BMJ Open

Barthel Index-based functional status as a prognostic factor in young and middle-aged adults with newly diagnosed gastric, colorectal and lung cancer: a multicentre retrospective cohort study

Toshitaka Morishima [ID] ,[1] Akira Sato,[1] Kayo Nakata,[1] Yoshifumi Matsumoto,[2] Nobuyuki Koeda,[3] Hiroko Shimada,[4] Tsutomu Maruhama,[5] Daisaku Matsuki,[6] Isao Miyashiro[1]

For numbered affiliations see end of article.

Correspondence to
Dr Toshitaka Morishima;
morishima.t@oici.jp

ABSTRACT

Objectives Functional status assessments of activities of daily living may improve prognostic precision during initial diagnostic evaluations in young and middle-aged adults with cancer. However, the association between pretreatment functional status and survival in these patients is poorly understood. This study aimed to evaluate the prognostic value of functional status in young and middle-aged patients with cancer.

Design Multicentre retrospective cohort study.

Setting We used a cancer registry from Osaka Prefecture, Japan. The data were linked to administrative claims data from 35 hospitals in the same prefecture.

Participants Patients aged 18–69 years who received new diagnoses of gastric, colorectal or lung cancer between 2010 and 2014.

Main outcome measure Cox proportional hazards models of 5-year all-cause mortality were developed to examine the prognostic impact of pretreatment functional status, which was categorised into three levels of functional disability (none, moderate and severe) based on Barthel Index scores. The models controlled for age, sex, comorbidities, cancer stage and tumour histology.

Results We analysed 12 134 patients. Higher mortality risks were significantly associated with moderate functional disability (adjusted HR 1.44 (95% CI 1.18 to 1.75), 1.35 (95% CI 1.08 to 1.68) and 1.74 (95% CI 1.50 to 2.03) in patients with gastric, colorectal and lung cancer, respectively) and severe functional disability (adjusted HR 3.56 (95% CI 2.81 to 4.51), 2.37 (95% CI 1.89 to 2.95) and 2.34 (95% CI 2.00 to 2.75) in patients with gastric, colorectal and lung cancer, respectively).

Conclusion Accounting for functional status at cancer diagnosis may improve the prediction of survival time in young and middle-aged adults with cancer. Functional status has potential applications in survival predictions and risk adjustments when analysing outcomes in patients with cancer.

Strengths and limitations of this study

► The linkage of administrative claims and cancer registry data enabled the examination of the association between pretreatment functional status and overall survival in young and middle-aged adults with newly diagnosed gastric, colorectal and lung cancer.

► This large multicentre study is the first to provide evidence of the long-term prognostic impact of pretreatment functional disability on overall survival in younger patients with specific cancer types from a single data set that accounted for potentially confounding clinical factors.

► Functionally disabled patients with cancer may be under-represented because the study population was restricted to subjects from designated cancer care hospitals, which tend to accommodate more functionally sound patients.

► We were unable to examine whether functional status and performance status, which are widely used in risk adjustments of survival outcomes, had similar predictive values for mortality.

INTRODUCTION

Cancer was the second leading cause of death in younger adults aged 20–69 years worldwide in 2016.[1] However, advances in cancer screening and therapeutic strategies have considerably extended patient survival times.[2]

Survival is a major outcome for cancer treatment, and its accurate prognostication is integral to clinical patient management and health policy design. The availability of precise prognoses can inform clinicians' decisions in therapeutic options and advanced care planning with patients and their caregivers. Furthermore, ascertaining

the variations in patient survival at the institutional and regional levels can aid policymakers in identifying opportunities to improve health services, although such analyses must account for differences in patient case mix. Patient factors that are consistently and strongly associated with cancer outcomes include age, sex, cancer type and disease progression.[3] In addition, performance status—which quantifies the general well-being of patients—is an established prognostic factor that is correlated with survival time in patients with cancer.[4] At present, performance status is commonly assessed using scoring instruments such as the Karnofsky and Eastern Cooperative Oncology Group scales.

A similar measure of patient well-being is functional status, which assesses a person's ability to maintain independence through their performance in activities of daily living (ADL). Among the various ADL evaluation tools, the Barthel Index is widely used for patients with chronic conditions, particularly in nursing and rehabilitation care settings. In the oncology setting, older patients with cancer frequently undergo comprehensive geriatric assessments that include functional status as a component.[5] However, cancer can also affect the functional status of younger and middle-aged adults, with a non-negligible proportion showing reduced ADL scores at the time of cancer diagnosis (9% in 45–64 years vs 19% in ≥65 years).[6]

Although performance status and functional status both describe the overall fitness of patients, they involve different components and objectives. Because the former is largely dependent on the assessing clinician's general impressions of each patient's activity level and ability to work, it can lack sufficient detail to identify seemingly minor but clinically important functional impairment.[7] In contrast, the latter involves the use of standardised multi-item tools for clinicians to rate the activities that an individual must perform in order to live independently at home and within society.

