Supplementary Material

Predictors of mortality in patients with advanced cancer – A systematic review and meta-analysis

Table S1. Search strategy for the online databases

Embase
('chronic disease'/de OR 'lung fibrosis'/exp OR 'obstructive airway disease'/exp OR 'neoplasm'/exp OR (((chronic* OR advance* OR palliative) NEAR/4 (ill* OR diseas* OR condition* OR lung OR pulmonar* OR cancer* OR neoplas* OR tumor* OR tumour* OR patient*)) OR ((lung OR pulmonar* OR airway) NEAR/3 (fibros* OR obstruct*)) OR COPD OR asthma* OR bronchitis):ab,ti**) AND** ('physical disease by body function'/de OR 'health status indicator'/exp OR 'cognition'/de OR 'hospital admission'/de OR 'hospital readmission'/de OR (condition OR conditions OR cognit* OR admission* OR readmission* OR ((symptom*) NEAR/3 (sign* OR digest* OR respirat* OR pathol*))):ab,ti) **AND** ('terminal care'/exp OR 'death'/exp OR ('end of life' OR ((mors* OR mortalit* OR died OR die OR dying OR death OR fatal*) NEAR/6 (year OR month OR months OR week OR weeks OR days OR time*)) OR ((end *OR EOL* OR palliat* OR terminal* OR final OR last) NEAR/3 (care OR phase* OR stage* OR month* OR week* OR year))):ab,ti) **AND** ('prediction'/de OR 'predictive value'/de OR 'prognosis'/exp OR 'prognostic assessment'/exp OR ('surprise question' OR ((predict* OR indicat* OR prognost*) NEAR/4 (value* OR factor* OR tool* OR index OR indices OR assess*)) OR ((early OR time*) NEXT/1 (identificat*))):ab,ti) **AND** english:la **AND (**'article'/it OR 'article in press'/it OR 'note'/it OR 'review'/it**)**
MEDLINE
("Chronic Disease"/ OR exp "Pulmonary Fibrosis"/ OR exp "Lung Diseases, Obstructive"/ OR exp "Neoplasms"/ OR (((chronic* OR advance* OR palliative) ADJ4 (ill* OR diseas* OR condition* OR lung OR pulmonar* OR cancer* OR neoplas* OR tumor* OR tumour* OR patient*)) OR ((lung OR pulmonar* OR airway) ADJ3 (fibros* OR obstruct*)) OR COPD OR asthma* OR bronchitis).ab,ti.**) AND** ("Signs and Symptoms"/ OR exp "Health Status Indicators"/ OR "Cognition"/ OR exp "Hospitalization"/ OR (condition OR conditions OR cognit* OR admission* OR readmission* OR ((symptom*) ADJ3 (sign* OR digest* OR respirat* OR pathol*))).ab,ti.) **AND** (exp "Terminal Care"/ OR exp "Death"/ OR ("end of life" OR ((mors* OR mortalit* OR died OR die OR dying OR death OR fatal*) ADJ6 (year OR month OR months OR week OR weeks OR days OR time*)) OR ((end *OR EOL* OR palliat* OR terminal* OR final OR last) ADJ3 (care OR phase* OR stage* OR month* OR week* OR year))).ab,ti.) **AND** ("Predictive Value of Tests"/ OR "Prognosis"/ OR ("surprise question" OR ((predict* OR indicat* OR prognost*) ADJ4 (value* OR factor* OR tool* OR index OR indices OR assess*)) OR ((early OR time*) ADJ1 (identificat*))).ab,ti.) **AND** English.lg. **AND** Journal Article.pt.
Cochrane Central
((((chronic* OR advance* OR palliative) NEAR/4 (ill* OR diseas* OR condition* OR lung OR pulmonar* OR cancer* OR neoplas* OR tumor* OR tumour* OR patient*)) OR ((lung OR pulmonar* OR airway) NEAR/3 (fibros* OR obstruct*)) OR COPD OR asthma* OR bronchitis):ab,ti**) AND** ((condition OR conditions OR cognit* OR admission* OR readmission* OR ((symptom*) NEAR/3 (sign* OR digest* OR respirat* OR pathol*))):ab,ti) **AND** (('end of life' OR ((mors* OR mortalit* OR died OR die OR dying OR death OR fatal*) NEAR/6 (year OR month OR months OR week OR weeks OR days OR time*)) OR ((end *OR EOL* OR palliat* OR terminal* OR final OR last) NEAR/3 (care OR phase* OR stage* OR month* OR week* OR year))):ab,ti) **AND** (('surprise question' OR ((predict* OR indicat* OR prognost*) NEAR/4 (value* OR factor* OR tool* OR index OR indices OR assess*)) OR ((early OR time*) NEXT/1 (identificat*))):ab,ti)
Web of Science
TS=((((((chronic* OR advance* OR palliative) NEAR/3 (ill* OR diseas* OR condition* OR lung OR pulmonar* OR cancer* OR neoplas* OR tumor* OR tumour* OR patient*)) OR ((lung OR pulmonar* OR airway) NEAR/2 (fibros* OR obstruct*)) OR COPD OR asthma* OR bronchitis)**) AND** ((condition OR conditions OR cognit* OR admission* OR readmission* OR ((symptom*) NEAR/2 (sign* OR digest* OR respirat* OR pathol*)))) **AND** (("end of life" OR ((mors* OR mortalit* OR died OR die OR dying OR death OR fatal*) NEAR/6 (year OR month OR months OR week OR weeks OR days OR time*)) OR ((end *OR EOL* OR palliat* OR terminal* OR final OR last) NEAR/2 (care OR phase* OR stage* OR month* OR week* OR year)))) **AND** (("surprise question" OR ((predict* OR indicat* OR prognost*) NEAR/2 (value* OR factor* OR tool* OR index OR indices OR assess*)) OR ((early OR time*) NEAR/1 (identificat*)))))**) AND LA=** English **AND DT=**Article
PubMed
(((chronic*[tiab] OR advance*[tiab] OR palliative[tiab]) AND (ill[tiab] OR illness[tiab] OR diseas*[tiab] OR condition*[tiab] OR lung[tiab] OR pulmonar*[tiab] OR cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR patient[tiab] OR patients[tiab])) OR ((lung[tiab] OR pulmonar*[tiab] OR airway[tiab]) AND (fibros*[tiab] OR obstruct*[tiab])) OR COPD[tiab] OR asthma*[tiab] OR bronchitis[tiab]**) AND (**condition[tiab] OR conditions[tiab] OR cognit*[tiab] OR admission*[tiab] OR readmission*[tiab] OR ((symptom*[tiab]) AND (sign[tiab] OR signs[tiab] OR digest*[tiab] OR respirat*[tiab] OR pathol*[tiab]))**) AND (**end of life[tiab] OR ((mors*[tiab] OR mortalit*[tiab] OR died[tiab] OR die[tiab] OR dying[tiab] OR death[tiab] OR fatal*[tiab]) AND (year[tiab] OR month[tiab] OR months[tiab] OR week[tiab] OR weeks[tiab] OR days[tiab] OR time*[tiab])) OR ((end[tiab] *OR EOL*[tiab] OR palliat*[tiab] OR terminal*[tiab] OR final[tiab] OR last[tiab]) AND (care[tiab] OR phase*[tiab] OR stage*[tiab] OR month*[tiab] OR week*[tiab] OR year[tiab]))) **AND (**surprise question[tiab] OR ((predict*[tiab] OR indicat*[tiab] OR prognost*[tiab]) AND (value*[tiab] OR factor*[tiab] OR tool*[tiab] OR index[tiab] OR indices[tiab] OR assess*[tiab])) OR early identif*[tiab] OR timely identif*[tiab]**) AND** publisher[sb]

