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ORIGINAL RESEARCH

Diabetes, Obesity, and the Metabolic Syndrome as Prognostic Factors in Stages I to III Colorectal Cancer Patients

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Abstract

Background Attempts to introduce prognostic factors for survival outcomes in localized colorectal cancer patients receiving surgical treatment with or without adjuvant therapies, beyond the classic staging parameters, have been met with limited success. Obesity and diabetes mellitus are among the conditions that predispose to colorectal cancer but their value as prognostic markers once the disease is diagnosed is controversial.

Patients and Methods This study examines the prognostic value of the components of metabolic syndrome in a retrospective series of colorectal cancer patients with stages I to III disease followed in a single center.

Results Among the four components of the metabolic syndrome, only diabetes was independently associated with progression-free survival (PFS) while obesity, hypertension, and dyslipidemia were not. No associations of the metabolic syndrome (MS) or its components with overall survival (OS) were observed in multivariate analysis.

Conclusion These data pinpoint to diabetes mellitus (DM) as a possible prognostic factor for PFS in localized colorectal cancer and further cast doubt for the value of obesity as measured by body mass index (BMI) on local stage colorectal cancer prognosis.

Keywords Metabolic syndrome · Obesity · Body weight · Diabetes · Hypertension · Colon · Rectal · Overall survival · Progression-free survival

Introduction

Colorectal cancer is an important cause of morbidity and mortality representing one of the top cancers in incidence in both men and women. Significant progress has been achieved in elucidating the pathogenesis of this cancer and, indeed, colorectal cancer was the first malignancy where a stepwise sequence of molecular events describing the evolution from normal bowel epithelium to adenoma to carcinoma has been proposed [1]. The presence of some of these lesions such as K-ras mutations is currently used clinically as predictive factors to specific therapies efficacy. Others such as DPC4 (SMAD4) and P53 debilitating mutations have been difficult to target [2]. Regarding therapeutics, besides EGFR and VEGF monoclonal antibodies and inhibitors, no other treatments have resulted from the increased knowledge of molecular pathogenesis of the disease, a fact implying that this knowledge is far from complete. In addition, there is a lack of prognostic and predictive factors to guide therapeutic decisions in many clinical situations in colorectal cancer and, thus, there is a clinical need for discovery of such factors in order to improve therapy and outcomes.

Both obesity and diabetes mellitus (DM) have been associated with an increased risk for development of colorectal cancer [3, 4]. Both have also been proposed as factors that affect colorectal cancer prognosis. Nevertheless, the prognostic value of either obesity, DM, or other components of the metabolic syndrome (MS) whence a colorectal cancer has been diagnosed is less well established with different studies describing associations in subsets of patients that are difficult to reconcile with underlying relevant pathophysiology [5]. The aim of this paper is to further investigate if MS as a syndrome, obesity and DM (versus normal weight and non-diabetic patients) as well as other components of the MS such as hypertension (HTN) or dyslipidemia carry information for survival outcomes in patients with newly diagnosed

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localized colorectal cancer. We aimed to additionally clarify whether the combined effect of any of these components could provide stronger predictions than individual components. These anthropometric and comorbidity data of the presence of MS components are available or easily obtained for all patients and, if confirmed to be of prognostic significance each one alone or in association, will constitute an ancillary information to guide therapeutic decisions and help discussions with patients for outcomes as well as guide lifestyle modifications post cancer diagnosis.

Patients and Methods

Data on all patients that have been diagnosed and treated for a localized colorectal adenocarcinoma in our center over a 5-year period have been retrospectively reviewed. Data on patients' age, sex, clinical presentation, histologic characteristics and site of tumor, stage, the Carcinoembryonic Antigen (CEA) tumor marker at diagnosis, and pathologic response (if neo-adjuvant treatment) were recorded. All oncologic treatments after diagnosis of colorectal cancer were also recorded. Body weight categories were assigned according to patients' body mass index (BMI) at the time of diagnosis, calculated as the weight in kilograms divided by the square of the height in meters. Body weight categories were defined as follows: A BMI of less than 25 kg/m^2 was considered normal weight, overweight category was defined as a BMI of 25 to less than 30 kg/m^2, and obesity as a BMI of 30 kg/m^2 or greater. Information for the presence of diabetes mellitus (DM) has been extracted from charts together with treatments for the disease. Hypertension (HTN) was confirmed for the purpose of the current analysis as either a previous diagnosis in the patients' charts or treatment with an anti-hypertensive medication. Dyslipidemia was defined similarly as either a previous diagnosis or treatment with a cholesterol-lowering agent. Metabolic syndrome (MS) was defined as the presence of at least three of the four (overweight or obesity, DM, HTN, dyslipidemia) components.

