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BRIEF REPORT

The McGill Brisbane Symptom Score in relation to survival in pancreatic adenocarcinoma: a validation study

Suhail A. R. Doi[1,2] · Luis Furuya-Kanamori[1] · Jessica M. Engel[3] · Mohammad H. Jamal[4] · Rachel V. Stankowski[5] · Jeffrey Barkun[6] · Adedayo A. Onitilo[3]

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Abstract
Purpose The McGill Brisbane Symptom Score (MBSS) is a clinical score for pancreatic cancer patients upon initial presentation that takes into account four variables (weight loss, abdominal pain, jaundice, and history of smoking) to stratify them into two MBSS intensity categories. Several studies have suggested that these categories are strongly associated with eventual survival in patients with resectable (rPCa) and unresectable (uPCa) pancreatic cancer. This study aimed to validate the MBSS in a cohort of patients with pancreatic cancer from a single institution.
Methods Survival time by resection status and MBSS intensity category were analyzed among 633 patients from our institution between 2001 and 2010. Hazard ratios for death using Cox proportional hazards models, with age as the timescale, adjustment for sex and year of diagnosis, and stratified by adjuvant chemotherapy status were estimated.
Results Median survival time was the longest in patients with low-intensity MBSS and rPCa (817 days), whereas the shortest survival time was found among patients with uPCa regardless of MBSS status (144–147 days). After consideration of age and chemotherapy status, high-intensity MBSS was associated with poorer survival for both rPCa (HR 1.64; 95 % CI 1.07–2.52) and uPCa (HR 1.35; 95 % CI 1.06–1.72).
Conclusions Preoperative MBSS intensity is a useful prognostic indicator of survival in resectable as well as unresectable pancreatic cancer.

Keywords Pancreatic neoplasms · Adenocarcinoma · Resectable · Unresectable · Non-resectable · McGill Brisbane Symptom Score · Validation

Introduction

Despite the significant progress in treating gastrointestinal cancers, pancreatic adenocarcinoma remains a particularly lethal disease; the American Cancer Society estimated that in the United States in 2013, 45,220 new cases of pancreatic cancer were diagnosed and 38,460 people died of the disease [1]. Pancreatic cancer can be classified into resectable (rPCa) and unresectable/metastatic (uPCa), of which, uPCa patients have the worse prognosis. Approximately 15–20 % of patients have rPCa [2], and the median survival of this selected "favorable" group of patients still remains poor [2–9]. In our experience with patients that underwent pancreaticoduodenectomy, the median survival time was 23 months with a 5 year survival of only 29 % [10]. This worrying clinical reality persists in spite of

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✉ Adedayo A. Onitilo
onitilo.adedayo@marshfieldclinic.org

1 Research School of Population Health, Australian National University, Canberra, ACT 2601, Australia

2 College of Medicine, Qatar University, Doha, Qatar

3 Department of Hematology/Oncology, Marshfield Clinic Weston Center, 3501 Cranberry Boulevard, Weston, WI 54476, USA

4 Department of Surgery, Kuwait University and Mubarak Alkabeer University Hospital, Kuwait City, Kuwait

5 Office of Scientific Writing and Publication, Marshfield Clinic Weston Center, Weston, WI 54476, USA

6 The McGill University Health Centre (Surgery), Royal Victoria Hospital, Montreal, QC H3A-1A1, Canada

numerous attempts at adjuvant, and more recently neoadjuvant therapy [11]. One reason for the persistence of poor outcomes may be the significant heterogeneity of pancreatic cancer inherent at the genetic level [12]. However, heterogeneity can also be seen at the time of clinical decision making in the evaluation of patients who may undergo pancreaticoduodenectomy [13].