Table S2. Domains and items for risk-of-bias assessment

Domain	Items	Total domain points
Study participation	1. Recruitment procedure 2. Study population 3. In- and exclusion criteria 4. Baseline study characteristics	8
Study attrition	5. Number of loss to follow-up 6. Reasons for loss to follow-up 7. Differences between completers and non-completers 8. Handling of missing data	8
Predictor measurement	9. Definition of predictor(s) 10. Measurement of predictor(s) 11. Handling of predictor(s) 12. Data presentation	8
Outcome measurement	13. Outcome definition 14. Outcome presentation	4
Statistical analysis and confounding	15. Method of selection of variables 16. Occurrence of mortality in relation to predictors 17. Presentation of crude variables (univariate analysis) 18. Presentation of adjusted variables (multivariate analysis) 19. Account for potential confounders 20. Selective reporting	12
Model performance	21. Discriminative ability 22. Internal validation 23. External validation	6

Each domain is scored as low risk-of-bias (≥80% of the total domain points), moderate risk-of-bias (60-79% of the total domain points), or high risk-of-bias (< 60% of the total domain points).

Table S3. Hazard ratios for mortality based on studies with low risk-of-bias

Predictor	N studies	N patients	Pooled HR (95% CI)
Age (per 10-year increase)	2[1,2]	782	1.22 (1.11–1.34)
Male sex (ref: female)	2[1,3]	1870	1.21 (1.08–1.35)
ECOG performance status 1+ (ref: 0–1)	2[1,4]	1154	2.22 (0.98–5.03)

CI: confidence interval; HR: hazard ratio; ref: reference; ECOG: Eastern Cooperative Oncology Group.

Table S4. Variables not included in the meta-analysis

Variable group	Variable	Number of studies
Age	• Age at bone metastases diagnosis >50 vs. ≤50 years • Age <50 vs. ≥60 years • Age 50–59 vs. ≥60 years • Age ≤60 vs. >60 • Age >64 vs. ≤64 years • Age ≥67 vs. <67 years • Age 75–79 vs. <75 years • Age ≥80 vs. <75 years	6[5-10]
Body mass index	• BMI kg/m2 Overweight (BMI >25) vs. normal (BMI 18.5–25) • BMI kg/m2 Underweight (BMI <18.5) vs. normal (BMI 18.5–25) • BMI <23 vs. ≥23 kg/m2	2[8,9]
Use of medication	• No of drugs • ACEi • Beta-blocker • Dexamethasone • Diuretic • Megestrol acetate • Use of morphine • Tamoxifen	2[11,12]
Comorbidity (score)	• Comorbidity Index CIRS (cont. Var) • Charlson score 1 vs. 0 • Charlson score 2 vs. 0 • Charlson score 1+ (ref 0) • Moderate to severe comorbidity vs. absent/mild • ASA (indicating comorbidity at time of surgery) score >1 (with comorbidity) vs. 1 (without comorbidity • ASA score (<3 or ≥3)	6[8,10,12-15]
Cardiovascular comorbidity	• Atrial fibrillation • Vascular disease as co-morbidity present vs. absent • IHD: ischemic heart disease • NYHA class • Hypertension • Diabetes • Higher LVEF	1[11]
Other comorbidity	• COPD • Syndromes yes vs. no • Psychiatric diseases yes vs. no	1[11,12]
Performance status	• ECOG performance status • Karnofsky PS 80–90% vs. normal (ECOG PS 0–1 vs. 0) • Karnofsky PS 50–70 vs. 80–100% (ECOG PS 1–2 vs. 0–1) • Karnofsky PS 70–80 vs. ≤60 (ECOG PS 1 vs. 2+) • ECOG PS 2 vs. 1 • Karnofsky performance score ≤60 vs. >60 (ECOG PS 2+ vs. 0–1) • Initial ECOG PS 2–3 vs. 0 • Performance status 2–3 vs. 0–1 • Performance status ECOG 2–4 vs. 0–1 • Karnofsky PS 30–40 vs. 90% (ECOG PS 3 vs. 0) • ECOG Performance status 3+ versus 0 • Performance status 3–4 vs. 0–2 • Karnofsky PS <50% (ECOG PS 3+ vs. unknown)	13[6,7,12,13,16-24]
Activities of daily living	• Instrumental Activities of daily living (IADL) • IADL (instrumental activities of daily living) • iADL Intermediate vs. Better • iADL Worse vs. Better • Dependence in instrumental activities of daily living (Lawton scale <20/24) • Activities of daily living (ADL) • ADL One or more dependence vs. no dependence	4[10,12,17,25]
Mobility	• Ambulation status With support or nonambulartory vs. Without support • Timed Get Up and Go Impaired vs. No impairments (≤ 20 seconds) • Usual gait speed (UGS): assessed over a 4-m course starting from a still position • Short physical performance battery (SPPB): chair-stand, balance and walking speed test • Walking ability 4–8 months after admission: unable to walk vs. able • 10 meter walk test (10MWT) at admission • Bergs Balance Scale (BBS) at admission	4[17,26-28]