Overall survival (OS) was calculated as the interval from the date of diagnosis to death. Progression-free survival (PFS) was defined as the interval from the date of diagnosis to disease progression or death, whichever happened first. PFS and OS of patients with the metabolic syndrome or its component diseases (overweight/obesity, DM, HTN and dyslipidemia) were compared with that of patients without the MS or its components respectively. Survival plots of patients in the different obesity and diabetes groups were constructed using the Kaplan-Meier method and were compared using the log-rank test. The x^2 test and Student's t test or ANOVA were used to evaluate differences in clinical and biologic characteristics in the groups. A Cox regression proportional hazard multivariate analysis was performed including factors found to be statistically significant in the univariate analysis in order to identify statistically significant factors associated with OS and PFS. All p values were considered to be significant at the level of $p < 0.05$.

The study protocol was approved by the Institutional Ethics Review Board of Sault Area Hospital.

Results

One hundred and forty-two patients were included in this analysis. The mean age was 68.9 (Table 1). A significant percentage of patients (70.4%) were 65 years old or older. About 20% of patients had stage I disease while the rest was almost equally distributed between stages II and III disease. Sixty-one patients (43%) had a right-sided cancer (from cecum to the transverse colon), 35 patients (24.6%) had a left-sided cancer (from the splenic flexure to sigmoid), and 46 patients (32.4%) had rectal adenocarcinomas. About half the patients in the series had received neo-adjuvant or adjuvant treatment (Table 1). Thirty-three patients (23.2%) had a diagnosis of DM and 109 (76.8%) were in the group without DM. There were no statistically significant differences between patients with DM and patients without DM in age, sex, clinical presentation (high risk presentation with changes in bowel habit, obstruction, or pain versus low risk presentation with bleeding or diagnosed by screening), stage, location of the tumor, grade of the tumor, CEA at diagnosis, or adjuvant treatments (Table 1). The prevalence of other metabolic syndrome elements in the series was 65.5% for a BMI in the overweight range or obesity, 61.3% for HTN, and 42.3% for hyperlipidemia (Table 2). The overall prevalence of the metabolic syndrome in the series was 37.3%. All three other MS components were significantly associated with the presence of DM.

When patients were categorized according to their BMI, 49 patients (34.5%) were in the normal weight group, 48 patients (33.8%) were overweight, and 45 patients (31.7%) were obese. More obese patients (44.4%) than patients in the two other categories (20.8 and 24.5%) were younger than 65 years old ($p = 0.028$) but no other significant differences were noted between the weight categories in sex, clinical presentation, stage, location of the tumor, grade of the tumor, CEA at diagnosis, or adjuvant treatments (Table 3). Higher BMI was significantly associated with dyslipidemia in addition to the association with DM, but not with HTN (Table 4).

Hypertensive patients in the series were more often (81.6%) older than 65 years old than normotensive patients (52.7%, $p = 0.0002$). There was also a smaller percentage of men in the HTN group (42.5%) than in the normotensive group (60%, $p = 0.007$) but no other associations of HTN with baseline tumor and therapy characteristics were found (data not shown). Regarding the group of patients with dyslipidemia versus those without dyslipidemia, a higher percentage

Table 1 Baseline characteristics of all patients in the series and comparison of the groups with and without diabetes (DM). Pre-operative CEA was available for 68 patients and grade was available in 133 patients