To our knowledge, beyond commonly used imaging tests and CA19.9, there is no published preoperative scheme that can predict survival and allow for a stratification of possible treatment strategies. The McGill Brisbane Symptom Score (MBSS) is a fully preoperative clinical score that takes into account four variables (weight loss greater than 10 %, abdominal pain, jaundice, and history of smoking) and stratifies the patients into low- and high-intensity categories. The MBSS has been shown to be an excellent predictor of survival in patients with both rPCa [10] and uPCa [14]. Although the association of this score with survival in uPCa patients was even found to be greater than that of conventional imaging studies, it has not yet been validated in an institution, separate from where it was developed. Therefore, the aim of this study was to validate the MBSS to predict survival in a modern cohort of patients with uPCa and rPCa in a different healthcare setting.

Materials and methods

Setting and data collection

The Marshfield Clinic system is a large multispecialty private group medical practice in Wisconsin, USA, servicing the predominantly rural northern, central, and western portions of the state at over 50 locations with over 80 different medical specialties. A retrospective cohort study of patients with pancreatic adenocarcinoma was conducted between 1 January 2001 and 30 May 2010. A multicenter cancer registry accredited by the American College of Surgeons Commission on Cancer was utilized, and these cases were followed for all-cause mortality. Data were entered into the cancer registry manually and verified for accuracy. Additional data were collected by manual and electronic extraction from the institution's comprehensive electronic medical record, which includes extensive information pertaining to clinical encounters, diagnoses, medication use, procedures, laboratory results, and pathology reports. Preoperative patient symptoms were captured during their first encounter with the oncologist; these included jaundice (clinical, confirmed by bilirubin >50 microM/l), weight loss > 10 %, persistent abdominal or back pain (as reported by the patient), onset of diabetes mellitus within a year of diagnosis, and a history of cigarette smoking for more than 5 years within 5 years of the current diagnosis of cancer. Note that determination of more than 10 % weight loss was mostly performed from medical records review, which means that intervals between weight records may vary somewhat. Weights are documented in the record by medical staff at each visit. Attempts were made to ensure that weight loss compared to baseline weight (patient's weight recorded during his/her first visit at the Marshfield Clinic system) was flagged at >10 % if data on baseline weights was available and indicated this degree of weight loss. All other subjects where baseline weight was unavailable were considered to be in the ≤10 % category so that we generated the most conservative results. MBSS was calculated for each patient depending on the symptoms they presented at baseline by adding the points of the four parameters (weight loss greater than 10 % [8 points], abdominal pain [5 points], jaundice [4 points], and history of smoking [4 points]) that are accounted in the score. The patients were categorized into low and high intensity if they scored 0–9 and 12–21 points, respectively. This study was approved by the Marshfield Clinic Institutional Review Board with waiver of informed consent.

Statistical analyses

Univariate analyses were conducted to describe the distribution of baseline variables. Median survival and estimated survival estimates at fixed time points were calculated using the Kaplan–Meier method. In patients surviving to the end of the study, the date of last contact was used to estimate survival and censored via the Kaplan–Meier method. Survival was calculated from the date of first imaging diagnosis.

A multivariable Cox regression model with age as the timescale [15] was used to evaluate the prognostic utility of the MBSS. Since this is a prognostic study, by adding other predictors (not confounders) into the multivariable regression model that are known to be associated with the outcome (survival) we were able to ascertain if MBSS intensity was a predictor independent of commonly considered prognostic variables. The latter are also predictors, but they are always considered in patient prognostication so the MBSS as a predictor needs to generate more information. The variables were therefore added to the model in order to ensure that prognostic information delivered by the MBSS was independent of these variables. We identified four of these variables, and the first was age, which was used as the timescale as it places similar subjects in the risk set together and allows a completely nonparametric age effect. Using age as the timescale, subjects are set up to enter the risk set at the age at diagnosis (delayed entry, since they do not enter the risk set at birth) and exit at their event/censoring age. This method was chosen over

adjustment for age, since the latter can still be associated with bias even when the MBSS is independent from age [15, 16]. Three additional variables were year of diagnosis (2001–2010), gender, and one related to treatment (adjuvant chemotherapy status) that are well known to impact on survival [17] and thus should not be the basis of prediction by the MBSS. The final analysis was also stratified by resectability of pancreatic cancer at presentation, as this is also routinely considered at diagnosis. Resectable were those that were deemed immediately suitable for surgical intervention (Whipple's procedure) and had this recorded as done in the patient record. All other patients were deemed to have had uPCa. Significance statements refer to p values of two-tailed tests that were <0.05. Stata version 13 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses and for graphical assessment of goodness of fit based on visual inspection of Arjas-like plots produced using stcoxgof as well as to test the link specifications using link test.