Handgrip strength	• Handgrip strength • Handgrip 25th percentile • Handgrip ≤10 percentile	2[17,29]
Tumor stage	• Stage of cancer • Tumor stage advanced (metastatic) vs. localized (nonmetastatic) • Cancer stage: more advanced (stages III and IV) vs. less advanced (stages I, II, and unknown) • Stage at diagnosis IV (ref: locoregional disease stages I–III) • Stage IV vs. IIIb • Stage IV vs. III • Severity of SCLC • Severity of NSCLC • Severity of breast cancer	7[3,10,11,28,30-32]
Metastases	• Visceral metastases • Visceral or cerebral metastases • Major organ metastases: unmovable vs. none • ≥ 4 metastatic sites • Metastatic spread to the brain • Number of brain metastases 1 vs. >3 • Number of brain metastases 2–3 vs. >3 • Extra-cranial metastatic disease Yes vs. No • Pleural metastasis • Pleural effusion Yes vs. No • Extrahepatic spread present vs. absent • Leptomeningeal disease yes vs. no • Cervical location of spinal metastasis (symptomatic metastases in cervical spine) • Pathological fracture • Site of metastases Others vs. Bone only • Multiple skeletal metastasis • Number of bone metastases 1–3 vs. >3 • Location of skeletal metastases 'appendicular and axial bone' vs. appendicular bone • Location of skeletal metastases axial bone vs. appendicular bone • No. Of bone lesions on initial bone scan 5–15/ >15/superscan vs. 0–4	13[5-7,16,18,19,21,24,33-37]
Ascites	• Presence of ascites • Persistent ascites	2[38,39]
Portal vein thrombosis	• Presence of portal vein thrombosis • Portal vein thrombosis • Thrombosis	3[22,38,39]
Antitumor therapy	• Treatment before baseline Yes/No • Prior treatment history (previously treated as reference) • No previous lung surgery • Cancer treatment yes vs. no • Chemotherapy Yes vs. No • Previous chemotherapy • Pre-operative chemotherapy present vs. absent • Cancer treatment intent (palliative vs. curative) • Curatively intended treatment of primary tumor • Palliative care vs. Chemotherapy • Palliative care vs. Sequential therapy • Palliative care vs. TKI (EGFR tyrosine kinase inhibitors) • Pembrolizumab after chemotherapy failure No vs. Yes • Without treatment vs. Surgery, Palliative therapy (chemotherapy or radiotherapy), and Combined surgery with chemotherapy • Radiotherapy Yes vs. No • Treatment EBRT (conventional radiotherapy) yes vs. no	14[1,3,7,9,12,15,16,24,25,31,33,36,40,41]
Weight change	• Fat-free mass (per kg increase) • Cachexia • Weight loss • Weight loss >8.1 kg vs. ≤8.1 kg • Rate of weight loss >2,75% per month • Baseline Weight Loss >11 lbs. vs. ≤10 lbs. • Lung cancer by weight loss >8.1 kg • Weight change ≥ -14% vs. -1.9 to 1.9% • Weight change -2 to -13.9% vs. -1.9 to 1.9% • Weight change >2% vs. -1.9 to 1.9%	8[11,13,15,20,30,41-43]
Nutrition / dietary intake	• Body surface area (BSA) 0.5 unit increase • Mini Nutritional Assessment at risk/ poor nutrition, score ≤23.5 vs. Good nutrition, score >23.5	4[28,36,43,44]

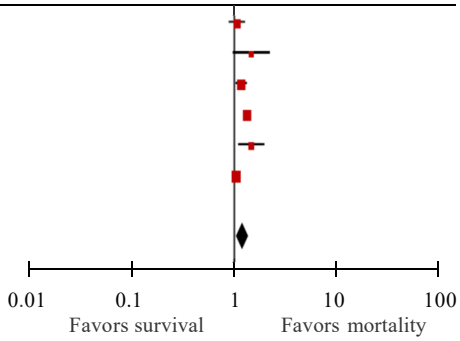
	• Nutritional decay presence vs. absence • Dietary intake normal food/reduced amount vs. normal food/normal amount • Dietary intake Abnormal intake vs. normal food/normal amount • Alcohol drinking Yes vs. No	
Re-hospitalization	• Inpatient [hospitalization] vs. outpatient • Reason for admission (cardiac/pulmonary, neurologic, pain, failure to thrive vs. GI/genitourinary, abnormal labs, bleeding, infection) • Readmission within 30 days • Discharge with hospice services	2[25,44]
Smoking	• Smoking Yes vs. No	1[36]
Social-related variables	• Income quintile 1 (low) vs. 5 • Income quintile 2 vs. 5 • Income quintile 3 vs. 5 • Income quintile 4 vs. 5 • Caregiver yes vs. no	2[12,14]
Dyspnea	• Severity of dyspnea • Dyspnea (Dyspnea at rest vs. No dyspnea) • Shortness of breath mild vs. none • Shortness of breath moderate vs. none • Shortness of breath severe vs. none	3[11,21,45]
Dysphagia	• Dysphagia	1[43]
Depression	• Depression mild vs. none • Depression moderate vs. none • Depression severe vs. none	1[45]
Nausea	• Nausea mild vs. none • Nausea moderate vs. none • Nausea severe vs. none • Moderate-to-severe nausea vs. absent-to-mild • Nausea constant vs. absent	3[11,13,45]
Appetite	• Loss of appetite • Appetite mild vs. none • Appetite moderate vs. none • Appetite severe vs. none	2[33,45]
Fatigue	• Fatigue mild vs. none • Fatigue moderate vs. none • Fatigue severe vs. none • Fatigue constant vs. absent	2[11,45]
Pain	• Pain Present vs. Absent • Pain mild vs. none • Pain moderate vs. none • Pain severe vs. none • Severity of pain • Subjective pain score from 0–10 (<6 vs. ≥6)	4[11,15,26,45]
Neurological symptoms	• Paresis Present vs. Absent • Neurological deficits	2[7,26]
Quality of life (domains)	• QoL Intermediate vs. Better • QoL Worse vs. Better • HRQoL Anorexia • QLQ-C30 scale QoL Domain Appetite loss • HRQOL Appetite loss >0 vs. ≤0 • Psychosocial variable (higher score= better status) Eating appetite • QLQ-C30 scale QoL Domain Cognitive • QLQ-C30 scale QoL Domain Constipation • QLQ-C30 scale QoL Domain Diarrhea • QLQ-C30 scale QoL Domain Dyspnea • HRQOL: Dysphagia (higher score= higher perception of symptom) • QLQ-C30 scale QoL Domain Emotional • QLQ-C30 scale QoL Domain Fatigue • EORTC QLQ-C30 Fatigue • HRQoL Role functioning • FACT-G (Ch: higher score= better HRQoL) Functional well-being • HRQOL Insomnia >33.3 vs. ≤33.3 • QLQ-C30 scale QoL Domain Nausea/vomiting • QLQ-C30 scale QoL Domain Pain • HRQOL: Pain (higher score= higher perception of symptom) • QLQ-C30 scale QoL Domain Physical • HRQoL Physical functioning • FACT-G(Ch: higher score= better HRQoL) Physical well-being • QLQ-C30 scale QoL Domain Role	8[2,3,10,19,30,31,37,46]

