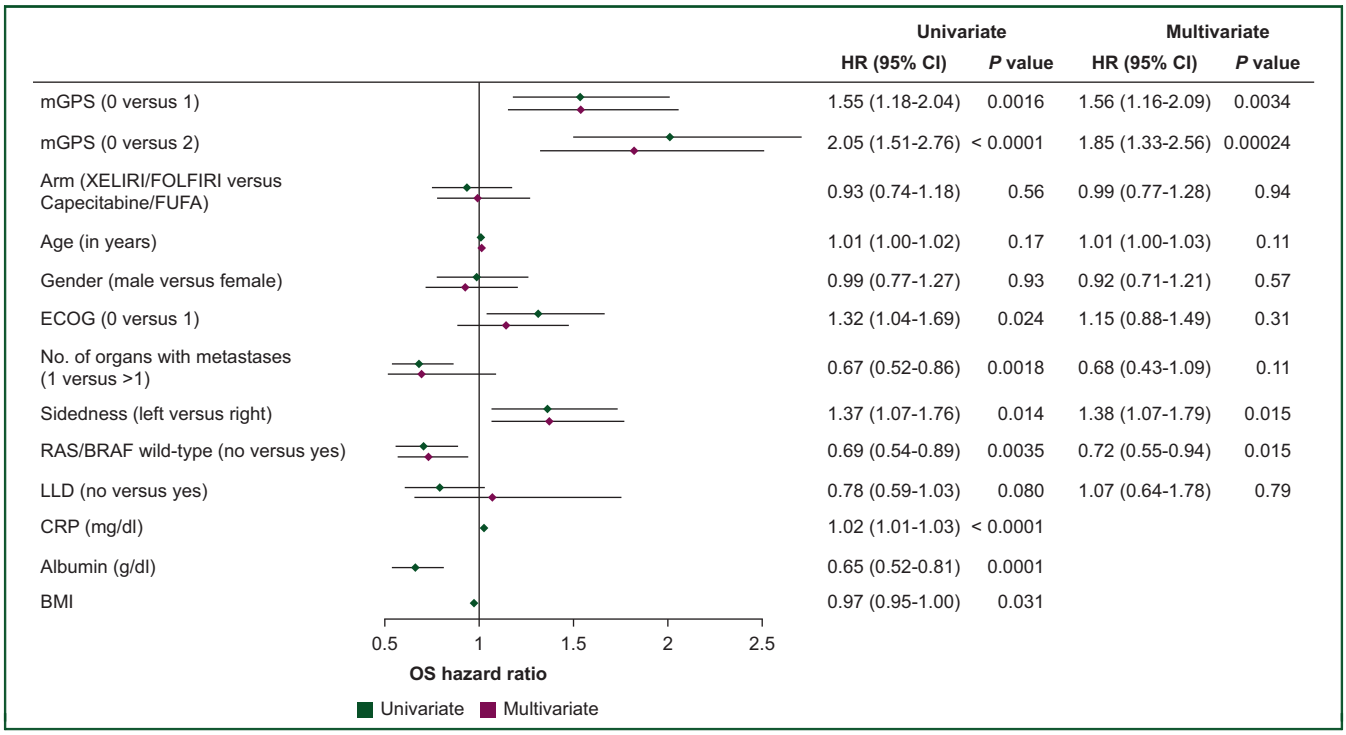

Figure 3. Forrest plot showing uni- and multivariate analysis for overall survival.
BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group Performance Status; LLD, liver limited disease; mGPS, modified Glasgow Prognostic Score; OS, overall survival.

1.55-fold higher risk for death and those with an mGPS of 2 had a 2.02-fold higher risk for death compared to patients with an mGPS of 0. These results are in line with published data from the meta-analysis carried out by Petrelli et al. that demonstrated a 1.69-fold higher risk for death in unselected CRC patients with an mGPS $\geq$1 in all tumor stages.[13] In pairwise comparisons, statistical differences with regard to OS were observed both between mGPS 0 versus 1 and 0 versus 2. However, in terms of PFS, statistical differences were only observed in mGPS 0 versus 2 (not 0 versus 1 or 1 versus 2). While the results regarding OS clearly indicate the prognostic value of mGPS, the lack of differentiation in mGPS 0 versus 1 with regard to PFS might suggest reduced accuracy and needs to be evaluated further.

