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ORIGINAL ARTICLE

Correlation of Metabolic Syndrome with Clinicopathological Characteristics and Treatment Outcome in Bladder Cancer: A Retrospective Observational Study

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ABSTRAK

Perhubungan antara sindrom metabolik (MetS) dengan ciri-ciri klinikopatologi, tindak balas terhadap kemoterapi dan kelangsungan hidup dalam kalangan pesakit kanser pundi kencing masih kurang dikaji dan sering bercanggah. Kami menganalisis secara retrospektif data 45 pesakit yang didiagnosis dengan kanser pundi kencing bukan invasif otot (NMIBC) atau kanser pundi kencing invasif otot (MIBC) dan telah menerima rawatan kemoterapi di Pusat Perubatan Universiti Malaya (UMMC) antara 2010 dan 2020. Secara keseluruhan, 24 pesakit (53.3%) mempunyai kriteria MetS semasa diagnosis. Tiada hubungan yang signifikan ditemui di antara MetS dan komponen-komponennya dengan tahap patologi dan histologi tumor, dan tindak balas terhadap kemoterapi dalam populasi pesakit kajian ini. Menariknya, terdapat perbezaan yang signifikan dalam kelangsungan hidup keseluruhan antara pesakit diabetes dan pesakit tanpa diabetes (masing-masing 62.47 ± 8.32 bulan dan 84.93 ± 3.96 bulan, p = 0.045). Walaupun tiada hubungan yang signifikan ditemui antara MetS dengan ciri-ciri klinikopatologi dan hasil rawatan untuk kanser pundi kencing, rawatan secara intensif dan perubahan gaya hidup wajar dipertimbangkan untuk pesakit kanser pundi kencing yang mempunyai sindrom metabolik.

Kata kunci: *diabetes mellitus, kelangsungan hidup, neoplasma pundi kencing, sindrom metabolik, terapi ubat*

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ABSTRACT

The relationship between metabolic syndrome (MetS) with the clinicopathological characteristics, chemotherapy responsiveness and survival outcome in bladder cancer is under-investigated and often conflicting. We retrospectively analysed data of 45 patients who were diagnosed with non-muscle invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC) and received chemotherapy at the University of Malaya Medical Centre (UMMC) between 2010 and 2020. Overall, 24 patients (53.3%) were presented with MetS criteria at the time of diagnosis. Across MetS and its components, no significant association was found with tumour pathological stage, histological grade, and chemotherapy response in our patient population. Interestingly, there was a significant difference in overall survival between patients with and without diabetes (62.47 $\pm$ 8.32 months and 84.93 $\pm$ 3.96 months respectively, p=0.045). Although no significant association between MetS with bladder cancer clinicopathological characteristics and treatment outcome was found, intensive care and lifestyle modification should be considered for bladder cancer patients with metabolic disorders.

Keywords: diabetes mellitus, drug therapy, metabolic syndrome, urinary bladder neoplasms, survival

INTRODUCTION

Bladder cancer represents 3% of global cancer diagnoses, with approximately 550,000 new cases estimated in 2018 (Bray et al. 2018). It is also the most expensive cancer to treat and has a stagnant 5-year mortality rate over decades despite current development of various treatment options. Non-muscle invasive bladder cancer (NMIBC) is reported in nearly 75% of total urothelium carcinoma, while the remaining is reported as muscle-invasive bladder cancer (MIBC). To minimise recurrence rate and enhance survival rate, cisplatin-based neoadjuvant systemic chemotherapy, including methotrexate, vinblastine, adriamycin, cisplatin (MVAC) or gemcitabine and cisplatin (GC) is given for patient in conjunction with local therapy, for NMIBC and MIBC, respectively.

