

**Figure A1.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (complete case analysis as sensitivity analysis).

**Figure A2.** Prognostic value of predictors for 90-day mortality in metastatic pancreatic cancer, expressed as Nagelkerke's partial  $R^2$  values (complete cases as sensitivity analysis, n=951).

**Table A1.** Definitions of biomarkers.

**Table A2.** Standard clinical factors for the prediction of 90-day mortality in patients with metastatic pancreatic cancer (best clinical model).

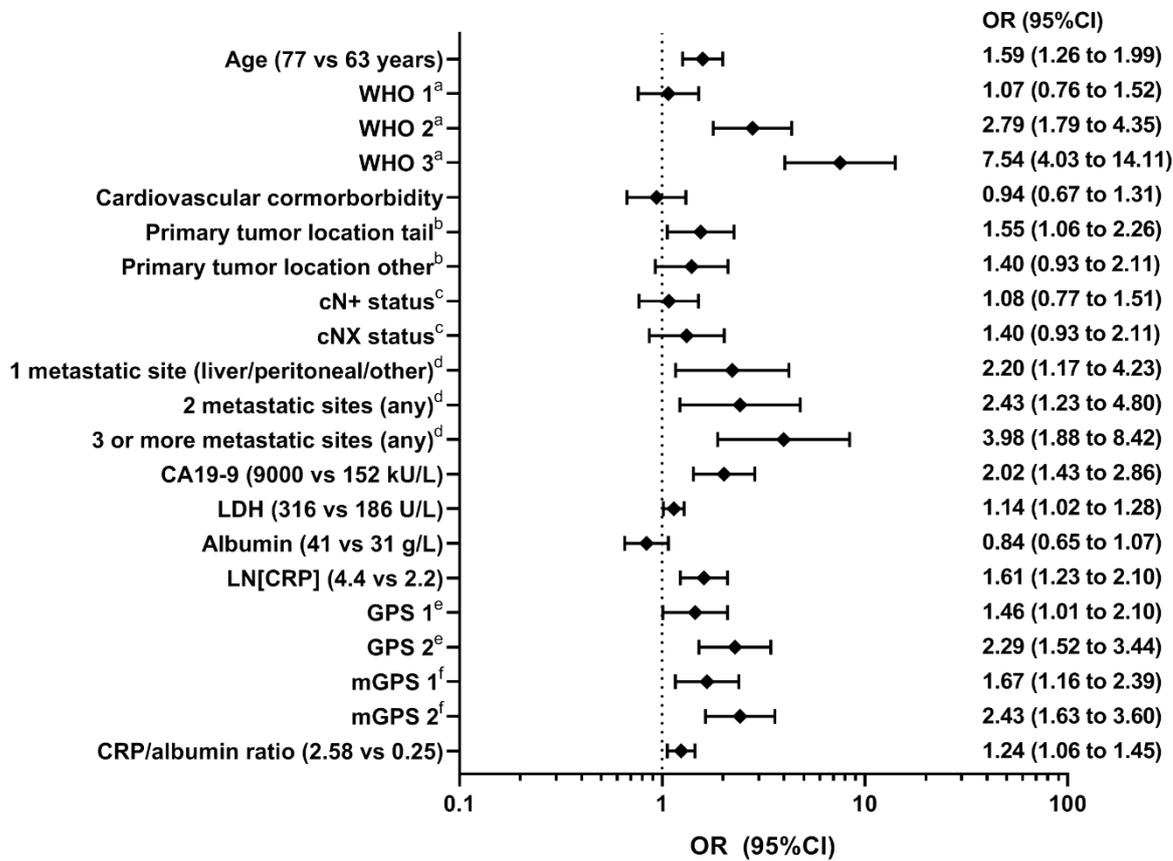
**Table A3.** Prognostic factors for overall survival (secondary outcome) after diagnosis in patients with metastatic pancreatic cancer (database after multiple imputation).

**Table A4.** Standard clinical factors for the prediction of 90-day mortality in patients with metastatic pancreatic cancer undergoing palliative chemotherapy (best clinical model).

**Table A5.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (complete case analysis as sensitivity analysis).

**Table A6.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (sensitivity analysis after multiple imputation of all predictors except for the biomarker under study).