Results

Six hundred and thirty-three patients with pancreatic cancer (140 with rPCa and 493 with uPCa) were seen at Marshfield Clinic during the study period (1 January 2001–30 May 2010). Median age at diagnosis was 71 years (IQR 60–79 years). The majority (82.6 %) of the patients had abnormal levels of CA 19-9 (at baseline). Among the patients with uPCa, 366 (74.4 %) and 302 (61.3 %) presented local invasion and metastatic disease, respectively.

Table 1 Patient characteristics at baseline

	rPCa N (%)	uPCa N (%)
Median age, years (IQR)	69 (23–93)	71 (36–100)
Sex		
Male	75 (54)	252 (51)
Female	65 (46)	241 (49)
CA 19-9		
$\leq$ 37 U/ml	30 (34)	39 (13)
$>$ 37 U/ml	57 (66)	271 (87)
Local invasion		
Yes	49 (35)	366 (74)
No	91 (65)	126 (26)
Metastatic disease		
Yes	37 (26)	302 (61)
No	103 (74)	191 (39)
Received adjuvant chemotherapy		
Yes	119 (85)	204 (41)
No	21 (15)	289 (59)

Adjuvant chemotherapy was given to 310 individuals (49 %), including almost all of the patients with rPCa (119/140; Table 1).

The majority of the patients, 63.4 % ($n = 390$), were classified as presenting with high-intensity MBSS (Table 2; Supplementary data). Patients in the rPCa group were fairly equally distributed between MBSS low (52 %)- and high (48 %)-intensity categories, whereas the majority of patients with uPCa (68 %) were in the high-intensity category. Overall median survival was 190 days; the highest survival was observed in rPCa with low-intensity MBSS patients followed by rPCa with high-intensity MBSS patients. Patients with uPCa and high-intensity MBSS had the worst prognosis (Table 2; Fig. 1), but median survival was similar as this differential occurred much later. No agreement was found between the MBSS intensity category and elevated serum levels of CA 19-9 ($\kappa = 0.06$, p value $= 0.106$).

The adjusted multivariable Cox regression with resection status*MBSS intensity category as an interaction term and stratified by adjuvant chemotherapy status indicated that high-intensity MBSS is associated with lower survival rates in both rPCa (HR 1.64; 95 % CI 1.07–2.52) and uPCa (HR 1.35; 95 % CI 1.06–1.72) patients (Table 3).

Discussion

The MBSS is a simple yet important clinical tool for patient selection and prognostication [10, 14, 18]. It makes use of symptom intensity, which has also been demonstrated to have survival implications in other studies. In patients with uPCa without metastasis who received chemoradiation therapy, weight loss of less than 5 % was found to be associated with overall survival in multivariable analysis [19]. Another study found pain to be independent predictor of poor survival in a multivariable analysis [20]. Cigarette smoking has also been found to be a risk factor for pancreatic cancer diagnosis, [21] while jaundice seems to associate with a worse prognosis [22]. The MBSS combines these predictors into a tool that has now been validated in an independent patient population.

This study validates in a large new cohort the utility of the MBSS in the stratification of patients with pancreatic adenocarcinoma. The hazard ratio we present here for rPCa (1.64; 95 % CI 1.07–2.52) was comparable with that in our original cohort from another center of 2.11 (95 % CI 1.06–4.17) [10]. The hazard ratio for uPCa (1.35; 95 % CI 1.06–1.72) was also comparable to that we previously reported in our derivation cohort of 2.90 (95 % CI 1.80–4.52) [14]. The variation in survival indicates that there is heterogeneity within patients with pancreatic adenocarcinoma, and the MBSS score can therefore be utilized