	Category	Total (%) ($n = 142$)	No DM (%) ($n = 109$)	DM (%) ($n = 33$)	x^2
Age	Mean	68.9	68.2	71	$t = 1.39$, $p = 0.16$
	< 65	42 (29.6%)	35 (32.1%)	7 (21.2%)	$p = 0.22$
	≥ 65	100 (70.4%)	74 (67.9%)	26 (78.8%)	
Sex	Male	70 (49.3%)	56 (51.4%)	14 (42.4%)	$p = 0.36$
	Female	72 (50.7%)	53 (48.6%)	19 (57.6%)	
Clinical presentation	Asymptomatic/bleeding	78 (54.9%)	58 (53.2%)	20 (60.6%)	$p = 0.53$
	Change transit/obstruction/pain	64 (45.1%)	51 (46.8%)	13 (39.4%)	
Clinical stage	I	29 (20.4%)	23 (21.1%)	6 (18.2%)	$p = 0.59$
	II	55 (38.7%)	44 (40.4%)	11 (33.3%)	
	III	58 (40.9%)	42 (38.5%)	16 (48.5%)	
Location	Right	61 (43.0%)	47 (43.1%)	14 (42.4%)	$p = 0.11$
	Left	35 (24.6%)	31 (28.4%)	4 (12.1%)	
	Rectum	46 (32.4%)	31 (28.4%)	15 (45.5%)	
Grade ($n = 133$)	Well differentiated	74 (55.6%)	53 (52.0%)	21 (61.7%)	$p = 0.27$
	Moderately differentiated	37 (27.8%)	30 (29.4%)	7 (21.2%)	
	Poorly differentiated	22 (16.5%)	19 (18.6%)	3 (9.1%)	
CEA ($n = 68$)	≤ 5	54 (79.4%)	38 (79.2%)	16 (80%)	$p = 0.9$
	> 5	14 (20.6%)	10 (20.8%)	4 (20%)	
(Neo)adjuvant therapy	Yes	72 (50.7%)	52 (47.7%)	20 (60.6%)	$p = 0.22$
	No	70 (49.3%)	57 (52.3%)	13 (39.4%)	

bold means statistically significant (< 0.05)

(85%) of patients in the dyslipidemia group than in the no dyslipidemia group (59.8%) were older than 65 years old ($p = 0.001$). No significant differences existed between the groups regarding sex, clinical presentation, grade and stage, location of the tumor, baseline CEA, or whether the patients had received adjuvant or neo-adjuvant chemotherapy.

Sixteen of the 142 patients had relapsed with a mean PFS of 24.9 months while 126 patients had not relapsed at a mean follow-up of 59.6 months. In univariate analysis, only DM was associated with PFS ($p = 0.018$) (Fig. 1a), while age equal or above 65 years old showed a trend towards association with PFS ($p = 0.07$). Other components of the MS [obesity (Fig. 1b), HTN, and dyslipidemia (not shown)] were not associated with PFS. Patients with the MS as a whole had also no statistically significant different PFS than patients without the syndrome ($p = 0.13$). Interestingly, stage was also not associated

Table 2 Associations of the groups with or without diabetes (DM) with other elements of the metabolic syndrome as well as baseline smoking habit and presence of cardiovascular (CV) or neurovascular (NV) disease. Information on smoking was available in 137 patients

	Category	Total (%) ($n = 142$)	No DM (%) ($n = 109$)	DM (%) ($n = 33$)	x^2
Weight	Normal weight	49 (34.5%)	43 (39.4%)	6 (18.2%)	*p = 0.012*
	Overweight	48 (33.8%)	38 (34.9%)	10 (30.3%)	
	Obese	45 (31.7%)	28 (25.7%)	17 (51.5%)	
Hypertension	Yes	87 (61.3%)	60 (55.0%)	27 (81.8%)	*p = 0.005*
	No	55 (38.7%)	49 (45.0%)	6 (18.2%)	
Dyslipidemia	Yes	60 (42.3%)	37 (33.9%)	23 (69.7%)	*p = 0.0003*
	No	82 (57.7%)	72 (66.1%)	10 (30.3%)	
Metabolic syndrome	Yes	53 (37.3%)	25 (22.9%)	28 (84.8%)	*p = 0.00001*
	No	89 (62.7%)	84 (77.1%)	5 (15.2%)	
CV/NV disease	Yes	46 (32.4%)	33 (30.3%)	13 (39.4%)	$p = 0.32$
	No	96 (67.6%)	76 (69.7%)	20 (60.6%)	
Current smoker ($n = 137$)	Yes	19 (13.9%)	16 (15.2%)	3 (9.4%)	$p = 0.40$
	No	118 (86.1%)	89 (84.8%)	29 (90.6%)	

bold means statistically significant (< 0.05)

Table 3 Baseline characteristics of all patients in the series and according to the three weight groups with normal weight (BMI = 18.6–24.9), overweight (BMI = 25–29.9), and obese (BMI ≥ 30) patients. Pre-operative CEA was available for 68 patients and grade in 133 patients