While the prognostic value of functional status in older patients with cancer has been documented,[8 9] its use in younger adults is less understood.[10–16] The prognostic relevance of functional disability has been explored in samples with heterogeneous mixtures of cancer types,[10 11] small-sized and single-centre samples,[10–12] narrowly defined groups (eg, specific cancer stages and treatment modalities)[12–15] and short-term outcomes.[11 13] Understanding the relationship between functional status and overall survival time in specific populations can aid clinicians in formulating more accurate prognoses, and enable more robust risk adjustments using routinely collected data (such as administrative claims and electronic health records) to support policymaking. Functional status may also present a viable proxy of performance status in risk adjustment models when the latter is unavailable. This study examined if pretreatment functional status was a long-term prognostic factor in young and middle-aged adults with newly diagnosed gastric, colorectal and lung cancer.

METHODS

Data sources

In this retrospective observational study, eligible patients were identified from a record-linked database comprising cancer registry and administrative claims data. This database has been previously used in a variety of studies.[9 17–20] The study region was Osaka Prefecture, the most densely populated prefecture in western Japan with a population of 8.8 million people. Registry data were drawn from the population-based Osaka Cancer Registry, and included patient-level information on cancer type, tumour histology, cancer diagnosis date, cancer stage and vital status. The registry acquires information on vital status from local government offices at 3, 5 and 10 years after diagnosis. These registry data were linked in part to Diagnosis Procedure Combination (DPC) administrative claims data, which are produced by Japanese acute care hospitals and submitted to insurers for reimbursements. DPC files were collected from 36 hospitals designated as cancer care hospitals by the national or prefectural government. These hospitals, mostly located in urban areas, provide first-line treatment to approximately half of all patients with cancer in the study region. The DPC data included inpatient clinical summaries for each patient as well as health insurance claims for outpatient and inpatient care.

Study population

We first identified 13 095 patients aged 18–69 years who were newly diagnosed with gastric, colorectal or lung cancer (designated the index cancer) at any of the 36 hospitals between 1 January 2010 and 31 December 2014; and had been hospitalised for the treatment of the index cancer within 3 months before or after the month of diagnosis. Patients aged 70 years or older were not included because this is a commonly used cut-off age to designate older adults in geriatric oncology studies.[5]

The three target cancer types were selected due to their high prevalence in the study region, and identified using the topography codes of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (C16.x for gastric cancer, C18.x–C20.x for colorectal cancer and C33.x–C34.x for lung cancer). Patients were excluded if they had recorded diagnoses of carcinoma *in situ* (n=536), sarcoma (ICD-O-3 morphology codes: 8800–8936, 8990–8991, 9020, 9040–9044, 9120–9133, 9150, 9170 and 9180–9251; n=47), haematological tumour (ICD-O-3 morphology codes: 9590–9989; n=12), melanoma (ICD-O-3 morphology codes: 8720–8790; n=3) or blastoma (ICD-O-3 morphology codes: 8970–8974; n=1). We also excluded patients without records of vital status (n=136), ADL on admission (n=38) or cancer stage (n=188). The final study population comprised 12 134 patients from 35 hospitals (one of the target hospitals had no eligible patients).

Study outcome

The outcome of interest was overall survival with a maximum of 5 years of follow-up. Survival time was calculated from the diagnosis date of the index cancer to the date of death from any cause (ie, all-cause mortality) or end of follow-up, whichever occurred first. Information on all-cause mortality was obtained from the registry data.

Functional status assessment

Functional status was assessed using the Barthel Index as measured by nursing staff.[21] Japanese hospitals are required to assess and record ADL in patients using the Barthel Index on admission for inpatient care, and the corresponding scores are included in administrative claims data. For patients who had undergone two or more hospitalisations within 3 months before or after the month of diagnosis, we examined data from the first hospitalisation that involved the index cancer.

The Barthel Index measures performance in the following domains: feeding (score: 0, 5 or 10), grooming (0 or 5), bathing (0 or 5), dressing (0, 5 or 10), bowel control (0, 5 or 10), bladder control (0, 5 or 10), toilet use (0, 5 or 10), chair/bed transfers (0, 5, 10 or 15), ambulation (0, 5, 10 or 15) and stair climbing (0, 5 or 10).[21] Total scores range from 0 to 100, with higher scores indicating better functional status. Based on a previous review study, the original continuous score was collapsed into a categorical variable according to the level of functional disability: no disability (score: 100), moderate disability (60–95) and severe disability (0–55).[22]

Covariates

Patient and tumour characteristics that were available in the data and expected to be associated with survival time were incorporated into the statistical models as covariates. Patient characteristics included age at diagnosis (18–59, 60–64 and 65–69 years), sex and baseline comorbidities. Age and sex were obtained from the registry data, and comorbid diagnoses were obtained from the administrative claims data. Comorbidity burden is a well-established prognostic factor that is negatively correlated with functional status.[20 23] Baseline comorbidities were measured using the Quan adaptation of the Charlson Comorbidity Index (CCI) based on International Classification of Diseases, Tenth Edition codes.[24] The CCI included 11 comorbid conditions (congestive heart failure, chronic pulmonary disease, dementia, connective tissue disease, mild liver disease, moderate or severe liver disease, diabetes with chronic complications, renal disease, hemiplegia or paraplegia, haematological and solid cancer diagnosed before the index cancer, and HIV infection).[25] Metastatic cancer was not included as it may represent an extension of the index cancer. The total CCI score was computed by summing up the individual component scores (ranging from 1 to 4) that account for their mortality risks.[25] Patients were grouped into three categories according to their CCI scores: no comorbidity (score:

0), moderate comorbidities (1–2) and severe comorbidities (≥3).