Recently, several epidemiological studies suggested that metabolic syndrome (MetS) is closely correlated with various cancer incidence and progression, including colorectal, breast and endometrial cancer (Guo et al. 2019). Metabolic syndrome is a cluster of physiological and biochemical abnormalities characterised by impaired glucose tolerance, central obesity, hypertension, as well as dyslipidemia with low high-density lipoprotein-cholesterol (HDL-C) and high triglyceride levels. In bladder cancer, MetS is significantly associated with high tumour stage and grade during

diagnosis, and may potentially act as the leading cause for the malignant potential of bladder cancer (Nagase et al. 2018). Analysing MetS as a whole may fail to unite all of its components into a single variable and may hinder each metabolic component's independent impact on cancer. Therefore, recently, a few studies have focused on correlating singular MetS components with pathological characteristics of bladder cancer (Jiang et al. 2020). To date, diabetes, obesity and low HDL-C has been significantly associated with higher stage and grade of bladder cancer (Nagase et al. 2018). However, due to the variation in MetS prevalence globally, especially in Asian countries that adopt a different lifestyle behaviour and have divergent ethnicities compared to European or American regions, the conclusion drawn by these regions' studies may not be applicable in Malaysia. Furthermore, the increasing trend of MetS prevalence observed when applying the Western MetS definition in Malaysia further questions the generalisability of these studies' findings among Malaysian.

In addition, many studies proposed MetS components to play a pivotal role in determining cancer patients' responsiveness towards cisplatin-based chemotherapy (Leiter et al. 2016). For example, cholesterol elevation is found to be associated with chemoresistance, possibly due to the consequently reduced permeability of cancer cell membrane and increase efflux of chemotherapeutic drugs (Rivel et al. 2019). This association had been proven in a number of cancers, including lung adenocarcinoma, prostate and breast cancer (Brindisi et al. 2020). Besides, breast cancer patients with high fasting plasma glucose were also found to have a lower response rate to neoadjuvant chemotherapy (Arici et al. 2020). However, the correlation of MetS and its components with the chemotherapy responsiveness in bladder cancer patients remain largely unexplored globally. Thus, this study aims to investigate the correlation of MetS with clinicopathological characteristics and treatment outcome in bladder cancer patients admitted to a teaching hospital in Malaysia.

MATERIALS AND METHODS

Study Setting, Design and Procedure

This retrospective study was conducted at the University Malaya Medical Centre (UMMC), a teaching hospital located in Kuala Lumpur, Malaysia. The study was conducted upon receiving ethics approval from Medical Ethics Committee (MRECID 2019618-7527). A total of 243 bladder cancer patients admitted to UMMC from January 2010 to December 2020 were retrospectively identified from UMMC Bladder Cancer Registry. These were patients who were pathologically diagnosed with primary NMIBC and MIBC during admission and received chemotherapy regimens as bladder cancer treatment. Patients with incomplete important medical records, such as the presence of MetS components or urothelial tumour stage and grade before and after chemotherapy, and patients diagnosed with other bladder

cancer histological types such as carcinoma in situ, squamous cell carcinoma or adenocarcinoma were excluded. Patients who received chemotherapy regimen concurrently with other treatment options such as Bacillus Calmette-Guérin (BCG) immunotherapy or radiotherapy were also excluded from the study.

Patients' information that was retrospectively collected includes demographic data, body mass index (BMI), clinicopathological data such as bladder cancer histology and grade, stage at diagnosis, comorbidities, and medication history (diabetes, hypertension and dyslipidemia), as well as blood pressure and blood test (blood glucose, HDL-C and triglyceride level) at the time of bladder cancer diagnosis. The pathological stage of the urothelial tumour was classified based on the 2009 Tumour-Node-Metastasis (TNM) classification staging system, where Tis, Ta and T1 tumours were identified as low stage while T2, T3, and T4 tumours were recognised as high stage bladder cancer. Bladder cancer patients' pathological grading of the urothelial tumour was based on the World Health Organisation 2004 grading system (Lopez-Beltran et al. 2004).

Metabolic Syndrome Definition

According to Joint Interim Statement "Harmonised Criteria", MetS was defined as the presence of at least 3 of the following abnormalities i.e.; i) BMI ≥25 kg/m^2; ii) fasting plasma glucose >5.6 mmol/L or previously diagnosed with type 2 diabetes; iii) blood pressure ≥135/85 mmHg or undergoing antihypertensive treatment; iv) HDL <1.03 mmol/L for male and <1.29 mmol/L for female or receiving treatment for a low HDL; or v) triglyceride ≥1.7 mmol/L or receiving treatment (Kassi et al. 2011). In this study, patients with BMI <25 kg/m^2 were categorised as normal weight, and ≥25 kg/m^2 were categorised as overweight/obese. Due to the absence of HDL-C and triglyceride in patients' medical records during bladder cancer diagnosis in our dataset, these two criteria were combined as dyslipidemia.