Performance status is recognized as an important prognostic factor in advanced cancer.[19] In the present analysis, ECOG performance status at baseline differed significantly between the mGPS groups, with higher mGPS being associated with higher ECOG status ($P = 0.00016$; Table 1). ECOG performance status as a single marker was significantly associated with survival in univariate analysis. However, it was not an independent predictor of survival in a multivariate model including also mGPS, likely because ECOG and mGPS were not independent variables. This is in line with previous literature in patients with advanced non-small-cell lung cancer.[20]

In order to assess the added value of mGPS as a prognostic biomarker, we also evaluated the prognostic impact of CRP and albumin as single markers. There was no evidence that the effect of CRP depends on albumin and vice versa. The mGPS model with incorporation of CRP and albumin was better than the model with albumin alone and tended to be better than the model with CRP alone (Supplementary Figure S5A and B, available at https://doi.org/10.1016/j.esmoop.2024.103374). This is in line with literature indicating an improved prognostic value of the combined mGPS as compared to CRP or albumin alone in advanced solid tumors.[1,21,22]

Since albumin may not only be considered an inflammation marker but also a malnutrition effect, we conducted analyses investigating albumin as a single marker compared to BMI. Albumin levels significantly depended on BMI and vice versa ($P = 0.0013$). However, BMI was not an independent predictor of survival in multivariate analysis including albumin as a single biomarker or mGPS. Furthermore, >93% of patients overall as well as in all mGPS groups had a BMI $\geq$18.5. This highlights mGPS as an inflammatory and not as a nutritional biomarker.

Novel biomarkers for the prediction of treatment efficacy and long-term outcome are urgently needed to better individualize treatment strategies for metastatic colorectal cancer. Recently, our study group published data on gender-specific treatment efficacy where male patients with unselected mCRC in the first-line setting clearly benefited from intensive upfront combination chemotherapy whereas female patients draw a comparable benefit from less-intensive treatment.[16] In the present analysis, we investigated whether mGPS when combined with gender could provide additional predictive information and further refine