**Figure A1.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (complete case analysis as sensitivity analysis).



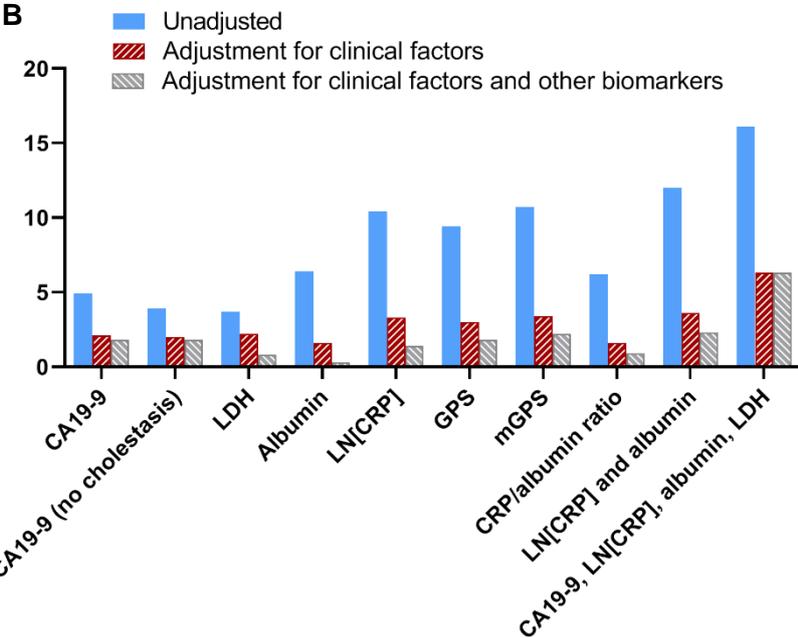
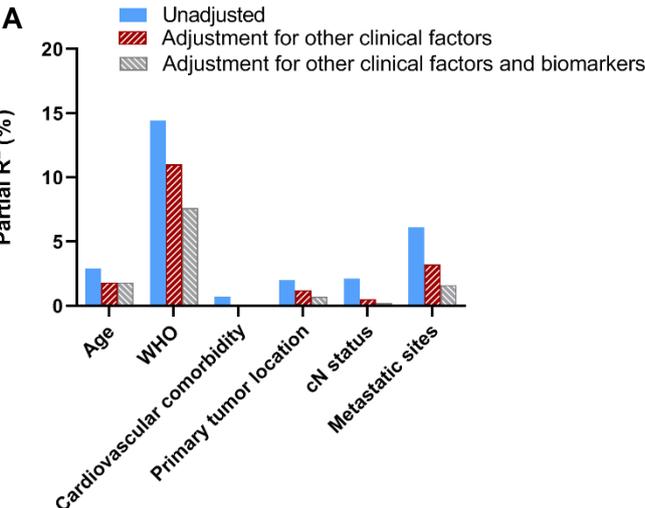
The odds ratios for the continuous variables (age and all biomarkers) are presented as an increase from the lower quartile (25<sup>th</sup> percentile) to the upper quartile (75<sup>th</sup> percentile);

Reference categories are the following: <sup>a</sup>WHO 0; <sup>b</sup>primary tumor location head; <sup>c</sup>cN- status; <sup>d</sup>1 metastatic site (lung/lymph nodes) <sup>e</sup>GPS 0; <sup>f</sup>mGPS 0

**Figure A2.** Prognostic value of predictors for 90-day mortality in metastatic pancreatic cancer, expressed as Nagelkerke’s partial R<sup>2</sup> values (complete cases as sensitivity analysis, n=951).

**A:** Clinical predictors

**B:** Biomarkers. The figure shows a) the prognostic value each individual biomarker (CA19-9, LDH, CRP, Albumin); unadjusted, adjusted for clinical factors, and after addition of also the biomarkers; b) the prognostic value of four combinations of CRP and albumin (GPS, mGPS, CRP/albumin ratio, and LN[CRP] and albumin as continuous variables), unadjusted, adjusted for clinical factors, and after addition of the remaining biomarkers (i.e. CA19-9 and LDH); c) all four biomarkers combined; unadjusted and adjusted for clinical factors (as there are no remaining biomarkers to add to the model, the red and grey bar show the same results).