Treatment Outcome

Treatment response towards chemotherapy was determined from the pathology report by comparing the difference in patients' tumour stages before and after chemotherapy; where downstaging (any decrease in stage) was identified as chemotherapy responsive while remaining at the same stage or upstaging was identified as non-responsive. In UMMC, NMIBC patients were generally followed-up with flexible cystoscopy every 3 months for the first 2 years following transurethral resection of bladder tumour (TURBT), biannually for the next 2 years, and yearly afterwards. For MIBC patients, a computerised tomography (CT) scan was performed annually after chemotherapy as a follow-up. For survival outcome, recurrence-free survival (RFS) and overall survival (OS) were determined as the time from the date of chemotherapy initiation till the date

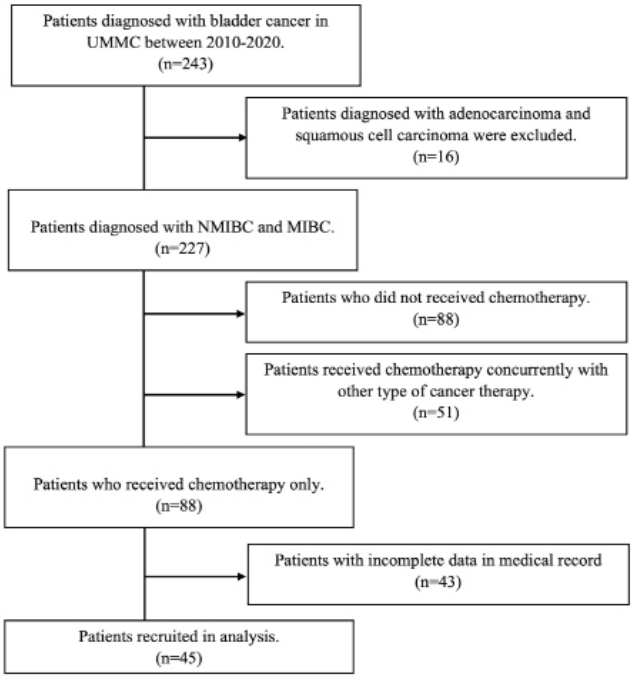

Figure 1: Patients' disposition (Abbreviations: MIBC=muscle-invasive bladder cancer; NMIBC=non-muscle invasive bladder cancer; UMMC=University Malaya Medical Centre)

of first recurrence or death from any cause, respectively. Disease recurrence was defined as a new histologically confirmed tumour relapse in the urinary bladder regardless of tumour stage. In patients without recurrence or death, they were censored at the date of the last follow-up visit.

Data Analysis

All analysis was conducted using Statistical Package for Social Science (SPSS) version 23 (IBM Corp., Armonk, NY, USA). Chi-square test of association and independence t-test were carried out to correlate the presence of MetS and its components with different clinicopathological characteristics and patients' responsiveness towards chemotherapy. Univariate survival analysis of OS and RFS was estimated using the Kaplan-Meier method and compared statistically using a log-rank test. The result with a p-value <0.05 was accepted to be statistically significant.

RESULTS

Baseline Characteristics of Bladder Cancer Patients in UMMC

A total of 243 patients diagnosed with bladder cancer between 2010-2020 were identified from the hospital bladder cancer registry. Of these, 155 (63.8%) were excluded as they failed to meet the inclusion criteria (Figure 1). Among the 45 patients who were analysed in our study, majority were males of Chinese ethnicity, with a

Table 1: Demographic and clinicopathological characteristics of all patients, and comparison between patients with or without metabolic syndrome