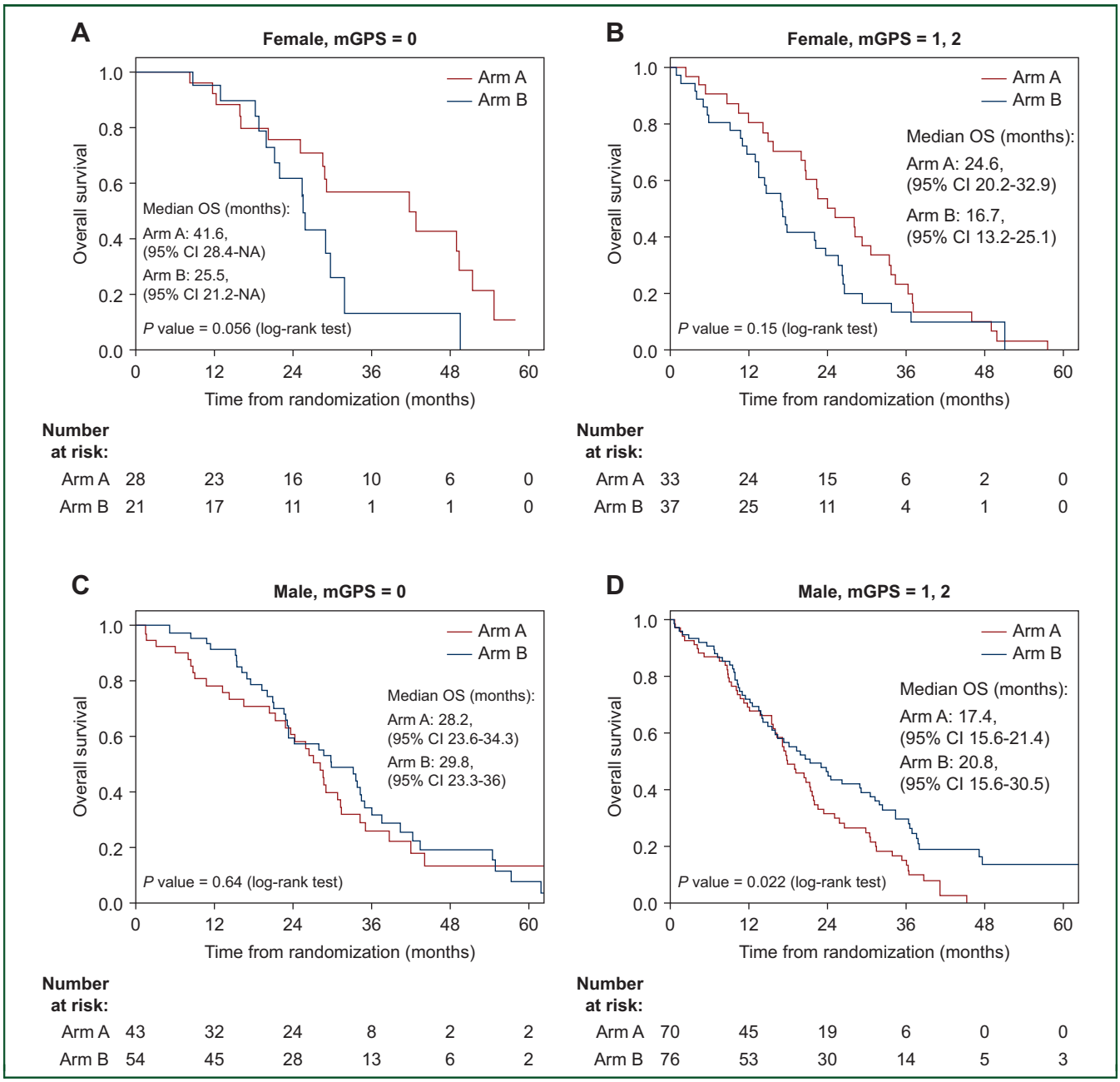

Figure 4. (A-D) Overall Survival in women (A, B) and men (C, D) according to mGPS and treatment arm.
CI, confidence interval; mGPS, modified Glasgow Prognostic Score; OS, overall survival.

the patient cohorts that benefit from intensive versus less-intensive treatment.

In the present analysis, female patients showed a trend towards a benefit from less-intensive upfront chemotherapy, with this effect being more pronounced and almost reaching statistical significance in female patients with an mGPS of 0 (OS 41.6 months with fluoropyrimidine/bevacizumab alone versus 25.5 months with fluoropyrimidine/bevacizumab/irinotecan; $P = 0.056$) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103374 and Figure 4A and B). In other words, female patients with a favorable mGPS of 0 may be optimal candidates to be offered less-intensive upfront chemotherapy. In contrast, male patients with an unfavorable mGPS of 1 or 2 did clearly benefit from intensive upfront treatment with fluoropyrimidine/bevacizumab/irinotecan compared to fluoropyrimidine/bevacizumab alone (20.8 versus 17.4 months; $P = 0.022$) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103374 and Figure 4C and D). Male subjects with an mGPS of 0 showed no survival difference between treatment arms. These data—if prospectively validated—indicate that mGPS may help identify a subset of male patients, who do not derive benefit from upfront intensive treatment and thus potentially spare them the unnecessary toxicities of combination chemotherapy.

Speculating about the potential reasons for the gender-specific results, we believe that they are attributable to various reasons, including variable drug metabolism and different toxicity profiles between male and female patients. One possible explanation is the potential variability of fluoropyrimidine clearance between male and female patients, which can explain higher fluoropyrimidine-related toxicities reported in female patients.[23,24] However, literature on this topic is largely inconclusive. Furthermore, variable metabolism of irinotecan between male and female patients might also be of relevance, a notion supported by literature indicating higher rates of neutropenia under irinotecan in female patients.[25,26]

One limitation of the present study is that the analysis followed a non-preplanned *post hoc* design. Nevertheless, the patient dataset was derived from the prospective randomized multicenter phase III XELAVIRI trial that included 421 molecularly unselected mCRC patients, of whom 362 were assessable for the present analysis. Another limitation of the study could be the use of individual site's laboratories for the determination of blood tests. However, as the analysis of the serum parameters albumin and CRP is standardized, this issue should be of inferior relevance. Moreover, all patients in the XELAVIRI trial received bevacizumab plus chemotherapy regardless of *RAS/BRAF* mutational status and tumor sidedness. Today, this does not represent the current standard of care which involves an anti- epidermal growth factor receptor monoclonal antibody (instead of bevacizumab) for left-sided *RAS/BRAF* wild-type tumors. Thus, it is possible that this subgroup of patients was not treated optimally according to current scientific evidence and findings on mGPS should be interpreted with caution for this specific patient subgroup. Furthermore, only one-third of all study patients were female ($N = 119$), which implicates limitations regarding the statistical value of gender-specific analyses. Hence, these data need to be prospectively validated.

Our results indicate that in future randomized clinical trials, baseline assessment and stratification according to gender and mGPS may be essential for patients with untreated mCRC receiving systemic chemotherapy. Serum CRP and albumin levels are simple to measure, routinely available and well standardized. Thus, determination of these two laboratory markers is compatible with clinical routine and can easily allow patient allocation into mGPS category 0, 1 or 2.

CONCLUSION

The present analysis demonstrated that mGPS was an independent prognostic factor in patients with mCRC receiving first-line treatment regardless of the applied treatment regimen, ECOG performance status, *RAS/BRAF* status, primary tumor sidedness and number of metastatic sites. Male patients with a favorable mGPS of 0 did not seem to derive benefit from upfront combination (versus less-intensive sequential) chemotherapy in contrast to their counterparts with a less favorable mGPS of 1-2, who clearly benefited from upfront intensive treatment. While female patients overall tended to benefit more from less-intensive, sequential treatment, this effect was markedly more pronounced in female patients with a favorable mGPS of 0. Thus, our data suggest that mGPS might help identify gender-specific subgroups of untreated mCRC patients who are more or less likely to benefit from upfront combination chemotherapy. These data warrant prospective validation.

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DISCLOSURE

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