**Table A1.** Definitions of biomarkers.

Marker	Units	Reference values*	Definitions^
CA19-9	kU/L	0-34	Highest value before start of treatment/decision to renounce treatment, values >9000 are coded as 9000
Albumin	g/L	35-50	Last value before start of treatment/decision to renounce treatment
CRP	mg/L	<5	Last value before start of treatment/decision to renounce treatment
LDH	U/L	0-247	Highest value before start of treatment/decision to renounce treatment
CRP/albumin ratio	CRP: mg/L Albumin: g/L	N/A	CRP divided by albumin
GPS	Scale 0-2	Score 0	1 point each for CRP >10 mg/L or albumin <35 g/L <sup>§</sup>
mGPS	Scale 0-2	Score 0	1 point in case of CRP >10 mg/L, 2 points in case of both CRP >10 mg/L and albumin <35 g/L <sup>§</sup>
Bilirubin (total)	µmol/L <sup>#</sup>	<20	Highest value before start of treatment/decision to renounce treatment; in the case of biliary drainage bilirubin before drainage

\* Reference values are derived from the Amsterdam UMC, location AMC, and are provided as an indication; reference values differ per laboratory; <sup>#</sup>1 µmol/L = 0.06 mg/dL; <sup>§</sup> The difference between the scores is that for an elevated albumin only, one point is allocated in the GPS, but none in the mGPS.

^The rationale behind these definitions was that CA19-9 and LDH are tumor-related markers, which will not decrease before tumor treatment is started; highest (generally also the last) value is the most relevant. CRP and albumin are also influenced by inflammatory and nutritional status. Inflammation and malnutrition will often be treated before start of treatment/decision to renounce treatment; therefore, the last value was considered the most relevant. Highest total bilirubin value was selected because of the relevance for drainage-related studies.

**Table A2.** Standard clinical factors for the prediction of 90-day mortality in patients with metastatic pancreatic cancer (best clinical model).

Characteristics	Univariable		Multivariable	
	OR (95%CI)	p	OR (95%CI)	p
Increasing age (per 10 years)	1.55 (1.45 to 1.65)	<0.001	1.48 (1.37 to 1.59)	<0.001
Gender		0.21		-
Male	Ref			
Female	0.92 (0.82 to 1.04)			
Socioeconomic status		0.01		<sup>a</sup>
Low	Ref			
Medium	0.81 (0.70 to 0.94)			
High	0.83 (0.71 to 0.97)			
WHO performance score		<0.001		<0.001
WHO 0	Ref		Ref	
WHO 1	1.42 (1.19 to 1.69)		1.25 (1.04 to 1.51)	
WHO 2	4.16 (3.10 to 5.56)		3.40 (2.52 to 4.58)	
WHO 3 to 4	11.92 (8.37 to 16.96)		9.67 (6.58 to 14.21)	
Cardiovascular comorbidity	1.71 (1.49 to 1.96)	<0.001	1.22 (1.04 to 1.43)	0.01
Pulmonal comorbidity	1.07 (0.88 to 1.30)	0.49		-
Diabetes Mellitus as comorbidity	1.17 (1.02 to 1.35)	0.03		<sup>a</sup>
Other malignancy in history	0.96 (0.82 to 1.12)	0.59		-
Primary tumor location		<0.001		<0.001
Head/corpus	Ref		Ref	
Tail	1.53 (1.32 to 1.78)		1.39 (1.17 to 1.66)	
Other/not otherwise specified/overlapping	1.37 (1.16 to 1.63)		1.16 (0.95 to 1.42)	
Primary tumor diameter (per cm increase)	1.03 (0.99 to 1.07)	0.10		-
cT stage (TNM 8)		<0.001		<sup>a</sup>
Tis/T0/T1/T2	Ref			
T3/T4	1.19 (1.04 to 1.36)			
TX	1.91 (1.56 to 2.34)			
cN status		<0.001		<0.001
N to	Ref		Ref	
N+	1.22 (1.07 to 1.40)		1.30 (1.11 to 1.53)	
NX	2.12 (1.78 to 2.52)		1.82 (1.49 to 2.23)	
Location/number metastatic sites		<0.001		<0.001
1 site (Lung/distant nodes)	Ref		Ref	
1 site (Liver/peritoneal/other)	3.28 (2.53 to 4.24)		3.61 (2.66 to 4.90)	
2 sites (any)	4.00 (3.04 to 5.25)		4.12 (2.98 to 5.71)	
3 or more sites (any)	6.41 (4.71 to 8.74)		5.64 (3.96 to 8.04)	