	All patients	Metabolic syndrome (MetS)		
		Patients without MetS	Patients with MetS	p-value
Number of patients, n (%)	45 (100)	21 (46.7)	24 (53.3)	
Age, years (mean ± SD)	66.69 ± 11.27	69.17 ± 8.72	63.89 ± 13.28	0.116
Gender, n (%)				
Male	39 (86.7)	19 (90.5)	20 (83.3)	0.670
Female	6 (13.3)	2 (9.5)	4 (16.7)	
Race, n (%)				
Malay	13 (28.9)	6 (28.6)	7 (29.2)	0.662
Chinese	25 (55.6)	12 (57.1)	13 (54.2)	
Indian	6 (13.3)	2 (9.5)	4 (16.7)	
Iranian	1 (2.2)	1 (4.8)	0	
Smoking cigarettes, n (%)				
Active smoker	8 (17.8)	5 (23.8)	3 (12.5)	0.620
Ex-smoker	7 (15.6)	2 (9.5)	5 (20.8)	
Non-smoker	22 (48.9)	10 (47.6)	12 (50.0)	
Unknown	8 (17.8)			
Bladder cancer type, n (%)				
NMIBC	34 (75.6)	17 (81.0)	17 (70.8)	0.503
MIBC	11 (24.4)	4 (19.0)	7 (29.2)	
Tumour grade, n (%)				
Low	15 (33.3)	8 (38.1)	7 (29.2)	0.546
High	30 (66.7)	13 (61.9)	17 (70.8)	
Tumour stage, n (%)				
Ta	17 (37.8)	8 (38.1)	9 (37.5)	0.330
T1	17 (37.8)	9 (42.9)	8 (33.3)	
T2	6 (13.3)	1 (4.8)	5 (20.8)	
T3	4 (8.9)	3 (14.3)	1 (4.2)	
T4	1 (2.2)	0	1 (4.2)	
Obesity, n (%)				
Normal/non-obese	23 (51.1)	15 (71.4)	7 (29.2)	0.007*
Overweight/obese	22 (48.9)	6 (28.6)	17 (70.8)	
Hypertension, n (%)				
Yes	35 (77.8)	11 (52.4)	24 (100.0)	0.001*
No	10 (22.2)	10 (47.6)	0	
Diabetes, n (%)				
Yes	22 (48.9)	4 (19.0)	18 (75.0)	0.001*
No	23 (51.1)	17 (81.0)		
Dyslipidemia, n (%)				
Yes	18 (40.0)	2 (9.5)	16 (66.7)	0.001*
No	27 (60.0)	19 (90.5)	8 (33.3)	
Chemotherapy regimen, n (%)				
Mitomycin C	34 (75.6)			
Gemcitabine/Cisplatin	10 (22.2)			
Gemcitabine/Carboplatin	1 (2.2)			

Abbreviations: MIBC=muscle-invasive bladder cancer; NMIBC=non-muscle invasive bladder cancer

Table 2: Comparison between metabolic syndrome and its individual components with tumour stage and grade in bladder cancer patients

	Tumour Stage			Tumour Grade		
	High stage	Low stage	p-value	High grade	Low grade	p-value
Obesity, n (%)						
Normal/non-obese	5 (45.5)	18 (52.9)	0.738	13 (43.4)	10 (66.7)	0.208
Overweight/obese	6 (54.5)	16 (47.1)		17 (56.7)	5 (33.3)	
Hypertension, n (%)						
Yes	10 (90.9)	25 (73.5)	0.228	25 (83.3)	10 (66.7)	0.205
No	1 (9.1)	9 (26.5)		5 (16.7)	5 (33.3)	
Diabetes, n (%)	7 (63.6)	15 (44.1)	0.314	17 (56.7)	5 (33.3)	0.208
Yes	4 (36.4)	19 (55.9)		13 (43.3)	10 (66.7)	
No						
Dyslipidemia, n (%)	5 (45.5)	13 (38.2)	0.671	11 (36.7)	7 (46.7)	0.538
Yes	6 (54.5)	21 (61.8)		19 (63.3)	8 (53.3)	
No						
Metabolic syndrome, n (%)						
Yes	7 (63.6)	17 (50.0)	0.503	17 (56.7)	7 (46.7)	0.546
No	4 (36.4)	17 (50.0)		13 (43.4)	8 (53.5)	

mean age of 66.69 ± 11.27 years (Table 1). Approximately three-quarters of the recruited patients presented with NMIBC (n=34, 75.6%) at admission. A total of 24 (53.3%) patients had more than 3 MetS components and were classified as having MetS during bladder cancer diagnosis. MetS components include obesity, hypertension, diabetes and dyslipidemia were found in 23 (51.1%), 35 (77.8%), 22 (48.9%) and 18 (40%) patients, respectively.