Tumour characteristics included surveillance, epidemiology and end results summary stage at diagnosis, which was classified into localised, regional and distant.[26] For lung cancer, tumour characteristics also included histology (small cell carcinoma as indicated by ICD-O-3 morphology codes 8041–8045, and non-small cell carcinoma as indicated by all other ICD-O-3 morphology codes) as it is a known prognostic factor for this cancer.[27] In summary, four baseline characteristics (ie, age, sex, comorbidities and cancer stage) were adjusted in multivariable analyses for gastric and colorectal cancer, whereas five baseline characteristics (ie, age, sex, comorbidities, cancer stage and tumour histology) were adjusted for lung cancer.

Statistical analysis

For the main analyses, Cox proportional hazards models were constructed to examine the association between functional status and overall survival for each cancer type while adjusting for the baseline characteristics. Using these models, we estimated the adjusted HRs (aHRs) and 95% CIs for all-cause mortality. A preliminary analysis found that Spearman's rank correlation coefficient between functional status and comorbidity was 0.033 (p=0.034), 0.073 (p<0.001) and −0.016 (p=0.33) for gastric, colorectal and lung cancer, respectively. Interactions between the main effects were tested, and no clinically important interaction was identified. Next, adjusted survival curves according to the three functional status categories were generated for each cancer type.[28] The estimates were produced by calculating the average of the individual predicted survival curves throughout the follow-up period. Functional status-specific 5-year survival rates were also extracted from the adjusted survival curves.[28] To examine the association of functional status with overall survival according to cancer stage, we constructed additional Cox proportional hazards models for each cancer type stratified by stage while adjusting for the baseline characteristics (excluding cancer stage). In addition, we also performed subgroup analyses to examine the association of functional status with overall survival in younger patients aged 18–59 years using Cox proportional hazards models that adjusted for the baseline characteristics. The assumption of proportional hazards was confirmed through visual inspection of the log-log survival curve plots (data not shown).

Statistical significance was defined as p<0.05 (two sided). Analyses were performed using SAS software, V.9.4 (SAS Institute).

Patient and public involvement

There was neither patient nor public involvement in this study.

Table 1 Patient characteristics, tumour characteristics and functional status at cancer diagnosis according to cancer type

	Gastric cancer	Colorectal cancer	Lung cancer
Total	4193	4112	3829
Follow-up, median, years (IQR)	4.02 (2.41–5.00)	4.15 (3.48–5.00)	3.02 (1.05–4.35)
All-cause mortality	1338 (31.9)	1084 (26.4)	2163 (56.5)
Age (years)			
18–59	1234 (29.4)	1470 (35.7)	1049 (27.4)
60–64	1248 (29.8)	1151 (28.0)	1101 (28.8)
65–69	1711 (40.8)	1491 (36.3)	1679 (43.8)
Sex			
Male	2934 (70.0)	2347 (57.1)	2616 (68.3)
Comorbidities*			
None	3471 (82.8)	3419 (83.1)	2834 (74.0)
Moderate	647 (15.4)	641 (15.6)	897 (23.4)
Severe	75 (1.8)	52 (1.3)	98 (2.6)
Cancer stage			
Localised	2369 (56.5)	1913 (46.5)	1146 (29.9)
Regional	844 (20.1)	1303 (31.7)	1018 (26.6)
Distant	980 (23.4)	896 (21.8)	1665 (43.5)
Tumour histology			
Small cell carcinoma	–	–	446 (11.6)
Functional status†			
No disability	3877 (92.5)	3733 (90.8)	3397 (88.7)
Moderate disability	220 (5.2)	226 (5.5)	240 (6.3)
Severe disability	96 (2.3)	153 (3.7)	192 (5.0)

Values are expressed as number (column percentage) unless otherwise indicated. Percentages may not add up to 100% because of rounding.

*Comorbidities were measured using the Charlson Comorbidity Index, with 0 point indicating none, 1–2 points indicating moderate comorbidities and ≥3 points indicating severe comorbidities.

†Functional status was measured using the Barthel Index, with 100 points indicating no disability, 60–95 points indicating moderate disability and 0–55 points indicating severe disability.

RESULTS

The analysis was conducted using 4193 patients with gastric cancer, 4112 patients with colorectal cancer and 3829 patients with lung cancer. Table 1 summarises the baseline patient and tumour characteristics of the study population. The median follow-up periods were 4.02, 4.15 and 3.02 years for patients with gastric, colorectal and lung cancer, respectively. During follow-up, all-cause mortality occurred in 1338 (31.9%) patients with gastric cancer, 1084 (26.4%) patients with colorectal cancer and 2163 (56.5%) patients with lung cancer. For all three cancer types, large proportions of the study population were aged 65–69 years (40.2%) and male (65.0%); no comorbidities were reported in 80.1% of patients. Approximately half of all patients with gastric (56.5%) and colorectal (46.5%) cancer were diagnosed with localised cancer, whereas 43.5% of patients with lung cancer had distant cancer. Small cell carcinoma was identified in 11.6% of patients with lung cancer.