Data after multiple imputation. In complete case analysis, the best possible clinical model contained the exact same predictors (n=2108 in final multivariable analysis); <sup>a</sup> Removed in backward selection

**Table A3.** Prognostic factors for overall survival (secondary outcome) after diagnosis in patients with metastatic pancreatic cancer (database after multiple imputation).

Biomarker	Univariable		Multivariable, adjusted for clinical factors only*		Multivariable, adjusted for clinical factors* and other biomarkers	
	HR (95%CI)	p	HR (95%CI)	p	HR (95%CI)	p
CA19.9 (per 1000 U/L increase)	1.04 (1.03 to 1.05)	<0.001	1.03 (1.02 to 1.05)	<0.001	1.03 (1.02 to 1.05)	<0.001
LDH (per 100 U/L increase)	1.05 (1.03 to 1.06)	<0.001	1.04 (1.03 to 1.05)	<0.001	1.03 (1.02 to 1.04)	<0.001
Albumin (per unit increase)	0.96 (0.95 to 0.96)	<0.001	0.97 (0.96 to 0.98)	<0.001	0.98 (0.97 to 0.99)	<0.001
LN[CRP]	1.28 (1.24 to 1.31)	<0.001	1.22 (1.18 to 1.26)	<0.001	1.17 (1.13 to 1.21)	<0.001
GPS		<0.001		<0.001		<0.001 <sup>#</sup>
0	Ref				Ref	
1	1.51 (1.37 to 1.67)		1.38 (1.25 to 1.52)		1.35 (1.22 to 1.49)	
2	2.55 (2.32 to 2.82)		2.00 (1.81 to 2.22)		1.94 (1.76 to 2.15)	
mGPS		<0.001		<0.001		<0.001 <sup>#</sup>
0	Ref		Ref		Ref	
1	1.50 (1.36 to 1.65)		1.37 (1.24 to 1.51)		1.34 (1.22 to 1.48)	
2	2.46 (2.24 to 2.70)		1.95 (1.77 to 2.15)		1.90 (1.73 to 2.08)	
CRP/albumin ratio (per unit increase)	1.11 (1.09 to 1.12)	<0.001	1.09 (1.07 to 1.10)	<0.001	1.09 (1.07 to 1.10)	<0.001 <sup>#</sup>

LN[CRP] = logarithmic transformation of CRP;

\*Adjusted for age, WHO performance status, cardiovascular disease, location of primary tumor, cN status, location/number of metastatic sites;

<sup>#</sup> Not adjusted for albumin and CRP as mGPS, GPS and CPR/albumin ratio are composed of these biomarkers

**Table A4.** Standard clinical factors for the prediction of 90-day mortality in patients with metastatic pancreatic cancer undergoing palliative chemotherapy (best clinical model).