Association of Metabolic Syndrome with Demographic and Clinicopathological Characteristics of Bladder Cancer Patients

The demographic and clinicopathological characteristics between patients with or without MetS are shown in Table 1. There were no statistically significant differences in the demographic and clinicopathological characteristics between patients with or without MetS, except for the individual components of MetS, such as obesity, hypertension, diabetes and dyslipidemia.

Association between Metabolic Syndrome and Its Individual Components with Tumour Staging, Grading and Chemotherapy Responsiveness

The relationship between MetS and its components with tumour T stage and grade are shown in Table 2. In our set of analysed patients, MetS and components of MetS were not significantly associated with tumour stage and grade in bladder cancer patients. There was also no significant association between MetS and its components with bladder cancer patients' responsiveness towards chemotherapy (Table 3). Even when

Table 3: Comparison between metabolic syndrome and its individual components with chemotherapy responsiveness in non-muscle invasive bladder cancer and muscle-invasive bladder cancer patients

	Chemotherapy Responsiveness								
	All patients			MIBC patients			NMIBC patients		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Obesity, n (%)									
Normal/non-obese	11 (52.4)	12 (50.0)	1.000	4 (66.7)	1 (20.0)	0.242	7 (46.7)	11 (57.9)	0.515
Overweight/obese	10 (47.6)	12 (50.0)		2 (33.3)	4 (80.0)		8 (53.3)	8 (42.1)	
Hypertension, n (%)									
Yes	15 (71.4)	20 (83.3)	0.476	5 (83.3)	5 (100.0)	1.000	10 (66.7)	15 (78.9)	0.462
No	6 (28.6)	4 (16.7)		1 (16.7)	0		5 (33.3)	4 (21.1)	
Diabetes, n (%)									
Yes	8 (38.1)	14 (58.3)	0.236	2 (33.3)	5 (100.0)	0.061	6 (40.0)	9 (47.4)	0.667
No	13 (61.9)	10 (41.7)		4 (66.7)	0		9 (60.0)	10 (52.6)	
Dyslipidemia, n (%)									
Yes	6 (28.6)	12 (50.0)	0.223	1 (16.7)	4 (80.0)	0.080	5 (33.3)	8 (42.1)	0.601
No	15 (71.4)	12 (50.0)		5 (83.3)	1 (20.0)		10 (66.7)	11 (57.9)	
Metabolic syndrome, n (%)									
Yes	9 (42.9)	15 (62.5)	0.238	3 (50.0)	4 (80.0)	0.545	6 (40.0)	11 (57.9)	0.300
No	12 (57.1)	9 (37.5)		3 (50.0)	1 (20.0)		9 (60.0)	8 (42.1)	

Abbreviations: MIBC=muscle-invasive bladder cancer; NMIBC=non-muscle invasive bladder cancer

subgroup analysis based on bladder cancer type was performed, there was no significant association between MetS and its components with patients' responsiveness towards chemotherapy in both MIBC and NMIBC subgroups.

Association of Metabolic Syndrome and Its Individual Components With Recurrence-Free and Overall Survival

Within a median follow-up of 28.29 ± 5.81 months, 15 patients experienced disease recurrence (7 and 8 in patients with and without MetS, respectively). The mean recurrence-free time (RFS) was 63.64 ± 9.40 months and 51.28 ± 9.56 months in patients with and without MetS, respectively. Kaplan Meier analysis shows no significant difference in RFS between patients with and without MetS, as well as all individual MetS components (Figure 2).

Throughout the follow-up period, 7 patients died (5 and 2 in patients with and without MetS respectively). There was no statistically significant difference in mean overall survival (OS) between patients with and without MetS (68.21 ± 7.47 months and 79.71