	Category	Total ($n = 142$)	Normal weight (%) ($n = 49$)	Overweight (%) ($n = 48$)	Obese (%) ($n = 45$)	x^2
Age	Mean	68.9	70.2	70.6	65.7	$F = 3.45$, *$p = 0.03$*
	< 65	42 (29.6%)	12 (24.5%)	10 (26.3%)	20 (44.4%)	*$p = 0.028$*
	≥ 65	100 (70.4%)	37 (75.5%)	38 (73.7%)	25 (55.6%)	
Sex	Male	70 (49.3%)	18 (36.7%)	29 (60.4%)	23 (51.1%)	$p = 0.06$
	Female	72 (50.7%)	31 (63.3%)	19 (39.6%)	22 (48.9%)	
Clinical presentation	Asymptomatic/bleeding	78 (54.9%)	26 (53.1%)	29 (60.4%)	23 (51.1%)	$p = 0.6$
	Change transit/obstruction/pain	64 (45.1%)	23 (46.9%)	19 (39.6%)	22 (48.9%)	
Clinical stage	I	29 (20.4%)	9 (18.4%)	10 (20.8%)	10 (22.2%)	$p = 0.9$
	II	55 (38.7%)	18 (36.7%)	19 (39.6%)	18 (40.0%)	
	III	58 (40.9%)	22 (44.9%)	19 (39.6%)	17 (37.8%)	
Location	Right	61 (43.0%)	23 (46.9%)	19 (39.6%)	19 (42.2%)	$p = 0.9$
	Left	35 (24.6%)	11 (22.5%)	12 (25.0%)	12 (26.7%)	
	Rectum	46 (32.4%)	15 (30.6%)	17 (35.4%)	14 (31.1%)	
Grade ($n = 133$)	Well differentiated	74 (55.6%)	22 (51.2%)	29 (64.5%)	23 (51.1%)	$p = 0.59$
	Moderately differentiated	37 (27.8%)	12 (27.9%)	10 (22.2%)	15 (33.3%)	
	Poorly differentiated	22 (16.5%)	9 (20.9%)	6 (13.3%)	7 (15.6%)	
CEA ($n = 68$)	≤ 5	54 (79.4%)	23 (76.7%)	14 (73.7%)	17 (89.5%)	$p = 0.42$
	> 5	14 (20.6%)	7 (23.3%)	5 (26.3%)	2 (10.5%)	
(Neo)adjuvant chemotherapy	Yes	72 (50.7%)	24 (49.0%)	26 (54.2%)	22 (48.9%)	$p = 0.77$
	No	70 (49.3%)	25 (51.0%)	22 (45.8%)	23 (51.1%)	

bold means statistically significant (< 0.05)

with PFS ($p = 0.19$). In multivariate analysis with DM and age included in the model, DM retained its significance (Table 5). In an additional exploratory analysis, the 17 patients with DM that had metformin as part of their DM treatment had a better PFS than patients with DM not receiving metformin, and similar to patients without DM ($p = 0.007$) (Fig. 1c).

Twenty-eight patients in the series had died at a mean of 25.5 months and 114 patients were still alive at a mean follow-up of 65.3 months. Factors associated with OS in the univariate analysis included age above 65 ($p = 0.0002$), HTN ($p = 0.0005$), dyslipidemia ($p = 0.004$), DM ($p = 0.04$) (Fig. 2a), and the MS as a whole ($p = 0.0007$). Obesity category (Fig. 2b) and stage were

Table 4 Associations of the groups with normal weight (BMI = 18.6–24.9), overweight (BMI = 25–29.9), and obese (BMI ≥ 30) patients with other elements of the metabolic syndrome as well as with baseline smoking habit and presence of cardiovascular (CV) or neurovascular (NV) disease. Information on smoking was available in 137 patients