	• QLQ-C30 scale QoL Domain Social • Baseline FACT-G Total score (increase in score)	
a-Fetoprotein level	• a-Fetoprotein level ≥400 ng/ml • AFP >400 ng/mL	2[39,47]
Albumin	• Albumin <28 g/dL • Albumin (per g/dL increase) • Albumin <3.0 vs. ≥3.0 g/dl • Serum albumin level <36 g/L by lymphocyte count <1x 109/L • Serum albumin level <36 g/L by weight loss >8.1 kg • Serum albumin level <35 g/L by time covariate	4[9,13,39,42]
Alkaline phosphatase	• Alkaline phosphatase • ALP (alkaline phosphatase) >450 vs. ≤450 U/L	1[37]
Bilirubin	• Bilirubin >1.3 mg/dL vs. ≤1.3 • Bilirubin >50 mmol/L	2[39,40]
C-reactive protein	• C-reactive protein (mg/L) • CRP ≥1.0 mg/dl • CRP ≥5 mg/dl vs. <5 mg/dl • C-reactive protein (>5 mg/l) • CRP (C-reactive protein) >32 vs. ≤32 mg/l	5[2,9,20,23,47]
Lactate dehydrogenase	• Abnormal LDH (>240 U/L vs. ≤240 U/L) • LDH (lactate dehydrogenase) >360 vs. ≤360 U/L • LDH >618 U/L vs. ≤618 U/L	3[9,13,21]
Lymfocyte	• Lymphocyte count <1 x 109/L vs. ≥ 1 x 109/L • Lymphocyte count <700 units/mm3 vs. ≥700 • Lymphocyte count <1600 vs. ≥1600 ul • WBC count Abnormal (≥ 10.8 x 103/uL) vs. normal (<10.8) • Elevated WBC • Neutrophil-lymphocyte ratio ≥3 vs. <3	5[9,13,21,48,49]
Platelets	• Platelets >500,000 mm3 (upper limit of normal) • Platelet <143 000/mm3	2[34,39]
Serum sodium	• Na (serum sodium) • Natremia <135 mEq/l (lower limit of normal)	2[34,38]
Other laboratory values	• CA 19-9 ≥10 000 U/ml vs. < 10 000 U/ml • Corrected calcium • Creatinine >1.3 mg/dL • Hemoglobin (continuous) • Hyperglycemia • High serum CEA (carcinoembryonic antigen) (unspecified) • High serum CYFRA211 (cytokeratin-19-fragment) (unspecified) • High serum NSE (neuron-specific enolase) (unspecified) • High serum ProGRP (progastrin-releasing peptide) (unspecified) • INR >1.2	5[4,11,23,36,39]
Survival estimate	• Clinical estimation of survival 2–6 mo. vs. ≤2 mo. • Clinical estimation of survival >6 mo. vs. ≤2 mo.	1[13]
Scales	• Palliative Performance Scale (per each 10-point decrease) • Palliative Prognostic Score (per point increase) • Significant functional decay (PPS [Palliative Performance Scale] ≤ 50%) • 15-item Geriatric Depression Scale >5 vs. ≤5 • GDS (≥5) • MELD >10 • MPI 0.3 unit increase in MPI • Cognitive impairment (Test of 9 or greater on the Short Blessed Test)	7[12,14,22,25,41,42,44]

Figure S1. Forest plots per individual predictor using random-effects model

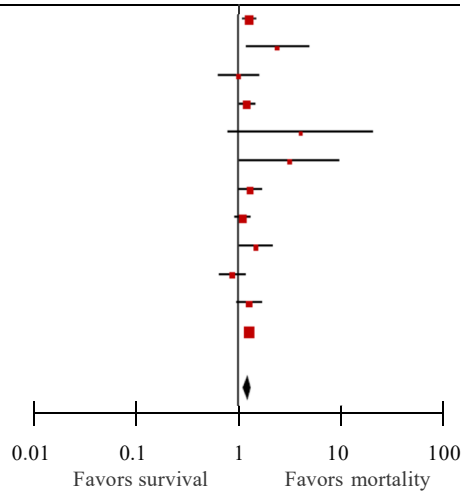
Age (per 10-year increase)

Study	N patients	HR (95% CI)
Moss, 2010	826	1.06 (0.88–1.28)
Brunello, 2016	658	1.48 (0.96–2.28)
Fielding, 2007	358	1.17 (1.03–1.33)
Filippini, 2008	676	1.34 (1.22–1.48)
Scott, 2002	106	1.48 (1.09–2.00)
Seow, 2013	11,342	1.04 (1.02–1.07)
Total (95% CI) $I^2 = 85\%$		1.20 (1.05–1.38) p= 0.007



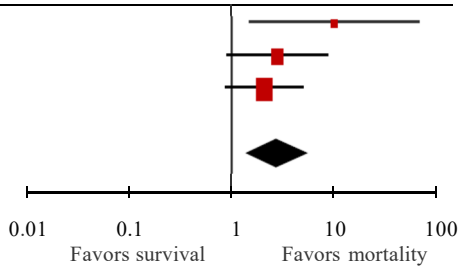
Male sex (ref: female)

Study	N patients	HR (95% CI)
Braun, 2011	1194	1.28 (1.11–1.49)
Soubeyran, 2012	348	2.40 (1.20–4.81)
Brunello, 2016	658	1.02 (0.65–1.60)
Jonna, 2016	803	1.23 (1.03–1.46)
Wei, 2019	71	3.99 (0.81–19.63)
Dharma-Wardene, 2004	42	3.12 (1.04–9.37)
Efficace, 2006	391	1.32 (1.03–1.69)
Filippini, 2008	676	1.11 (0.93–1.32)
Bartels, 2007	219	1.49 (1.05–2.13)
Katagiri, 2005	350	0.89 (0.67–1.18)
Maione, 2005	566	1.28 (0.92–1.69)
Seow, 2013	11,342	1.28 (1.20–1.37)
Total (95% CI) $I^2 = 39\%$		1.24 (1.14–1.36) p< 0.00001



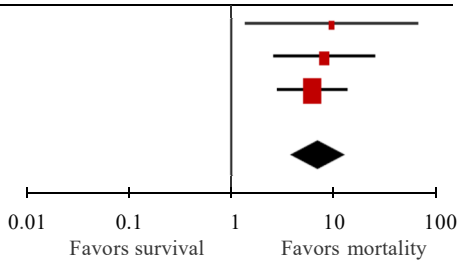
Disease stage III (ref: I)

Study	N patients	HR (95% CI)
Norman, 2010	399	10.81 (1.50–78.07)
Deans, 2007	220	2.88 (0.89–9.34)
Brunello, 2016	658	2.13 (0.85–5.31)
Total (95% CI) $I^2 = 7\%$		2.89 (1.42–5.90) p= 0.003



Disease stage IV (ref: I)

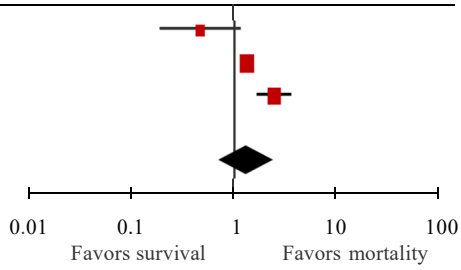
Study	N patients	HR (95% CI)
Norman, 2010	399	10.45 (1.38–79.36)
Deans, 2007	220	8.83 (2.70–28.84)
Brunello, 2016	658	6.69 (2.95–15.17)
Total (95% CI) $I^2 = 0\%$		7.58 (4.00–14.36) p< 0.00001



Continuation Figure S1

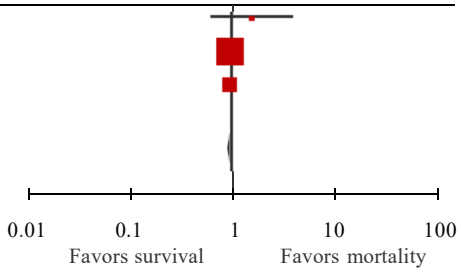
Liver metastases

Study	N patients	HR (95% CI)
Chow, 2008	395	0.47 (0.19–1.15)
Hoang, 2005	1436	1.32 (1.13–1.5)
Vigano, 2000	227	2.40 (1.65–3.50)
Total (95% CI) $I^2 = 86\%$		1.31 (0.71–2.39) p= 0.39