Table 2 McGill Brisbane Symptom Score (MBSS) characteristics by resection status

	rPCa N (%)	uPCa N (%)
MBSS components[a]		
Weight loss > 10 %	65 (47)	330 (67)
Abdominal pain	76 (54)	258 (53)
Jaundice	70 (50)	360 (73)
History of smoking	63 (46)	135 (28)
MBSS categories		
Low intensity (0–9 points)	71 (52)	154 (32)
High intensity (12–21 points)	66 (48)	324 (68)
Median survival by MBSS category, days (IQR)		
Low intensity (0–9 points)	817 (336–)[b]	144 (46–394)
High intensity (12–21 points)	459 (230–1,022)	147 (56–299)

[a] MBSS components are not mutually exclusive; column totals do not sum to 100 %

[b] Less than 75 % cumulative mortality by end of follow-up

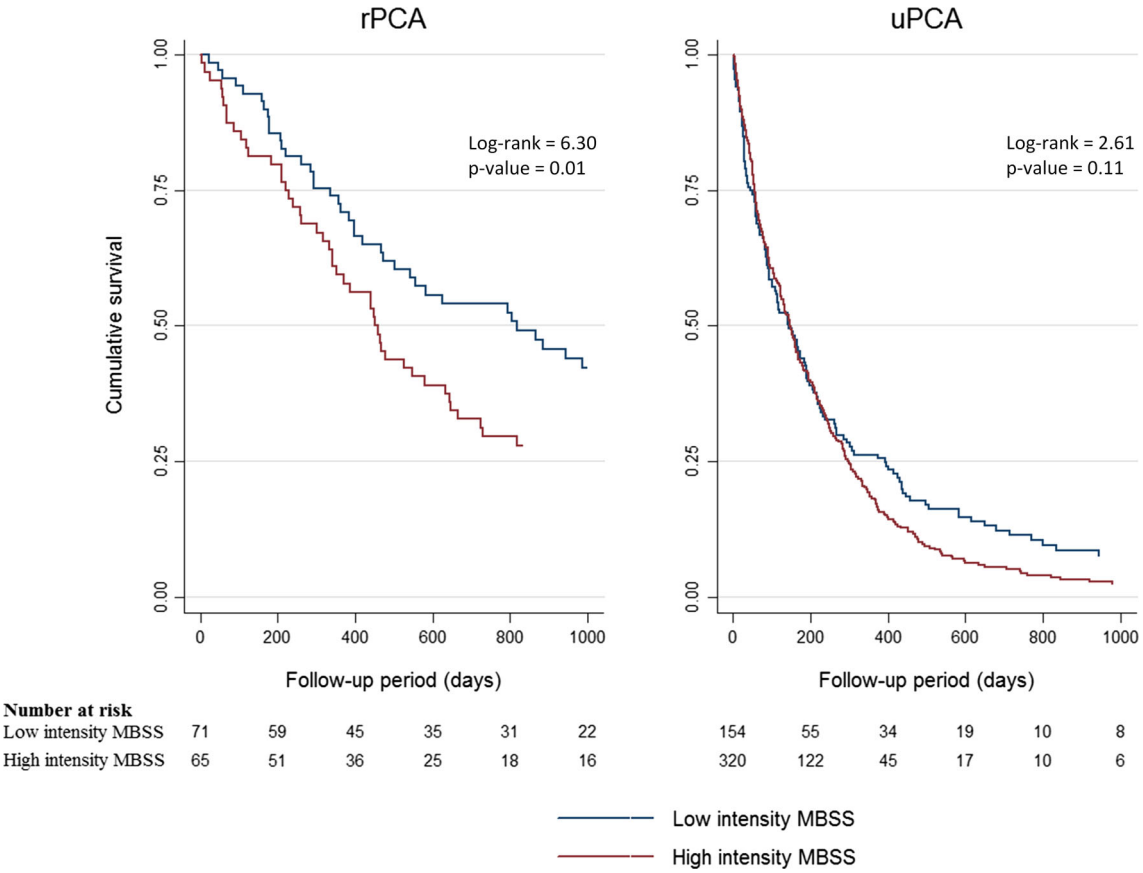

Fig. 1 Unadjusted Kaplan–Meier survival curves for rPCa (left panel) and uPCa (right panel) by MBSS category

in stratifying these patients and tailor their treatment accordingly.