	Category	Total (%) ($n = 142$)	Normal weight ($n = 49$)	Overweight ($n = 48$)	Obese ($n = 45$)	x^2
DM	Yes	33 (23.2%)	6 (12.2%)	10 (20.8%)	17 (37.8%)	*$p = 0.012$*
	No	109 (76.8%)	43 (87.8%)	38 (79.2%)	28 (62.2%)	
Hypertension	Yes	87 (61.3%)	25 (51.0%)	31 (64.6%)	31 (68.9%)	$p = 0.17$
	No	55 (38.7%)	24 (49.0%)	17 (35.4%)	14 (31.1%)	
Dyslipidemia	Yes	60 (42.3%)	11 (22.4%)	28 (58.3%)	21 (46.7%)	*$p = 0.001$*
	No	82 (57.7%)	38 (77.6%)	20 (41.7%)	24 (53.3%)	
Metabolic syndrome	Yes	53 (37.3%)	4 (8.2%)	24 (50.0%)	25 (55.6%)	*$p < 0.00001$*
	No	89 (62.7%)	45 (91.8%)	24 (50.0%)	20 (44.4%)	
CV/NV disease	Yes	46 (32.4%)	13 (26.5%)	17 (35.4%)	16 (35.6%)	$p = 0.55$
	No	96 (67.6%)	36 (73.5%)	31 (64.6%)	29 (64.4%)	
Current smoker ($n = 137$)	Yes	19 (13.9%)	11 (22.9%)	4 (9.5%)	4 (9.3%)	$p = 0.07$
	No	118 (86.1%)	37 (77.1%)	42 (90.5%)	39 (90.7%)	

bold means statistically significant (< 0.05)