The distribution of functional status categories is also presented in table 1. The majority (92.5%) of patients with gastric cancer had no disability; 5.2% and 2.3% had moderate and severe disability, respectively. Similarly, the majority (90.8%) of patients with colorectal cancer had no disability; 5.5% and 3.7% had moderate and severe disability, respectively. A slightly smaller proportion of patients with lung cancer (88.7%) had no disability; 6.3% and 5.0% had moderate and severe disability, respectively.

Survival analysis

Table 2 shows the all-cause mortality rates according to the baseline characteristics and functional status categories. All-cause mortality occurred in 29.7%, 50.0% and 78.1% of patients with gastric cancer with no disability, moderate disability and severe disability, respectively; 24.4%, 38.1% and 57.5% of patients with colorectal cancer with no disability, moderate disability and severe disability, respectively; and 53.3%, 76.7% and 87.5% of patients with lung

Table 2 Adjusted HRs and CIs for all-cause mortality in patients with gastric cancer, colorectal cancer and lung cancer

	Gastric cancer (n=4193)			Colorectal cancer (n=4112)			Lung cancer (n=3829)		
	Mortality (%)	aHR (95% CI)	P value	Mortality (%)	aHR (95% CI)	P value	Mortality (%)	aHR (95% CI)	P value
Age (years)									
18–59	338 (27.4)	Reference		369 (25.1)	Reference		567 (54.1)	Reference	
60–64	408 (32.7)	1.19 (1.03 to 1.38)	0.018	307 (26.7)	1.05 (0.90 to 1.22)	0.54	611 (55.5)	1.18 (1.05 to 1.33)	0.004
65–69	592 (34.6)	1.30 (1.13 to 1.49)	<0.001	408 (27.4)	1.10 (0.95 to 1.27)	0.201	985 (58.7)	1.29 (1.16 to 1.43)	<0.001
Sex									
Female	410 (32.6)	Reference		419 (23.7)	Reference		522 (43.0)	Reference	
Male	928 (31.6)	1.11 (0.99 to 1.25)	0.085	665 (28.3)	1.16 (1.02 to 1.31)	0.019	1641 (62.7)	1.67 (1.51 to 1.84)	<0.001
Comorbidities*									
None	1069 (30.8)	Reference		837 (24.5)	Reference		1584 (55.9)	Reference	
Moderate	242 (37.4)	1.23 (1.07 to 1.42)	0.003	228 (35.6)	1.37 (1.18 to 1.59)	<0.001	525 (58.5)	1.16 (1.05 to 1.28)	0.005
Severe	27 (36.0)	1.32 (0.90 to 1.94)	0.151	19 (36.5)	2.13 (1.35 to 3.36)	0.001	54 (55.1)	1.14 (0.87 to 1.49)	0.36
Cancer stage									
Localised	148 (6.2)	Reference		123 (6.4)	Reference		158 (13.8)	Reference	
Regional	300 (35.5)	6.60 (5.42 to 8.04)	<0.001	263 (20.2)	3.33 (2.69 to 4.13)	<0.001	560 (55.0)	4.81 (4.03 to 5.75)	<0.001
Distant	890 (90.8)	40.91 (34.20 to 48.92)	<0.001	698 (77.9)	22.77 (18.76 to 27.65)	<0.001	1445 (86.8)	14.03 (11.85 to 16.60)	<0.001
Tumour histology									
Non-small cell carcinoma	–	–	–	–	–	–	1782 (52.7)	Reference	–
Small cell carcinoma	–	–	–	–	–	–	381 (85.4)	1.34 (1.19 to 1.50)	<0.001
Functional status†									
No disability	1153 (29.7)	Reference		910 (24.4)	Reference		1811 (53.3)	Reference	
Moderate disability	110 (50.0)	1.44 (1.18 to 1.75)	<0.001	86 (38.1)	1.35 (1.08 to 1.68)	0.009	184 (76.7)	1.74 (1.50 to 2.03)	<0.001
Severe disability	75 (78.1)	3.56 (2.81 to 4.51)	<0.001	88 (57.5)	2.37 (1.89 to 2.95)	<0.001	168 (87.5)	2.34 (2.00 to 2.75)	<0.001