Characteristics	Univariable		Multivariable	
	OR (95%CI)	p	OR (95%CI)	p
Increasing age (per 10 years)	1.07 (0.91 to 1.25)	0.44		-
Gender		0.10		-
Male	Ref			
Female	0.79 (0.59 to 1.05)			
Socioeconomic status		0.67		-
Low	Ref			
Medium	0.87 (0.62 to 1.23)			
High	0.99 (0.69 to 1.43)			
WHO performance score		<0.001		<0.001
WHO 0	Ref		Ref	
WHO 1	1.90 (1.25 to 2.89)		1.56 (1.04 to 2.33)	
WHO 2 to 4	4.52 (2.70 to 7.58)		4.92 (3.09 to 7.84)	
Cardiovascular comorbidity	0.81 (0.56 to 1.17)	0.26		-
Pulmonal comorbidity	0.91 (0.54 to 1.52)	0.71		-
Diabetes Mellitus as comorbidity	1.14 (0.82 to 1.58)	0.45		-
Other malignancy in history	1.14 (0.78 to 1.67)	0.49		-
Primary tumor location		<0.001		<0.001
Head/corpus/other/not otherwise specified/overlapping	Ref		Ref	
Tail	1.93 (1.42 to 2.62)		1.82 (1.31 to 2.53)	
Tumor diameter (per cm increase)	1.03 (0.99 to 1.06)	0.12		-
cT stage (TNM 8)		0.004		0.05
Tis/T0/T1/T2	Ref		Ref	
T3/T4	1.56 (1.10 to 2.23)		1.45 (1.00 to 2.09)	
TX	2.17 (1.30 to 3.61)		1.76 (1.02 to 3.06)	
cN status		0.14		<sup>a</sup>
N to	Ref			
N+	1.22 (0.89 to 1.67)			
NX	1.49 (0.99 to 2.24)			
Location/number metastatic sites		<0.001		<0.001
1 site (Lung/distant nodes)	Ref		Ref	
1 site (Liver/peritoneal/other)	6.16 (3.66 to 10.34)		5.89 (2.09 to 16.61)	
2 sites (any)	8.44 (3.09 to 23.06)		7.07 (2.47 to 20.24)	
3 or more sites (any)	10.94 (3.78 to 31.69)		7.83 (2.62 to 23.38)	

Data after multiple imputation. In complete case analysis, the best possible clinical model contained the exact same predictors (n=902 in final multivariable analysis);

<sup>a</sup> Removed in backward selection

**Table A5.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (complete case analysis as sensitivity analysis).

Biomarker	Univariable		Multivariable, adjusted for clinical factors only*		Multivariable, adjusted for clinical factors* and other biomarkers	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
<b>Total group</b>						
CA19 to 9 (per 1000 U/L increase)	1.09 (1.07 to 1.12)	<0.001	1.07 (1.04 to 1.11)	<0.001	1.08 (1.04 to 1.13)	<0.001
LDH (per 100 U/L increase)	1.31 (1.25 to 1.38)	<0.001	1.21 (1.13 to 1.30)	<0.001	1.11 (1.01 to 1.21)	0.03
Albumin (per unit increase)	0.92 (0.91 to 0.93)	<0.001	0.95 (0.94 to 0.97)	<0.001	0.98 (0.96 to 1.01)	0.16
LN[CRP]	1.75 (1.65 to 1.85)	<0.001	1.39 (1.28 to 1.50)	<0.001	1.24 (1.10 to 1.40)	<0.001
GPS		<0.001		<0.001		<0.001 <sup>#</sup>
0	Ref		Ref		Ref	
1	2.55 (2.08 to 3.13)		1.98 (1.46 to 2.69)		1.46 (1.02 to 2.20)	
2	6.33 (5.10 to 7.86)		2.97 (2.15 to 4.12)		2.29 (1.52 to 3.44)	
mGPS		<0.001		<0.001		<0.001 <sup>#</sup>
0	Ref		Ref		Ref	
1	2.86 (2.35 to 3.49)		2.31 (1.71 to 3.11)		1.67 (1.16 to 2.39)	
2	6.37 (5.18 to 7.84)		3.14 (2.29 to 4.30)		2.43 (1.63 to 3.60)	
CRP/albumin ratio (per unit increase)	1.31 (1.26 to 1.37)	<0.001	1.12 (1.07 to 1.18)	<0.001	1.10 (1.03 to 1.17)	0.007 <sup>#</sup>
<b>Chemotherapy group</b>						
CA19 to 9 (per 1000 U/L increase)	1.11 (1.06 to 1.16)	<0.001	1.10 (1.04 to 1.16)	0.001	1.10 (1.03 to 1.17)	0.007
LDH (per 100 U/L increase)	1.19 (1.09 to 1.30)	<0.001	1.12 (0.99 to 1.26)	0.06	0.94 (0.77 to 1.15)	0.53
Albumin (per unit increase)	0.95 (0.93 to 0.98)	<0.001	0.96 (0.93 to 1.00)	0.02	0.97 (0.93 to 1.02)	0.23
LN[CRP]	1.56 (1.38 to 1.76)	<0.001	1.31 (1.13 to 1.53)	<0.001	1.37 (1.11 to 1.69)	0.004
GPS		<0.001		0.001		0.001 <sup>#</sup>
0	Ref		Ref		Ref	
1	2.14 (1.33 to 3.43)		1.97 (1.09 to 3.56)		1.80 (0.91 to 3.59)	
2	4.30 (2.62 to 7.07)		3.30 (1.74 to 6.26)		3.92 (1.85 to 8.30)	
mGPS		<0.001		<0.001		<0.001 <sup>#</sup>
0	Ref		Ref		Ref	
1	2.93 (1.83 to 4.27)		2.51 (1.39 to 4.54)		2.28 (1.15 to 4.51)	
2	5.03 (3.06 to 8.24)		3.73 (1.98 to 7.03)		4.45 (2.12 to 9.32)	
CRP/albumin ratio (per unit increase)	1.18 (1.10 to 1.26)	<0.001	1.07 (0.99 to 1.17)	0.09	1.14 (1.03 to 1.27)	0.02 <sup>#</sup>