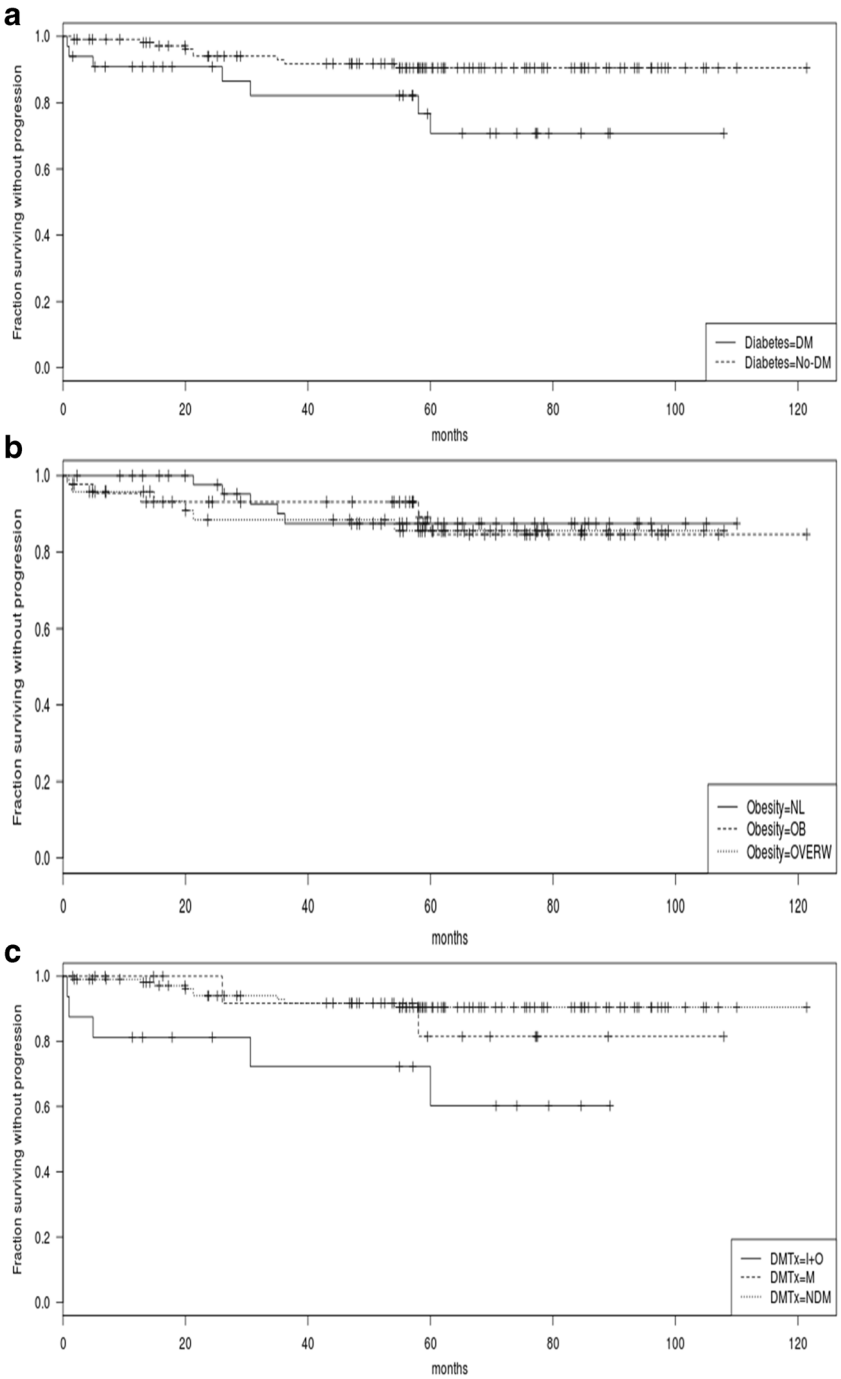

Fig. 1 Progression-free survival (PFS) curves. **a** Patients with DM (DM, solid line) versus non-diabetics (No-DM, interrupted line). Log-rank test $X^2 = 5.5$, $p = 0.018$. **b** Patients with normal weight (NL, solid line) versus overweight (OVERW, pointed line) and obese patients (OB, interrupted line). Log-rank $X^2 = 0.125$, $p = 0.93$. **c** Patients receiving metformin versus diabetics on other treatments and non-diabetics. Solid line, patients with diabetes treated by insulin or other non-metformin treatments; interrupted line, patients with diabetes on metformin; pointed line, non-diabetic patients. Log-rank test $X^2 = 9.8$, $p = 0.007$

not associated with OS. In multivariate analysis, only age retained significance ($p = 0.0002$), while the three metabolic parameters and MS as a syndrome were not significantly associated anymore (Table 6).

Discussion

The metabolic syndrome (MS) and its components have been studied both as risk factors and prognostic factors in colorectal cancer [6]. Although obesity and DM are established risk factors for development of colorectal cancer, the literature on these diseases and the MS as a whole as prognostic factors of colorectal cancer is characterized by conflicting evidence and reports mostly including part of the elements and showing associations in variable subsets such as only men or women [7]. In this paper, we aimed to retrospectively study components of the metabolic syndrome (MS) spectrum and the metabolic syndrome as a disease to clarify their prognostic implications in localized colorectal cancer. The main result of the current study consists of a

Table 5 Univariate survival analysis (log-rank test) of age as well as metabolic syndrome and components as variables for PFS. Multivariate Cox regression analysis was carried out with significant (or approaching significance) variables from the univariate analysis (age and DM) as variables in the model

Variable	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95% CI	*p* value
Age	0.07	1.07	1.01–1.13	0.018
HTN	0.7	–		
Dyslipidemia	0.1	–		
DM	0.018	2.98	1.11–8.02	0.03
Obesity	0.93	–		
Metabolic syndrome	0.13	–		

PFS progression-free survival, *CI* confidence interval

confirmation of the association of DM with PFS in our population, in contrast to all other metabolic elements, including obesity and the MS as a total, which were not associated with inferior PFS. Nevertheless, neither DM nor any other MS components were associated with OS in a multivariate analysis. In fact, the only factor associated with OS in this cohort was age and this may explain the discordance of DM being a prognostic factor for PFS but not for OS, in the multivariate analysis, as the group of patients with DM was older, albeit not statistically significantly, than those without DM (mean age 71 versus 68 years old).

Stage was also not statistically associated with either PFS or OS in our cohort, although stage I had better outcomes from the two other more advanced stages. This may relate to several factors including the good outcomes in all localized stages, as well as the effects of adjuvant chemotherapy and radiation in improving outcomes of stage III patients and a possible over-staging of some stage III patients with rectal cancer, given that the staging in these patients was done usually clinically and radiologically before starting neo-adjuvant treatment.

The current findings suggest that DM maybe the main prognostic element for PFS among metabolic syndrome components in stages I to III colorectal cancer. This has been reported in other patient populations [8–11]. A SEER (Surveillance, Epidemiology, and End Results) database report that analyzed 36,079 patients with colorectal cancer of all stages found that hyperglycemia or DM and HTN were associated with both worse OS and RFR (recurrence-free rate). The MS as a whole