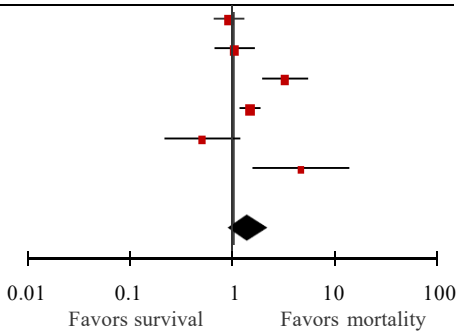
Karnofsky performance status

Study	N patients	HR (95% CI)
Cesari, 2013	200	1.42 (0.70–2.89)
Pointillart, 2011	142	0,98 (0.96–0.99)
Scott, 2002	106	0.96 (0.94–0.99)
Total (95% CI) $I^2 = 7\%$		0.97 (0.96–0.99) p= 0.0001



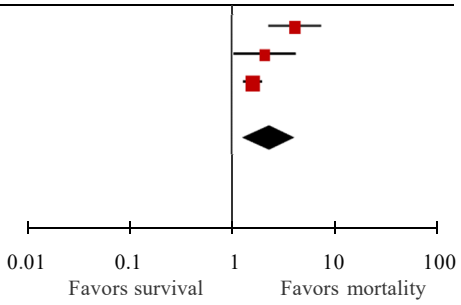
ECOG performance status 1 (ref: 0)

Study	N patients	HR (95% CI)
Collette, 2004	391	0.89 (0.64–1.24)
Deans, 2007	220	1.01 (0.65–1.58)
Brunello, 2016	658	3.12 (1.88–5.19)
Griguolo, 2018	668	1.43 (1.14–1.79)
Dharma-Wardene, 2004	42	0.49 (0.21–1.14)
Bartels, 2007	219	4.45 (1.53–12.93)
Total (95% CI) $I^2 = 82\%$		1.37 (0.88–2.13) p= 0.17



ECOG performance status 1+ (ref: 0–1)

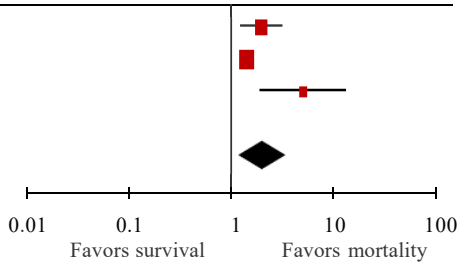
Study	N patients	HR (95% CI)
Motzer, 2004	251	3.50 (2.09–5.87)
Penel, Hollebecque, 2008	119	1.92 (1.04–3.54)
Filippini, 2008	676	1.52 (1.26–1.82)
Total (95% CI) $I^2 = 78\%$		2.09 (1.23–3.56) p= 0.006



Continuation Figure S1

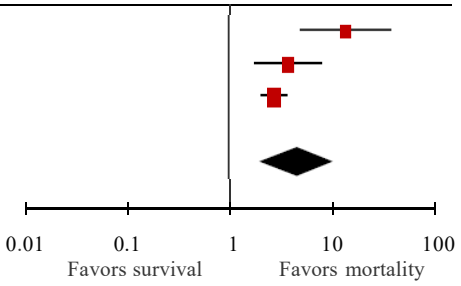
ECOG performance status 1–2 (ref: 0)

Study	N patients	HR (95% CI)
Deans, 2007	220	2.08 (1.26–3.43)
Hoang, 2005	1436	1.46 (1.26–1.70)
Bartels, 2007	219	5.67 (2.03–15.84)
Total (95% CI) $I^2 = 75\%$		2.13 (1.21–3.75) p= 0.009



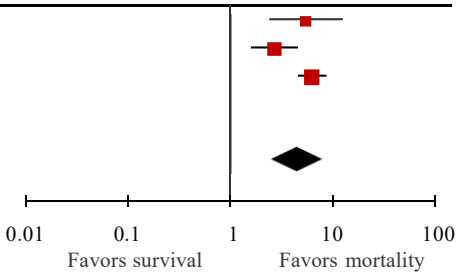
ECOG performance status 2 (ref: 0)

Study	N patients	HR (95% CI)
Marrero, 2005	244	14.29 (5.05–40.41)
Brunello, 2016	658	3.83 (1.78–8.24)
Griguolo, 2018	668	2.79 (2.06–3.78)
Total (95% CI) $I^2 = 78\%$		4.73 (2.06–10.85) p= 0.0002



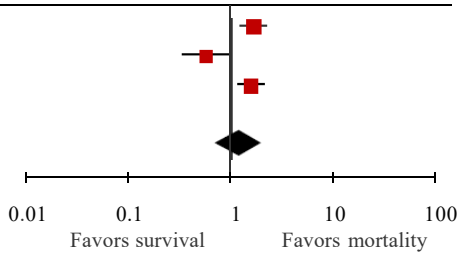
ECOG performance status 2+ (ref: 0)

Study	N patients	HR (95% CI)
Deans, 2007	220	4.83 (2.23–10.16)
Villa, 2011	285	2.50 (1.55–4.03)
Griguolo, 2018	668	5.48 (4.11–7.31)
Total (95% CI) $I^2 = 74\%$		4.06 (2.36–6.98) p< 0.00001



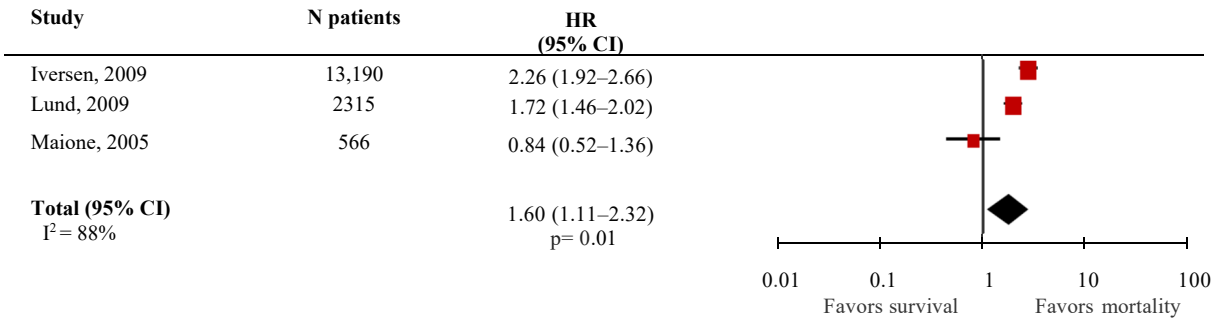
ECOG performance status 2 (ref: 0–1)

Study	N patients	HR (95% CI)
Park, 2016	403	1.53 (1.19–1.96)
Efficace, 2006	391	0.62 (0.39–0.96)
Maione, 2005	566	1.46 (1.13–1.89)
Total (95% CI) $I^2 = 85\%$		1.16 (0.74–1.82) p= 0.53