Mortality is expressed as patient number (percentage of all patients at risk as indicated in table 1). aHRs were calculated from Cox proportional hazards models that adjusted for age, sex, comorbidities, cancer stage and functional status. Tumour histology was also adjusted for lung cancer, but not for gastric and colorectal cancer.
*Comorbidities were measured using the Charlson Comorbidity Index, with 0 point indicating none, 1–2 points indicating moderate comorbidities and ≥3 points indicating severe comorbidities.
†Functional status was measured using the Barthel Index, with 100 points indicating no disability, 60–95 points indicating moderate disability and 0–55 points indicating severe disability.
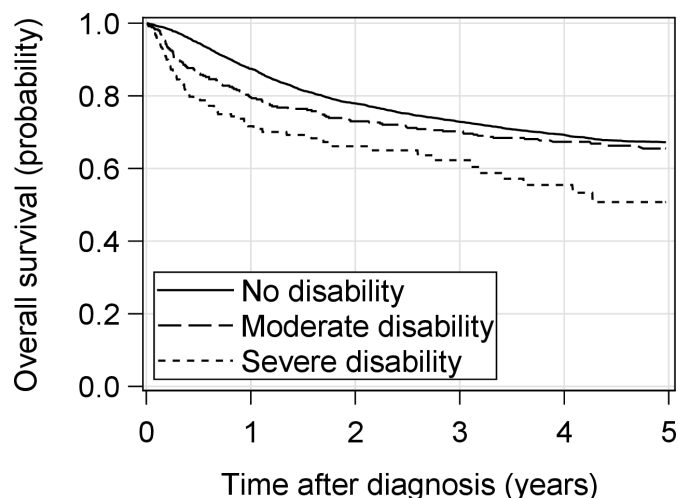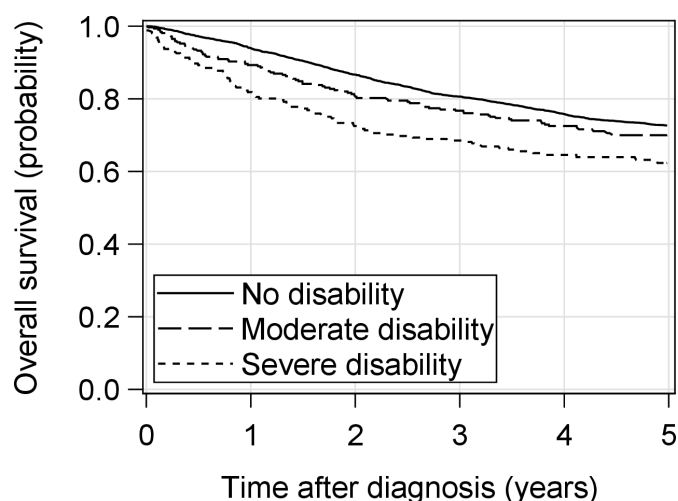aHR, adjusted HR.

Figure 1 Adjusted overall survival curves stratified by functional status in patients with gastric cancer. Age, sex, comorbidities and cancer stage were adjusted.

Figure 3 Adjusted overall survival curves stratified by functional status in patients with lung cancer. Age, sex, comorbidities, cancer stage and tumour histology were adjusted.

cancer with no disability, moderate disability and severe disability, respectively.

The results of the Cox proportional hazards models that described the association of functional status with overall survival are also presented in table 2. In patients with gastric cancer, functional disability was significantly associated with a higher mortality risk relative to no disability (moderate disability: aHR=1.44 (95% CI 1.18 to 1.75); severe disability: aHR=3.56 (95% CI 2.81 to 4.51)). In patients with colorectal cancer, functional disability was significantly associated with a higher mortality risk relative to no disability (moderate disability: aHR=1.35 (95% CI 1.08 to 1.68); severe disability: aHR=2.37 (95% CI 1.89 to 2.95)). In patients with lung cancer, functional disability was significantly associated with a higher mortality risk relative to no disability (moderate disability: aHR=1.74 (95% CI 1.50 to 2.03); severe disability: aHR=2.34 (95% CI 2.00 to 2.75)).

Figures 1–3 present the adjusted overall survival curves stratified by functional status for patients with gastric, colorectal and lung cancer, respectively. The adjusted 5-year survival rates of patients with no disability, moderate disability and severe disability were 67.2%, 65.5% and 50.8% for gastric cancer; 72.6%, 70.0% and 62.3% for colorectal cancer; and 42.3%, 33.0% and 31.3% for lung cancer, respectively.

The results of the Cox proportional hazards models stratified by cancer stage are provided in table 3. Among patients with localised cancers, moderate disability was significantly associated with a higher mortality risk for gastric cancer, and severe disability was significantly associated with a higher mortality risk for all three cancer types. Among patients with regional cancers, moderate disability was not associated with a higher mortality risk; however, severe disability was significantly associated with a higher mortality risk for colorectal and lung cancer. Among patients with distant cancers, moderate disability was significantly associated with a higher mortality risk for gastric and lung cancer, and severe disability was significantly associated with a higher mortality risk for all three cancer types. Each of the baseline characteristics yielded aHRs similar to those from the primary models without stratification of cancer stage (data not shown).

In the subgroup analyses of patients aged 18–59 years, we analysed 1234 patients with gastric cancer, 1470 patients with colorectal cancer and 1049 patients with lung cancer. The baseline characteristics of these patients are summarised in online supplemental table 1, and the results of the Cox proportional hazards models are provided in online supplemental table 2. Restricting the study population to younger patients did not markedly affect the results of the survival analyses, which remained similar to those of the main analyses. Functional disability was significantly associated with a higher mortality risk,