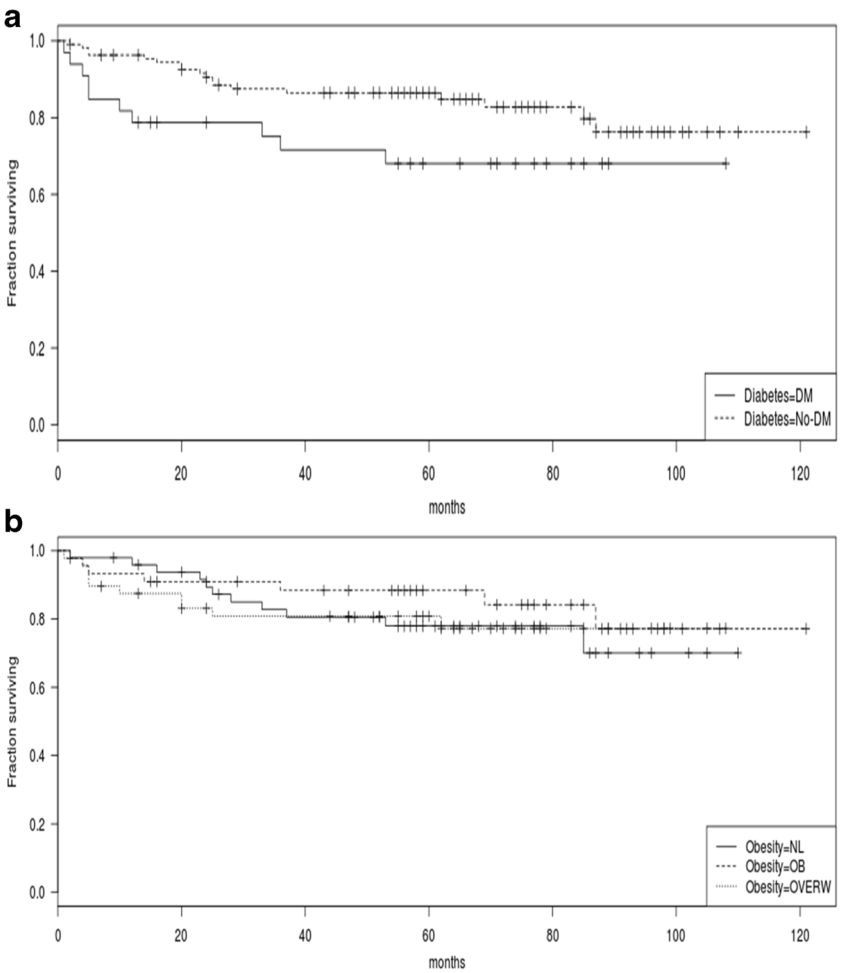

Fig. 2 Overall survival (OS) curves. **a** Patients with diabetes mellitus (DM, solid line) versus non-diabetic patients (No-DM, interrupted line). Log-rank test $X^2 = 4$, $p = 0.045$. **b** Patients normal weight (NL, solid line) versus overweight patients (OVERW, pointed line) versus obese patients (OB, intermittent line). Log-rank $X^2 = 0.8$, $p = 0.67$

Table 6 Univariate survival analysis (log-rank test) of age as well as metabolic syndrome and components as variables for OS. Multivariate Cox regression analysis was carried out with significant variables from the univariate analysis (age, HTN, dyslipidemia, DM, and MS) as variables in the model

Variable	Univariate analysis	Multivariate analysis		
	p value	Hazard ratio	95% CI	*p* value
Age	0.0002	1.1	1.04–1.16	0.0002
HTN	0.0005	3.1	0.83–12.22	0.08
Dyslipidemia	0.004	1.86	0.58–5.97	0.29
DM	0.045	1.32	0.51–3.4	0.5
Obesity	0.67	–		
Metabolic syndrome	0.007	1.09	0.27–4.3	0.9

OS overall survival, *CI* confidence interval

had no prognostic impact due to a counter-intuitive protective effect of dyslipidemia. Authors hypothesize that treatment of this condition with statins may be the actual protective factor, although they could not prove this protective association due to lack of information on drug treatments of the SEER database at the time of the study [8]. Two other studies that included only patients with localized disease, similarly to our study, showed a prognostic value of fasting glucose (the one) [10] and of DM (the other) [11] and in the first the MS as a total was also associated with worse survival. An additional study that included only patients with liver metastatic disease showed worse OS and disease-free survival in patients with DM [9]. In contrast, other reports do not confirm the prognostic association of either DM or obesity for survival either of colorectal cancer patients with localized disease [12] or disease across stages [13]. In addition, the first of these studies showed a prognostic association of MS with DFS but not OS while the second study showed no such associations. A meta-analysis of DM as it pertains to colorectal cancer prognosis including 36 studies with about 2.3 million patients found a moderate adverse effect of DM for OS with a relative risk of 1.18 [14].