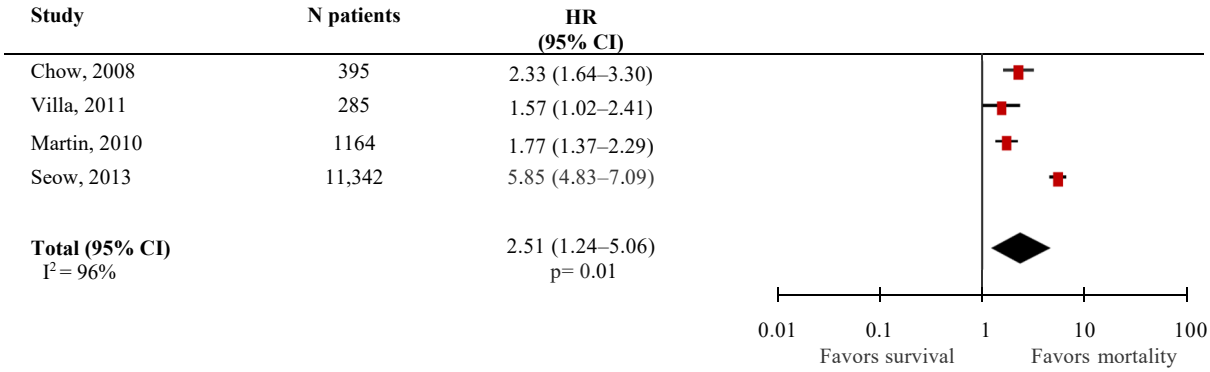


Continuation Figure S1

Charlson comorbidity index score 3+ (ref: 0)



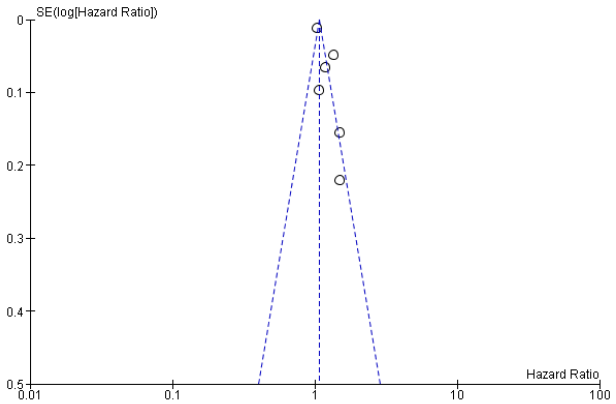
Lung cancer (ref: breast cancer)



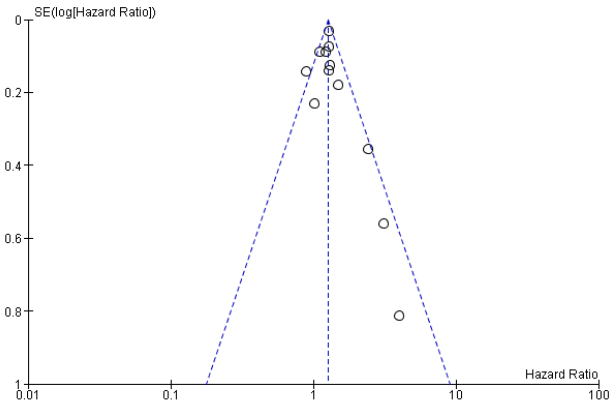
CI: confidence interval; HR: hazard ratio; mo.: months; N: number of; ECOG: Eastern Cooperative Oncology Group.

Figure S2. Funnel plots

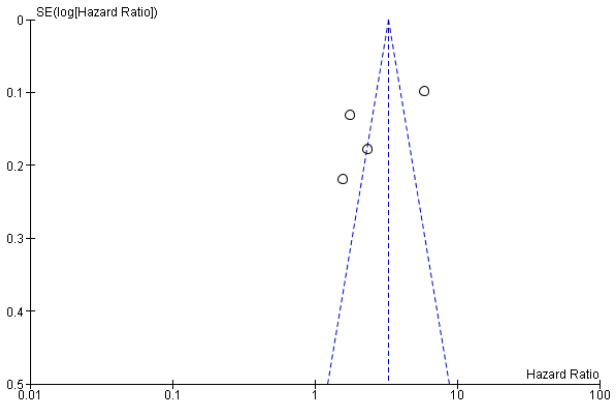
Age (per 10-year increase)



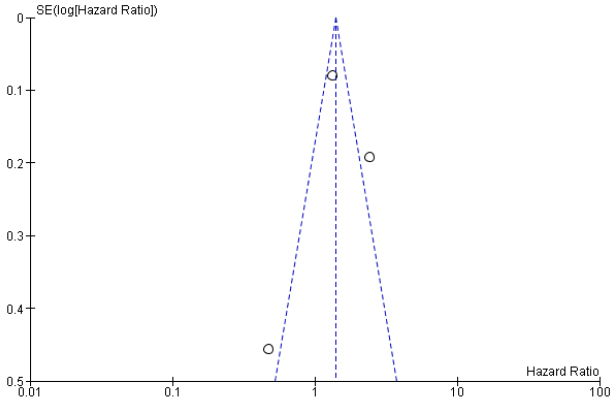
Male sex (ref: female)



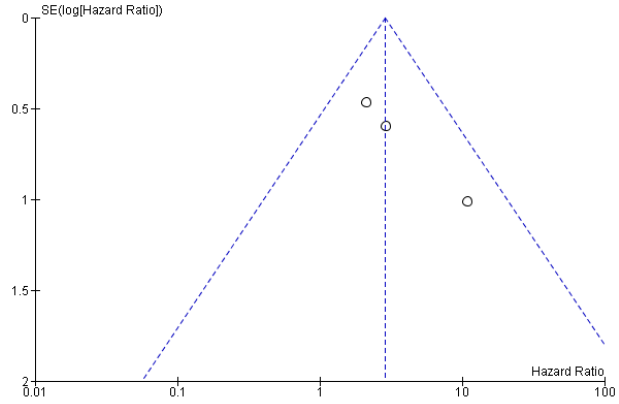
Lung cancer (ref: breast cancer)



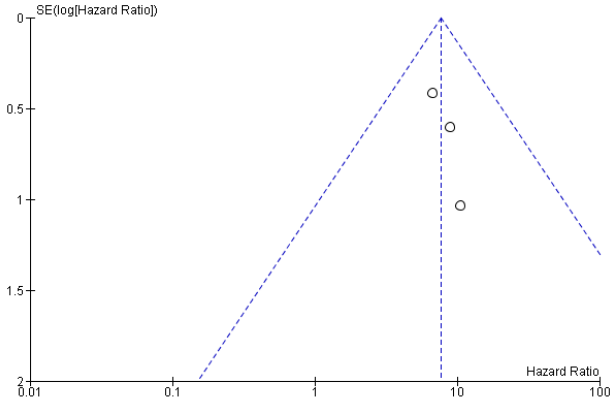
Liver metastases



Disease stage III (ref: I)

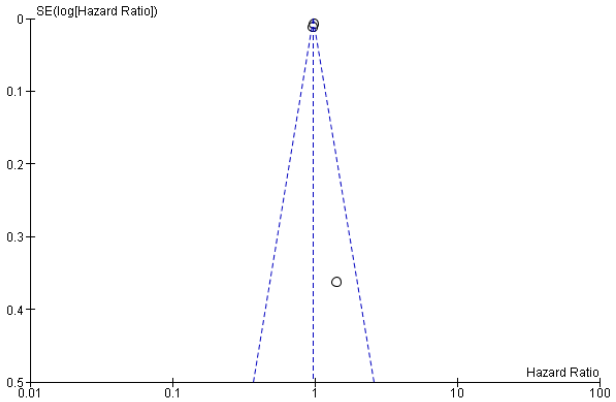


Disease IV (ref: I)