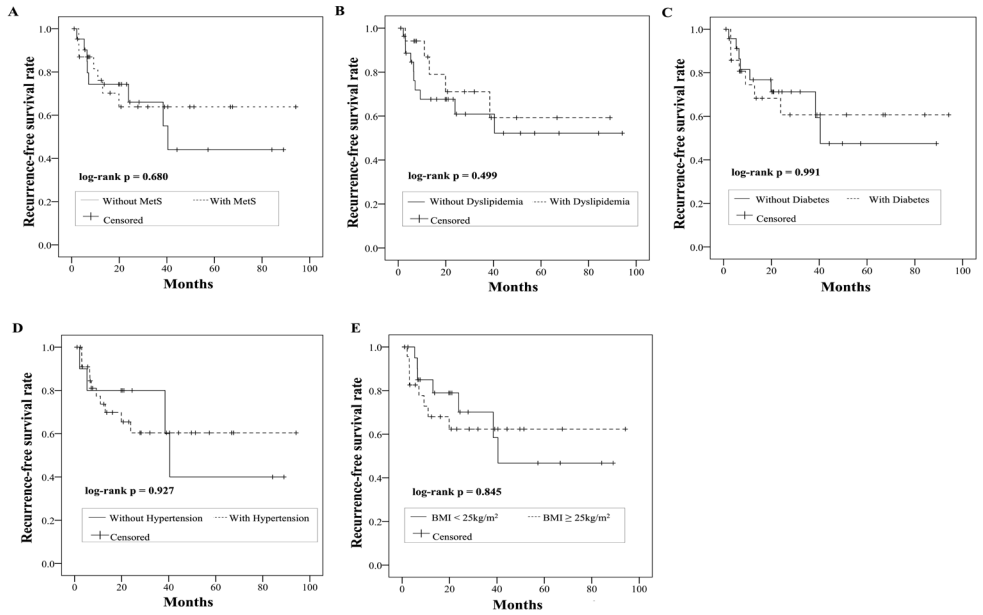

Figure 2: Kaplan-Meier curves displaying recurrence-free survival in non-muscle invasive bladder cancer and muscle-invasive bladder cancer patients who received chemotherapy, stratified by (A) metabolic syndrome, (B) dyslipidemia, (C) diabetes, (D) hypertension and (E) obesity (Abbreviations: BMI=body mass index; MetS=metabolic syndrome)

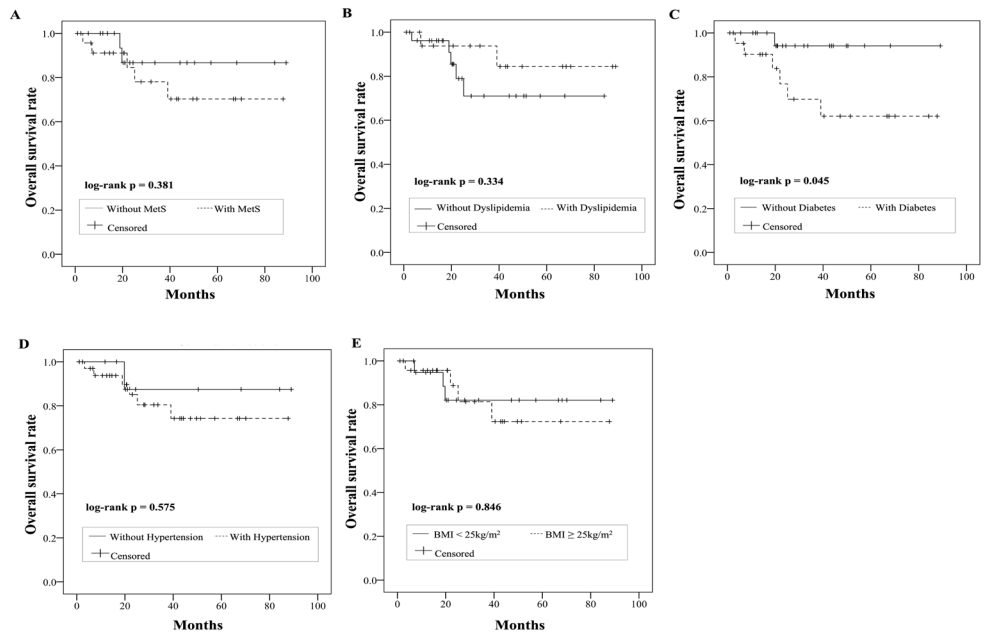

Figure 3: Kaplan-Meier curves displaying overall survival in non-muscle invasive bladder cancer and muscle-invasive bladder cancer patients who received chemotherapy, stratified by (A) metabolic syndrome, (B) dyslipidemia, (C) diabetes, (D) hypertension and (E) obesity (Abbreviations: BMI=body mass index; MetS=metabolic syndrome)

± 6.12 months, respectively, p=0.381), as shown in Figure 3. When analysed in terms of the individual components of MetS, a significant difference in OS between patients with and without diabetes (62.47 ± 8.32 months and 84.93 ± 3.96 months respectively, p=0.045) was found.