Figure 2 Adjusted overall survival curves stratified by functional status in patients with colorectal cancer. Age, sex, comorbidities and cancer stage were adjusted.
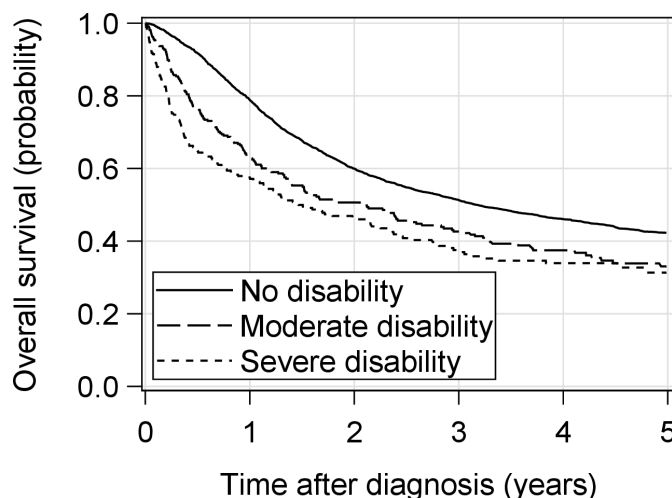
Table 3 Adjusted HRs and CIs for all-cause mortality according to cancer stage in patients with gastric cancer, colorectal cancer and lung cancer

	Gastric cancer				Colorectal cancer				Lung cancer			
	n	Mortality (%)	aHR (95% CI)	P value	n	Mortality (%)	aHR (95% CI)	P value	n	Mortality (%)	aHR (95% CI)	P value
Cancer stage, localised	2369	148 (6.2)			1913	123 (6.4)			1146	158 (13.8)		
Functional status*												
No disability	2264	132 (5.8)	Reference		1783	100 (5.6)	Reference		1082	140 (12.9)	Reference	
Moderate disability	84	11 (13.1)	2.17 (1.17 to 4.03)	0.014	79	9 (11.4)	1.62 (0.81 to 3.22)	0.172	46	11 (23.9)	1.72 (0.93 to 3.18)	0.086
Severe disability	21	5 (23.8)	2.98 (1.21 to 7.31)	0.017	51	14 (27.5)	4.72 (2.66 to 8.38)	<0.001	18	7 (38.9)	4.43 (2.06 to 9.53)	<0.001
Cancer stage, regional	844	300 (35.5)			1303	263 (20.2)			1018	560 (55.0)		
Functional status*												
No disability	784	272 (34.7)	Reference		1191	225 (18.9)	Reference		947	511 (54.0)	Reference	
Moderate disability	49	22 (44.9)	1.43 (0.92 to 2.21)	0.108	72	19 (26.4)	1.45 (0.90 to 2.32)	0.125	39	24 (61.5)	1.18 (0.78 to 1.77)	0.44
Severe disability	11	6 (54.5)	1.84 (0.82 to 4.14)	0.142	40	19 (47.5)	3.38 (2.11 to 5.41)	<0.001	32	25 (78.1)	2.54 (1.70 to 3.80)	<0.001
Cancer stage, distant	980	890 (90.8)			896	698 (77.9)			1665	1445 (86.8)		
Functional status*												
No disability	829	749 (90.3)	Reference		759	585 (77.1)	Reference		1368	1160 (84.8)	Reference	
Moderate disability	87	77 (88.5)	1.40 (1.11 to 1.77)	0.005	75	58 (77.3)	1.24 (0.95 to 1.63)	0.115	155	149 (96.1)	1.85 (1.56 to 2.19)	<0.001
Severe disability	64	64 (100)	3.70 (2.85 to 4.80)	<0.001	62	55 (88.7)	1.93 (1.46 to 2.56)	<0.001	142	136 (95.8)	2.26 (1.89 to 2.70)	<0.001

Mortality is expressed as patient number (percentage of all patients at risk as indicated in the leftmost column). aHRs were calculated from Cox proportional hazards models that adjusted for age, sex, comorbidities, cancer stage and functional status. Tumour histology was also adjusted for lung cancer, but not for gastric and colorectal cancer.

*Functional status was measured using the Barthel Index, with 100 points indicating no disability, 60–95 points indicating moderate disability and 0–55 points indicating severe disability.

aHR, adjusted HR.

with the exception of moderate disability in patients with gastric cancer.

DISCUSSION

Using a record-linked database of administrative claims and cancer registry data, this study examined the association between pretreatment functional status and overall survival in young and middle-aged adults with newly diagnosed gastric, colorectal and lung cancer. This large multicentre study is, to our knowledge, the first to provide evidence of the long-term prognostic impact of pretreatment functional disability on overall survival in younger patients with specific cancer types from a single data set that accounted for potentially confounding clinical factors. The main finding was that functional disability prior to initial cancer treatment was consistently and significantly associated with a higher risk of all-cause mortality. Although the importance of functional status as a prognostic factor has been well established in older cancer populations,[8 9] our results provide new evidence from younger patients with cancer. Overall, our results are concordant with those of previous reports that involved heterogeneous samples, smaller samples and shorter follow-up periods.[10–16]