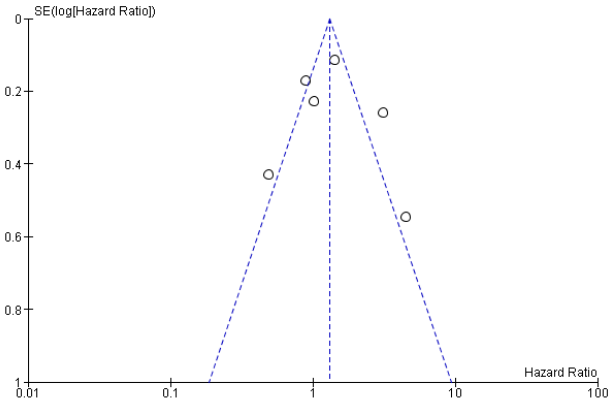


Continuation Figure S2

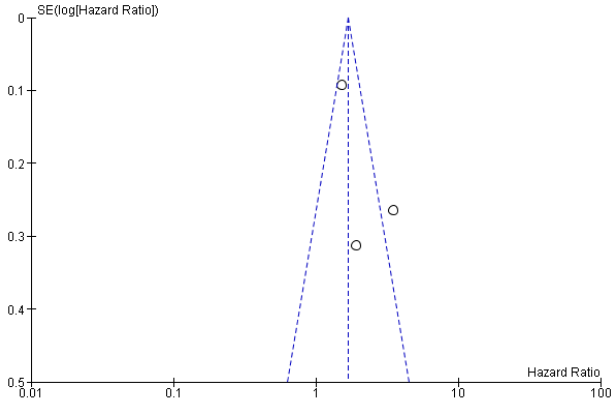
Karnofsky performance status



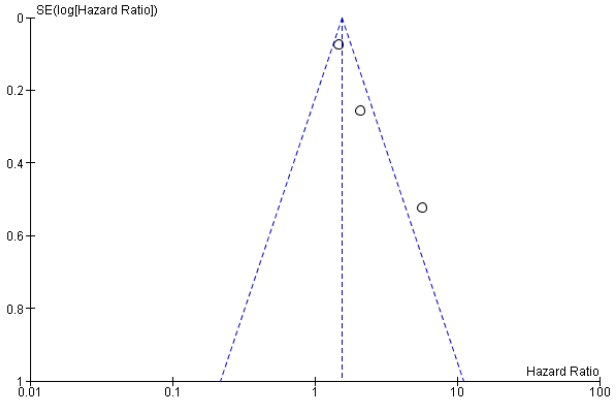
ECOG performance status 1 (ref: 0)



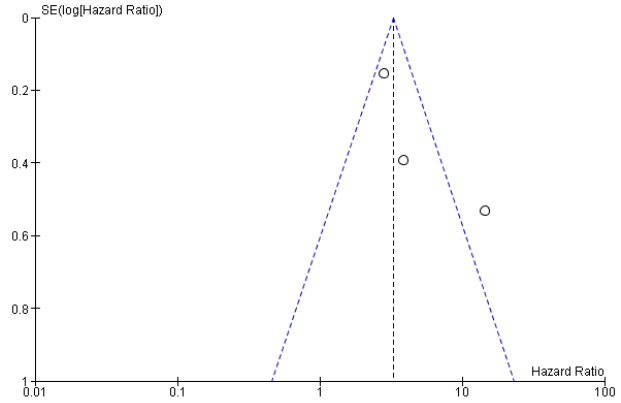
ECOG performance status 1+ (ref: 0–1)



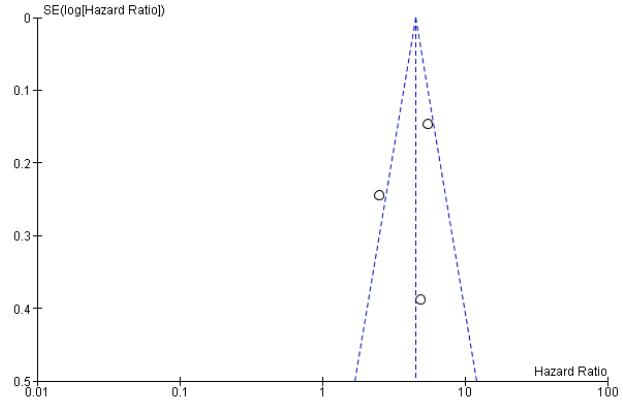
ECOG performance status 1–2 (ref: 0)



ECOG performance status 2 (ref 0)

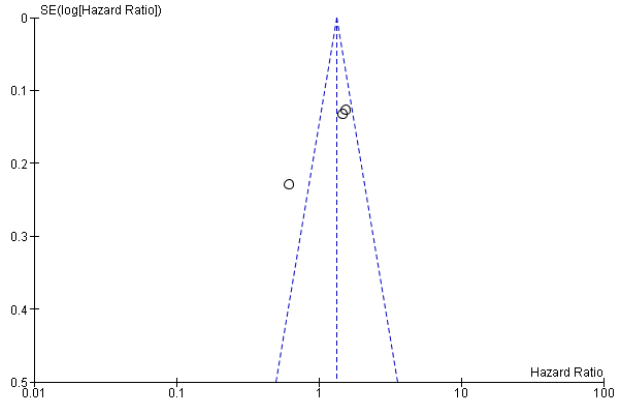


ECOG performance status 2+ (ref: 0)

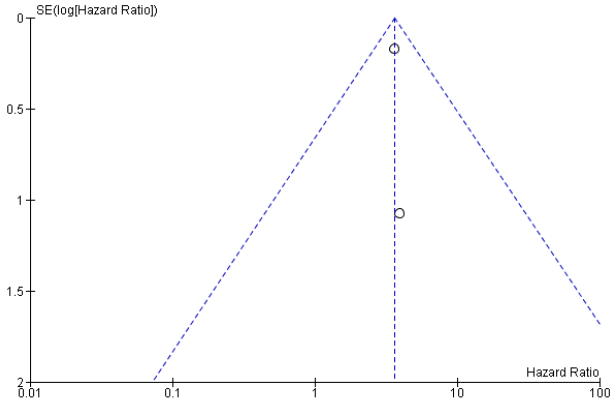


Continuation Figure S2

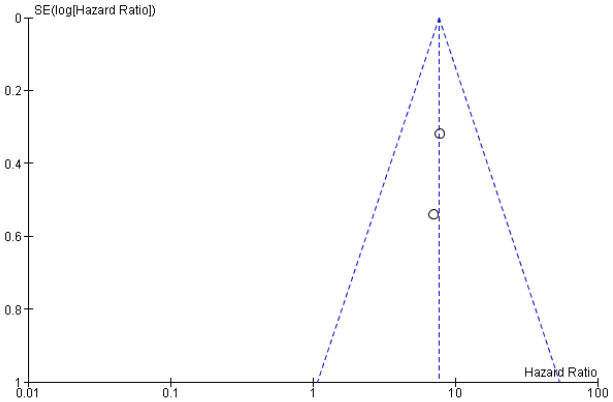
ECOG performance status 2 (ref: 0–1)