Controversial results have also been reported for the influence of obesity in colorectal cancer prognosis. Some reports but not others find an association of increased BMI with a reduced colorectal cancer survival [15, 16]. These inconsistencies may be at least partially due to confounding associations of obesity with other factors, such as, for example, DM, as seen in the current report, or physical activity [17]. In addition, the association of obesity with colorectal cancer prognosis may not be linear but more J-shape with the higher normal and overweight category presenting a decrease risk before increase of the risk in obesity I (BMI 30–34 kg/m^2), obesity II (BMI 35–39 kg/m^2), and morbidly obese (BMI ≥ 40 kg/m^2) categories [18]. Additional complexity is produced by the fact that type of adiposity (central versus peripheral) may not be prognostically equivalent.

HTN is a less well-studied MS component as a prognostic factor of colorectal cancer. A recent report in rectal cancer patients receiving neo-adjuvant treatment showed HTN to be an adverse prognostic factor for response to treatment, while DM and obesity were not associated with response to neo-adjuvant treatment [19]. Dyslipidemia has been studied as part of the MS in the prognosis of colorectal cancer and has been found not to be prognostic in most studies except in the SEER-based report mentioned above which actually found it to be associated with improved outcomes [8]. It is unclear if this is a direct association but an alternative explanation of a protective role of anti-lipidemic medications such as statins appears more plausible, as mentioned above. In our series, both HTN and dyslipidemia were associated with decreased OS but not PFS in univariate analysis but both lost their significance in multivariate analysis.

An additional interesting finding of the current report is that the use of metformin in the treatment of the diabetic patients in the series improved their PFS outcomes compared with patients treated with insulin or other oral anti-diabetic medications. Although this result is derived from a univariate analysis and the drug treatment variable has not been included in the multivariate analysis, improved outcomes with metformin have been also previously reported in other studies. A population study from Denmark found OS of diabetic patients treated with the drug to be improved compared with patients treated with insulin [20]. Another retrospective analysis reached similar conclusions [21]. A meta-analysis of six studies confirmed an improved OS and cancer-specific survival in metformin users compared with non-users with hazard ratios of 0.56 (95% CI, 0.41 to 0.77) and 0.66 (95% CI, 0.5 to 0.87) respectively [22].

The pathophysiologic cause of diabetes association with adverse colorectal cancer outcomes may relate to the underlying hyperinsulinemia. The insulin/IGF (insulin-like growth factor) system, activated due to increased levels of circulating insulin through ligation of IR-A (insulin receptor A) expressed on colorectal cancer cells, promotes activity of the PI3K/Akt and Ras/Raf/MEK/ ERK pathways. These axes, when dysregulated, have pro-carcinogenic actions that include proliferation, inhibition of apoptosis, and promotion of angiogenesis [23]. STAT3 may also be activated through insulin and IGF receptors and is involved in promotion of stemness and metastasis through the EMT (epithelial to mesenchymal transition) process [24, 25]. An additional critical pathway in colorectal cancer, this of Wnt/β-catenin, has connections with hyperglycemia [26].

There are several limitations in the current study. Retrospective data have obviously to be interpreted with caution given the possibility of bias despite multivariate analysis. Moreover, although our series included 142 patients with extensive follow-up, it is smaller than population-based studies and some predictive associations may have been missed due to sample size. Assertion of some components of the MS,

specifically HTN and dyslipidemia, relied on pharmacologic treatment, in addition to history of the respective diseases in patients' charts. Given that there are different indications for some of the anti-hypertensive and anti-dyslipidemia medications, this may have introduced bias in the analysis regarding these diseases as prognostic factors. Nevertheless, almost all the indications for these drugs are related to the MS and atherosclerosis spectrum of diseases.

The current results add to the body of literature on MS components in the prognosis of localized colorectal cancer. DM appears to be an independent adverse prognostic factor for PFS but not for OS. This could be due to other competing factors affecting OS in this older population. Other MS components and the MS as a syndrome are not independent predictors of survival outcomes. A protective effect of metformin in diabetic patients, observed also by others, appears to be present in our series and it provides a rational to include this drug in the treatment of diabetic patients with localized colorectal cancer, if possible. Metformin has been studied in adjuvant breast cancer treatment [results of a randomized trial (NCT01101438) pending] and could be considered for further studies for the same indication in colorectal cancer.

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Compliance with Ethical Standards The study protocol was approved by the Institutional Ethics Review Board of Sault Area Hospital.

Conflict of Interest The authors declare that they have no conflicts of interest.

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