DISCUSSION

In this study, we retrospectively reviewed the patients who were diagnosed with MIBC and NMIBC in UMMC between 2010-2020 to correlate MetS with the clinicopathological characteristics of patients during diagnosis. In our patient dataset, there was no significant association between MetS with the tumour stage and grade in bladder cancer patients at the time of diagnosis. Previous studies have demonstrated that MetS patients have significantly higher tumour pathological stage and histological grade (Jiang et al. 2020; Ozbek et al. 2014). Apart from the sample size, the difference in our results may be due to the varying definition of MetS used in the investigations. The absence of universally defined diagnostic criteria for MetS had led to controversies on the accuracy of comparing results from different studies (Kassi et al. 2011). Ozbek et al. (2014) used the NCEP/ATP III MetS definition, which employed waist circumference >102 cm in men and >88 cm in women as a surrogate for abdominal obesity, instead of BMI. Sha et al. (2016) defined MetS with modified Chinese Diabetes Society definition where MetS was diagnosed only if the patient had obesity, diabetes and hypertension, regardless of dyslipidemia diagnosis. It is also worth noting that our study was unable to ascertain whether the difference in pathological stage and grade of bladder cancer was due to the delay of diagnosis or an actual biological propensity for more aggressive illness in patients with MetS.

We also investigated the relationship of MetS and its components with chemotherapy responsiveness in bladder cancer patients. To the best of authors' knowledge, this is the first study that investigate the correlation of MetS with bladder cancer patients' responsiveness towards chemotherapy; although we did not find any significant association when both MIBC and NMIBC groups were analysed separately or as a whole. The evidence on the association between MetS and survival outcome among bladder cancer patients were equally sparse and inconsistent, with the majority of studies involving patients undergoing surgery with or without chemotherapy. We found no significant difference in RFS and OS between patients with or without MetS, which is in line with a previous retrospective study (Garg et al. 2020).

We also investigated the association of individual MetS components (hypertension, dyslipidemia, obesity and diabetes) with the clinicopathological characteristics and treatment outcome. Similar to our studies, all studies published so far found no significant association between hypertension and bladder cancer stage and grade (Jiang et al. 2020; Sha et al. 2016). While we found no significant

association between hypertension with RFS and OS, a previous study had found a higher bladder cancer-specific mortality rate for patients with pre-existing hypertension at the time of bladder cancer diagnosis, attributed to less aggressive bladder cancer and hypertension treatments (Teleka et al. 2021).

In most studies, when analysed as part of MetS components, dyslipidemia was separated as triglyceride and HDL-C, as defined by Joint Interim Statement (Kassi et al. 2011). Abnormal triglyceride level has been correlated to the risk of several cancers such as breast and colorectal cancer (Okamura et al. 2020). However, it is not associated with bladder cancer in the currently available evidence (Jiang et al. 2020). Similarly, majority of studies did not find a significant association between low HDL-C level with bladder tumour stage except a study that suggested that HDL-C was a potential risk factor for bladder cancer upstaging (Nagase et al. 2018). A proper prospective study documenting HDL-C and triglyceride levels in our patient population would greatly help in alienating the association of these components with tumour stage and grade. While many *in vitro* studies have demonstrated the role of elevated cholesterol in the emergence of chemoresistance in various cancers, limited studies had investigated the correlation between pre-treatment cholesterol level and bladder cancer chemotherapy outcome in clinical settings. Interestingly, a high HDL-C level before treatment was reported as an independent predictor of the response to chemotherapy in breast cancer patients (Qu et al. 2020). On the other hand, no significant association between dyslipidemia with RFS and OS was found in our study, which was consistent with previously published research in breast and prostate cancer patients (Bahl et al. 2005; Cheng et al. 2019).