The following three mechanisms have been proposed to explain the relationship between functional disability and premature mortality in patients with cancer: (1) compromised cancer treatment plans, (2) poorer cancer treatment outcomes, and (3) poorer health conditions prior to cancer occurrence. In the first mechanism, functional disability is thought to shift the treatment course away from more aggressive options.[29] This concept is supported by the significant associations between severe functional disability and increased mortality irrespective of cancer stage in our analyses. In particular, patients with severe functional disability may be limited to less aggressive treatments. In the second mechanism, functionally disabled patients may be more likely to experience treatment-related adverse events such as increased chemotoxicity,[30] thereby resulting in poorer outcomes. This explanation is supported by the greater impact of functional disability on survival in advanced-stage tumours (relative to early-stage tumours) regardless of cancer type or level of functional disability in our cancer stage-stratified analyses. These findings also agree with those of a prior study on lung cancer that observed larger differences in mortality risk among different levels of performance status in non-surgical patients than in surgical patients.[31] In the third mechanism, functionally disabled patients may die as a result of other conditions apart from the index cancer.[32] As functional disability can be the result of pre-existing diseases or conditions, it may not be an independent cause of mortality, but instead reflect the patients' underlying health conditions. In addition to these three mechanisms, another possible mechanism may be that functional disability results in reduced physical activity, which contributes to chronic inflammation that elevates the risk of mortality.[14]

Implications

The present study demonstrated that Barthel Index scores acquired from administrative claims data have potential applications in risk adjustment models for survival in younger patients with cancer, which has been previously shown in older patients.[8 9] In Japan's acute care hospitals, Barthel Index scores are required to be calculated for each patient on admission. The availability of functional status in routinely collected data varies among and within countries, but Barthel Index scores are regularly recorded in several types of facilities in some countries.[33 34] As information on functional status has potential value in clinical practice and research, hospitals in other countries may find it beneficial to include such measures in routine data collection for administrative or auditing purposes.

Furthermore, the Barthel Index may have applications in rehabilitation services and inpatient nursing care in some specific hospitals, units and wards due to its widespread use as an ADL assessment tool. Knowledge of probable outcomes based on comprehensive, individualised and evidence-based consideration of patient and tumour characteristics (including functional status) can inform the clinical decision-making process in cancer treatment strategies.

Our finding that patients with cancer with pre-existing functional disability at the time of diagnosis had significantly poorer survival indicates a need for interventions to improve prognoses, such as the early initiation of rehabilitation services that focus on improving functional status. These results provide useful insight for healthcare professionals to plan and deliver such services.[35]

Future work

Future studies should examine if functional status and performance status have similar predictive values for mortality in younger patients with cancer. While performance status measures are widely used for risk adjustments of survival outcomes, these are not available in Japan's administrative claims data. Moreover, these measures are also not included in the cancer registry data of Japan and numerous other countries. Further research should also explore the specific types of physical activities that require assistance. Simply summing the scores of various ADL domains may not provide an accurate representation of the full extent or characteristics of functional disability.

Limitations

This study has several limitations. First, functionally disabled patients with cancer may be under-represented in our study because the study population was limited to subjects from designated cancer care hospitals, which tend to accommodate more functionally sound patients. As a consequence, further analyses that evaluate patients with cancer in other settings are needed to confirm or

refute our findings. Second, we did not have information on the causes of death. By using overall survival instead of cancer-specific survival, our analysis describes the gross effects of functional disability. Access to information on cause-specific mortality would shed more light on the detailed mechanisms by which functional disability exerts its effects.

CONCLUSIONS

This study provides novel findings on functional status as a prognostic factor for young and middle-aged adult patients with cancer. Our results suggest that incorporating pretreatment functional status into prognostic tools can enhance the prediction of outcomes in patients with gastric, colorectal and lung cancer. In addition, the inclusion of functional status can improve risk adjustment models for survival rates in patients with newly diagnosed cancer when comparing outcomes among institutions or regions.

Author affiliations
[1]Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan
[2]Osaka Medical and Pharmaceutical University Hospital, Takatsuki, Japan
[3]Yao Municipal Hospital, Yao, Japan
[4]National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan
[5]Department of Health Information Management, Higashisumiyoshi Morimoto Hospital, Osaka, Japan
[6]Saiseikai Suita Hospital, Suita, Japan

peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iD
Toshitaka Morishima http://orcid.org/0000-0002-0747-3287

REFERENCES

1 GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017;390:1151–210.

2 Allemani C, Matsuda T, Di Carlo V, *et al*. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;391:1023–75.

3 Young J, Badgery-Parker T, Dobbins T, *et al*. Comparison of ECOG/WHO performance status and ASA score as a measure of functional status. *J Pain Symptom Manage* 2015;49:258–64.

4 Guyatt GH, Deyo RA, Charlson M, *et al*. Responsiveness and validity in health status measurement: a clarification. *J Clin Epidemiol* 1989;42:403–8.

5 Wildiers H, Heeren P, Puts M, *et al*. International Society of geriatric oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595–603.

6 Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci* 2003;58:M82–91.

7 Takahashi M, Takahashi M, Komine K, *et al*. The G8 screening tool enhances prognostic value to ECoG performance status in elderly cancer patients: a retrospective, single institutional study. *PLoS One* 2017;12:e0179694.

8 Couderc A-L, Boulahssass R, Nouguerède E, *et al*. Functional status in a geriatric oncology setting: a review. *J Geriatr Oncol* 2019;10:884–94.