Perhaps the greatest immediate utility of the MBSS does not relate to possible decision making but rather to meaningfully stratifying patients in an objective way similar to that already used subjectively by astute clinicians and surgeons. Preoperative MBSS stratification of patients is simple yet may allow investigators to detect a true possible therapeutic effect more effectively and with fewer patients, by controlling for severity of illness what has until now

Table 3 Multivariable Cox regression results

	Low-intensity MBSS HR (95 % CI)	High-intensity MBSS HR (95 % CI)	HR (95 % CI) for MBSS within strata of resectability
uPCa	1.00	1.35 (1.06–1.72)	1.35 (1.06–1.72)
		p value = 0.014	p value = 0.014
rPCa	0.17 (0.11–0.24)	0.27 (0.19–0.39)	1.64 (1.07–2.52)
	p value < 0.001	p value < 0.001	p value = 0.023

Measure of effect interaction on multiplicative scale: ratio of HRs = 1.22 (95 % CI 1.06–1.72), p value = 0.434

Regression model using age as the timescale, adjusted for sex and year of diagnosis, and stratified by adjuvant chemotherapy status

been an inherent confounding. This ability may prove especially useful to better evaluate the results of newer prospective treatment options in the neoadjuvant context, particularly in patients with rPCa, in whom stratification becomes important, especially because of the interaction between neoadjuvant chemotherapy and intensity of symptoms.

Curative treatment of pancreatic cancer involves surgery only in the absence of distant metastasis or local vascular invasion of major vessels (i.e., superior mesenteric artery) [23]; in addition, vein resection has been accepted as having a similar prognosis providing the resection margin is negative [24]. Neoadjuvant therapy is most often utilized in such patients (i.e., borderline resectable) to make them amenable to surgical resection [11, 25]; however, neoadjuvant therapy is also being more often considered in broader groups of patients because of the recent advent of more effective regimens [26] and given that recurrent disease often involves distant sites (e.g., liver or peritoneum). The MBSS may assist in stratifying patients enrolled in neoadjuvant trials, as data from our clinic and from the original cohort suggest that patients with low MBSS may proceed directly to surgery, whereas those with high MBSS may benefit from neoadjuvant therapy.

The majority of patients with pancreatic adenocarcinoma are, however, not amenable to surgical cure, and palliation of their symptoms is the major clinical goal. Endoscopic and surgical methods exist for palliation, with endoscopy having better short-term results (usually over 6 months) and surgery yielding superior results should the patient survive longer [27]. However, the potential complications associated with surgery make surgical palliation less widely implemented, partly because of the inability to predict those with longer survival in this cohort of patients. Here is where the MBSS becomes useful, as it can select out patients with a predicted longer survival (i.e., with low MBSS) who could benefit from a surgical palliation rather than endoscopic methods.

We acknowledge that the study is limited by a number of factors, probably the most important being that the MBSS was computed from patient self-reported information (i.e., abdominal pain and weight loss), which may have led to some degree of information bias; however, it is expected to be a non-differential bias toward the null effect. In addition, the study was conducted in a tertiary hospital; therefore, patients included in the analyses were highly selected and may represent more advanced cases compared to non-specialized centers, which could have decreased the ability of the MBSS to discriminate survival, particularly among patients with uPCa.

Modern advances in the treatment of pancreatic cancer include improvements in diagnosis, endoscopic procedures, chemotherapy combinations, and palliative support for patients. These advances, in combination with molecular oncology, have made patient selection for appropriate therapy even more important to target aggressive approaches to therapy when appropriate, while reserving the best supportive care for patients with high risk and poor prognosis. This validation study finds that MBSS intensity indeed stratifies both uPCa and rPCa by survival status and is thus a useful preoperative indicator of eventual prognosis.

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Compliance with ethical standards

Conflict of interest None declared.

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