Obesity is a major health concern that has been shown to be significantly associated with bladder cancer grade and stage (Jiang et al. 2020). Among the proposed mechanism includes high plasma level of vascular endothelial growth factor and leptin secretion by adipose tissue, which promotes epithelial cells proliferation and angiogenesis, eventually leading to tumour development, as well as the involvement of insulin resistance and elevated plasma insulin-like growth factor (IGF-1) (Lega & Lipscombe 2020). While we and others found no significant association between obesity and bladder cancer tumour stage and grade (Nagase et al. 2018; Ozbek et al. 2014), the different parameters used to determine obesity in the study population is of note. While we relied on BMI, this parameter has been suggested as a sub-optimal measure for abdominal obesity given its poor predictor of visceral fat and is easily influenced by patients' physical changes that coincide with aging. Waist circumference and visceral fat have been suggested as better measures of adiposity (Ozbek et al. 2014). The use of different obesity indicators should be further tested to validate the association between obesity and bladder cancer clinicopathological characteristics. Obesity also has been proposed to

reduce chemotherapy responsiveness due to the elevated circulating insulin, metabolic hormones and inflammatory cytokines level in obese patients that may limit apoptosis and promote tumour proliferation (Warner et al. 2016). Besides, chemotherapy underdosing in obese patients may affect the therapeutic effects of chemotherapy (Litton et al. 2008). However, this is not observed so far among metastatic urothelial cancer patients in a clinical setting (Leiter et al. 2016). In our sample population, obese bladder cancer patients treated with chemotherapy had similar RFS and OS with non-obese patients. While this is also observed in other studies (Leiter et al. 2016; Teleka et al. 2021), a systematic review suggested that the association of BMI elevation was linked to increased recurrence risk in NMIBC patients (Zuniga et al. 2020).

With respect to diabetes, similar to our findings, retrospective analysis by Jiang et al. (2020) did not find any significant association between this disorder with tumour grade and stage in bladder cancer. In contrast, Ozbek et al. (2014) and Sha et al. (2016) demonstrated a significant association between diabetes with bladder tumour stage and grade. The proposed mechanism for this significant association is reduced insulin sensitivity and increased IGF-1 level that promote cell proliferation and inhibit apoptosis, which in turn contribute to bladder cancer development (Yang et al. 2013). Besides, dysfunction of the cellular signal system, regulated by protein C kinase family, in hyperglycaemic patients can also promote tumour growth (Sha et al. 2016). It is known that the level of glycaemic control (HbA1c measurement) and duration of diabetes can both impact the tumour aggressiveness at the time of diagnosis (Ozbek et al. 2014); thus the availability of these data would greatly improve the study. The co-existence of obesity and diabetes could also contribute to the prognosis, as obesity is the main predisposing factor for diabetes and both sharing a similar signalling pathway in carcinogenesis. In our dataset, 11 of the patients were both obese and diabetic. While we found no correlation between diabetes and chemotherapy responsiveness in our bladder cancer patient population, diabetes and high fasting plasma glucose have been associated with chemotherapy non-responsiveness in breast cancer (Arici et al. 2020).

Interestingly, we found diabetic bladder cancer patients that received chemotherapy for bladder cancer treatment had shorter OS compared to non-diabetic patients. Diabetes had been associated with increased incidence and poor prognosis of several cancers such as breast, pancreatic and colorectal cancer (Han et al. 2021; Kleeff et al. 2016). Although the direct biological mechanism is unclear, our finding is consistent with the previously published meta-analysis of 21 cohort studies that suggested diabetes was associated with elevated bladder cancer mortality (Xu et al. 2017). In terms of tumour recurrence, our result supports the previous studies that found no significant association of diabetes with tumour recurrence in bladder cancer (Evers et al. 2020;

Huang et al. 2020). However, taking glycaemic control into account, studies had demonstrated that poor glycaemic control diabetes (HbA1c 7.0%) during bladder cancer treatment will result in elevated bladder cancer recurrence risk and shorter RFS duration compared to those with good glycaemic controlled diabetes (Hwang et al. 2011; Tai et al. 2015).

CONCLUSION

Albeit the small sample size, the present study demonstrated diabetic bladder cancer patients that received chemotherapy for bladder cancer treatment had shorter OS compared to chemotherapy-receiving, non-diabetic bladder cancer patients. Hence, a more intensive and close monitoring may be necessary for bladder cancer patients with diabetes to improve patients' survival rates. A more carefully designed prospective study that accounts for all the complete parameters, including changes in metabolic disorders throughout the chemotherapy courses and follow-ups, such as level of glycaemic control and cholesterol level alteration-would be beneficial in delineating the true role of these metabolic disorders in bladder cancer.

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