9 Morishima T, Sato A, Nakata K, *et al*. Geriatric assessment domains to predict overall survival in older cancer patients: an analysis of functional status, comorbidities, and nutritional status as prognostic factors. *Cancer Med* 2020;9:5839–50.

10 Wedding U, Röhrig B, Klippstein A, *et al*. Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. *J Cancer Res Clin Oncol* 2007;133:945–50.

11 Stommel M, Given BA, Given CW. Depression and functional status as predictors of death among cancer patients. *Cancer* 2002;94:2719–27.

12 Comella P, Casaretti R, Manzo R, *et al*. Baseline physical functioning status of metastatic colorectal cancer patients predicts the overall survival but not the activity of a front-line oxaliplatin-fluoropyrimidine doublet. *Acta Oncol* 2010;49:50–6.

13 Guldberg TL, Christensen S, Zachariae R, *et al*. Prognostic factors in early breast cancer associated with body mass index, physical functioning, physical activity, and comorbidity: data from a nationwide Danish cohort. *Breast Cancer Res Treat* 2017;162:159–67.

14 Marinac C, Patterson RE, Villasenor A, *et al*. Mechanisms of association between physical functioning and breast cancer mortality: evidence from the women's healthy eating and living study. *J Cancer Surviv* 2014;8:402–9.

15 Braithwaite D, Satariano WA, Sternfeld B, *et al*. Long-Term prognostic role of functional limitations among women with breast cancer. *J Natl Cancer Inst* 2010;102:1468–77.

16 Boakye D, Jansen L, Schneider M, *et al*. Personalizing the prediction of colorectal cancer prognosis by incorporating comorbidities and functional status into prognostic nomograms. *Cancers* 2019;11:1435.

17 Kawamura H, Morishima T, Sato A, *et al*. Effect of adjuvant chemotherapy on survival benefit in stage III colon cancer patients stratified by age: a Japanese real-world cohort study. *BMC Cancer* 2020;20:19.

18 Fuji S, Kida S, Morishima T, *et al*. Clinical outcomes of patients with adult T cell leukemia-lymphoma in a nonendemic metropolitan area: a retrospective analysis of the population-based Osaka cancer registry. *Biol Blood Marrow Transplant* 2020;26:1433–8.

19 Shigemi D, Morishima T, Shibata A, *et al*. Comparison of overall mortality between hysterectomy and concurrent chemoradiotherapy for the primary treatment of localized or regionally extended cervical cancer. *Annals of Clinical Epidemiology* 2020;2:75–83.

20 Morishima T, Matsumoto Y, Koeda N, *et al*. Impact of comorbidities on survival in gastric, colorectal, and lung cancer patients. *J Epidemiol* 2019;29:110–5.

21 Mahoney FI, Barthel DW. Functional evaluation: the BARTHEL index. *Md State Med J* 1965;14:61–5.

22 Balu S. Differences in psychometric properties, cut-off scores, and outcomes between the Barthel index and modified Rankin scale in pharmacotherapy-based stroke trials: systematic literature review. *Curr Med Res Opin* 2009;25:1329–41.

23 Extermann M, Overcash J, Lyman GH, *et al*. Comorbidity and functional status are independent in older cancer patients. *J Clin Oncol* 1998;16:1582–7.

24 Quan H, Sundararajan V, Halfon P, *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.

25 Quan H, Li B, Couris CM, *et al*. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge Abstracts using data from 6 countries. *Am J Epidemiol* 2011;173:676–82.

26 Young JL, Roffers SD, Ries LAG. *SEER summary staging manual - 2000: Codes and coding instructions*. Bethesda, MD: National Cancer Institute, 2020. https://seer.cancer.gov/tools/ssm/ssm2000

27 Asamura H, Goya T, Koshiishi Y, *et al*. A Japanese lung cancer registry study: prognosis of 13,010 resected lung cancers. *J Thorac Oncol* 2008;3:46–52.

28 Zhang X, Loberiza FR, Klein JP, *et al*. A SAS macro for estimation of direct adjusted survival curves based on a stratified COX regression model. *Comput Methods Programs Biomed* 2007;88:95–101.

29 Jacobs BL, Lopa SH, Yabes JG, *et al*. Association of functional status and treatment choice among older men with prostate cancer in the Medicare advantage population. *Cancer* 2016;122:3199–206.

30 Sweeney CJ, Zhu J, Sandler AB, *et al*. Outcome of patients with a performance status of 2 in eastern cooperative Oncology Group study E1594: a phase II trial in patients with metastatic nonsmall cell lung carcinoma. *Cancer* 2001;92:2639–47.

31 Kawaguchi T, Takada M, Kubo A, *et al*. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. *J Thorac Oncol* 2010;5:620–30.

32 Balducci L, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000;5:224–37.

33 Witham MD, Fulton RL, Wilson L, *et al*. Validation of an individualised quality of life measure in older day hospital patients. *Health Qual Life Outcomes* 2008;6:27.

34 Kannegaard PN, Vinding KL, Hare-Bruun H. National database of geriatrics. *Clin Epidemiol* 2016;8:731–5.

35 Neo J, Fettes L, Gao W, *et al*. Disability in activities of daily living among adults with cancer: a systematic review and meta-analysis. *Cancer Treat Rev* 2017;61:94–106.