LN[CRP] = logarithmic transformation of CRP;

Total group: n=4248, n=952 in analyses with adjustment for clinical factors and other biomarkers;

Chemotherapy group: n=1218, n=498 in analyses with adjustment for clinical factors and other biomarkers;

\*Total group: Adjusted for age, WHO performance status, cardiovascular disease, primary tumor location, cN status, location/number of metastatic sites (best clinical model, see Table A1). In

complete case analysis, the best clinical model was the exact same model as after multiple imputation;

Chemotherapy group: Adjusted for WHO performance score, primary tumor location, cT stage (TNM8), location/number of metastatic sites (best clinical model, see Table A2). In complete case analysis, the best clinical model was the exact same model as after multiple imputation;

# Not adjusted for albumin and CRP as (m)GPS and CPR/albumin ratio are composed of these.

**Table A6.** Prognostic factors for 90-day mortality after diagnosis in patients with metastatic pancreatic cancer (sensitivity analysis after multiple imputation of all predictors except for the biomarker under study).

		Univariable		Multivariable, adjusted for clinical factors only*		Multivariable, adjusted for clinical factors* and other biomarkers	
Biomarker	n	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
CA19.9 (per 1000 U/L increase)	2490	1.09 (1.07 to 1.12)	<0.001	1.08 (1.05 to 1.10)	<0.001	1.08 (1.05 to 1.10)	<0.001
LDH (per 100 U/L increase)	3719	1.31 (1.25 to 1.38)	<0.001	1.29 (1.22 to 1.36)	<0.001	1.18 (1.12 to 1.25)	<0.001
Albumin (per unit increase)	3244	0.92 (0.91 to 0.93)	<0.001	0.94 (0.93 to 0.96)	<0.001	0.98 (0.96 to 0.99)	<0.001
LN[CRP]	3482	1.75 (1.66 to 1.85)	<0.001	1.55 (1.46 to 1.65)	<0.001	1.40 (1.30 to 1.50)	<0.001
GPS	2818		<0.001		<0.001		<0.001 <sup>#</sup>
0		Ref				Ref	
1		2.55 (2.08 to 3.13)		2.14 (1.71 to 2.69)		1.87 (1.48 to 2.36)	
2		6.33 (5.10 to 7.86)		4.23 (3.32 to 5.38)		3.55 (2.77 to 4.53)	
mGPS	2818		<0.001		<0.001		<0.001 <sup>#</sup>
0		Ref		Ref		Ref	
1		2.86 (2.35 to 3.49)		2.35 (1.88 to 2.94)		1.88 (1.49 to 2.36)	
2		6.37 (5.18 to 7.84)		4.16 (3.29 to 5.24)		3.51 (2.73 to 4.51)	
CRP/albumin ratio (per unit increase)	2818	1.31 (1.26 to 1.37)	<0.001	1.23 (1.18 to 1.28)	<0.001	1.20 (1.15 to 1.26)	<0.001 <sup>#</sup>

LN[CRP] = logarithmic transformation of CRP;

\*Adjusted for age, WHO performance status, cardiovascular disease, location of primary tumor, cN status, location/number of metastatic sites (Table A1);

<sup>#</sup> Not adjusted for albumin and CRP as mGPS, GPS and CPR/albumin ratio are composed of these biomarkers