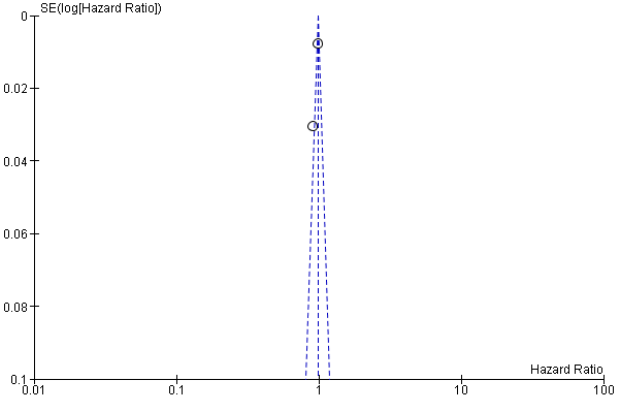
ECOG performance status 3–4 (ref: 0–1)



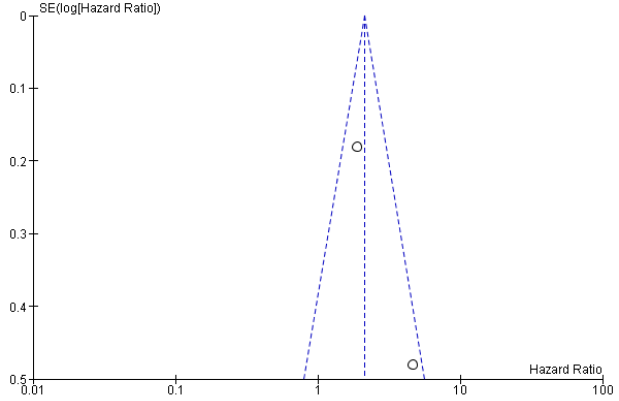
Surprise question ‘no’ (ref: ‘yes’)



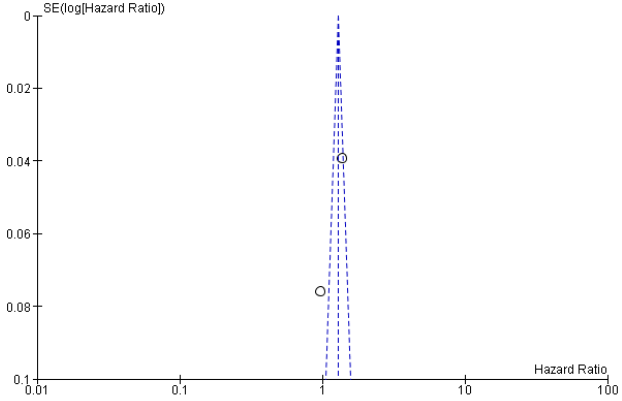
Body mass index (kg/m^2), per unit increase



(Sub)cutaneous metastasis

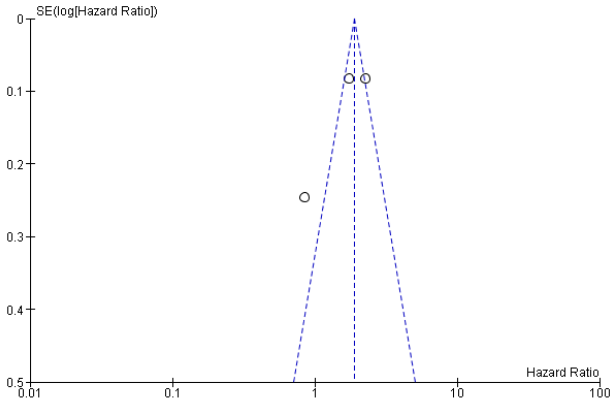


Charlson comorbidity score 1–2 (ref: 0)

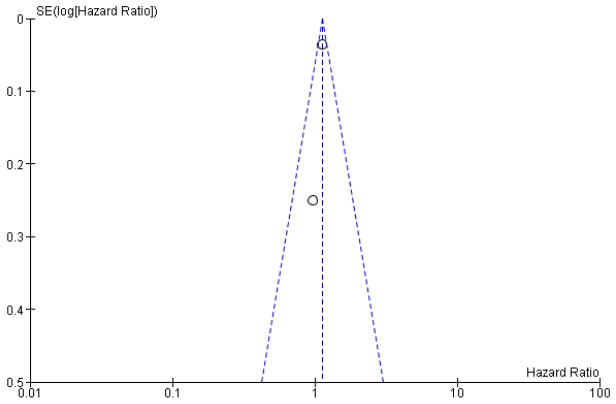


Continuation Figure S2

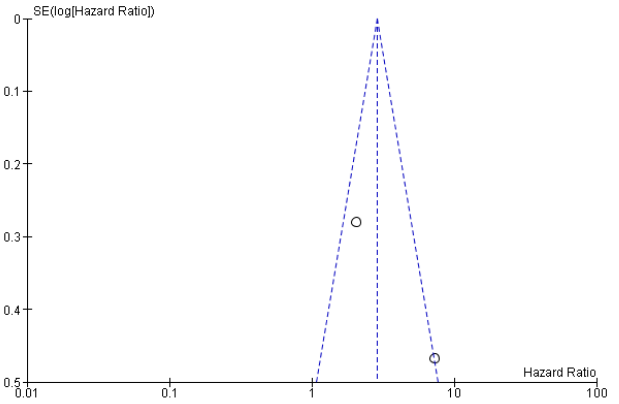
Charlson comorbidity index score 3+ (ref: 0)



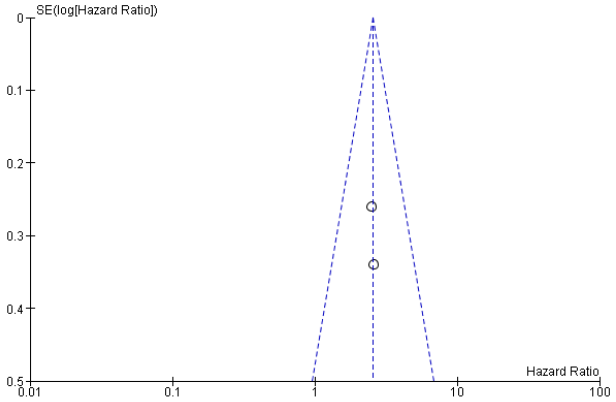
Mini-mental state examination <24 (ref: 24)



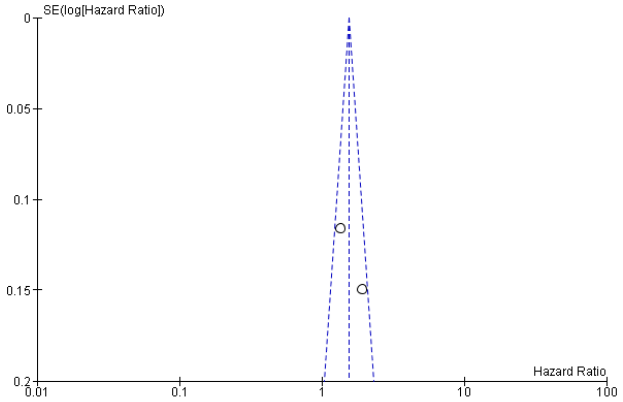
Albumin ≤35 g/L (ref >35 g/L)



Albumin ≤38 g/L (ref >38 g/L)



Hemoglobin <12 g/dL (ref: ≥ 12 g/dL)



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