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Associations between patient sociodemographic characteristics and lack of treatment for locally advanced or metastatic urothelial carcinoma: results from a complete nationwide, unselected, real-world register study in Denmark

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Abstract

Background Previous studies have investigated treatment patterns among patients with locally advanced or metastatic urothelial carcinoma (mUC) in Denmark and found that, in an unselected nationwide Danish registry cohort, only 36% of patients received systemic anticancer therapy. The objective of this study was to identify socioeconomic factors associated with the receipt of systemic treatment in patients with mUC in Denmark, a country with universal free access to healthcare.

Methods This retrospective, population-based study was based on data from the Danish national healthcare registers. We identified all patients diagnosed with mUC from 2010 to 2017 who were potentially eligible for systemic chemotherapy (cohort 1). Two sub-cohorts of interest were identified: patients who received systemic anticancer treatment (cohort 2) and patients who did not receive any systemic anticancer treatment or surgery following the diagnosis of mUC (cohort 3).

Results A total of 3,206 patients diagnosed with mUC were identified (cohort 1), of whom 1,223 (38%) did not meet the study inclusion criteria (i.e., received treatments other than those pre-specified). For patients who received systemic anticancer treatment (cohort 2; $n=1,141$ [36%]), the mean time to treatment was 1.3 months. Among untreated patients (cohort 3; $n=842$ [26%]), 246 patients died within 1.3 months after the diagnosis of metastatic disease; thus, to account for immortal time bias, these 246 patients were excluded from analyses. Comparing the

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remaining 596 patients in cohort 3 with all patients in cohort 2, increasing age and region of residence were found to be associated with a lower probability of receiving systemic treatment. Moreover, completion of at least a high school education and being married were associated with a higher probability of receiving systemic treatment.

Conclusions We found significant and measurable inequality in access to treatment for mUC. Among other factors, residence in two relatively rural regions was associated with lower probability of receiving systemic anticancer treatment compared to residence in other regions. In addition, marital status and education level had a significant impact on treatment rates.

Keywords Urothelial carcinoma, Nationwide register analysis, Access to treatment, Inequality

Background

Cancer diagnostics and treatments continue to improve, which, along with other factors, has led to an increase in the number of cancer survivors [1, 2]. Urothelial carcinoma (UC) is the seventh most common malignancy in Denmark, with approximately 2,200 patients newly diagnosed each year. Among these patients, 43% have a tumour that is or will become invasive [3]. The age-standardised incidence of UC in Denmark has decreased slightly since 2014, which is presumed to be due to a reduction in the number of people who smoke cigarettes, the most important risk factor for UC [3]. Although the prognosis for patients with UC has improved, studies from different countries suggest that inequality in both the incidence of UC [4, 5] and survival rates [2], as estimated using income, has increased over the past three decades.

Denmark has a tax-financed healthcare system in which patients have free and universal access to treatment and care. General practitioners have a gatekeeping role, providing patients with the necessary referral before they can receive specialised or hospital care, unless emergency care is required. The primary and secondary healthcare sectors are organised into five regions. Compared with other countries, the private hospital sector in Denmark is relatively small; cancer treatment is provided exclusively at public hospitals.

In a previous study [6], we investigated treatment patterns among patients with metastatic UC (mUC) and found that in an unselected nationwide Danish registry cohort, 36% of patients received systemic anticancer therapy. The objective of this study was to investigate and identify socioeconomic factors that are correlated and, therefore, associated with the receipt of systemic anticancer treatment prior to the introduction of immuno-oncology agents for the treatment of mUC. Given the free access to healthcare in Denmark, identifying such factors is relevant for improving future clinical practice. Equal and just access to healthcare in Denmark is a focus among others because studies have proven that socioeconomic inequality, for example, in survival after cancer [2].

Methods

This retrospective, population-based study included all patients diagnosed with mUC in the pre–immuno-oncology era between 2010 and 2017 who were potentially eligible for systemic chemotherapy. We used the Danish national healthcare registers to identify the study population and included follow-up data through 2018, as well as information on survival through 2019.

Data sources

We used the following data sources: the Danish Civil Registration System [7], the Danish National Patient Register (NPR) [8, 9], the Danish Cancer Register [10], and the Danish Pathology Register [11], along with the Income Register, Education Register, Migration Register and Cause of Death Register [12]. These registers hold information at the individual level, and data are linked via unique personal identification numbers, which have been assigned to all Danish residents since 1968. The Danish national registers are exhaustive and contain comprehensive healthcare data from the early 1990s onwards. The linkage of data at the individual level, among other things, allows for the establishment of individuals' healthcare journeys.The Civil Registration System contains the date of birth, sex, vital status, region of residence and family relationships. Patient-specific data were collected from the NPR, Cancer Register and Pathology Register. The NPR contains information on all hospitalisations in Denmark since 1977 and all outpatient contacts since 1995. For admissions and outpatient contacts, the NPR contains information about diagnoses (*International Classification of Diseases, Tenth Revision* [*ICD-10*] [13]), treatments, and procedures performed. We retrieved the date of diagnosis of UC from the Danish Cancer Register, which contains data on the incidence of cancer and tumour characteristics for all Danish residents diagnosed with cancer since 1943. The Pathology Register contains information on all pathology diagnoses made in Denmark since 1997 registered by means of Systemized Nomenclature of Medicine codes. We obtained data on death and emigration from the Causes of Death Register and Migration Register, respectively. Finally, we obtained information regarding income and education level at the

time of UC diagnosis from the Income Register and Education Register, respectively.

Study population

As described previously [6], we identified the population of patients with UC in the NPR as individuals who had a registered *ICD-10* diagnosis code of C65, C66, C67 or C68. The population was cross-checked and verified in the Cancer Register.

We identified patients with mUC as patients with UC who, according to Danish treatment guidelines [14], were potential candidates for systemic treatment (cohort 1). According to the guidelines, potential candidates were patients with tumour stage T4b, N2/3 or M1 and patients' general condition should be assessed to determine whether they were suitable for cisplatin treatment [14]. Patients with mUC at the initial diagnosis and those who later progressed to mUC were included, and we established additional criteria to ensure the inclusion of all relevant patients, including those who had a later record of metastatic disease. Exclusion criteria: did not receive prespecified treatments 39% ($n=477$), last systemic treatment was before surgery 42% ($n=510$), received curative-intent radiotherapy after neoadjuvant chemotherapy 1% ($n=12$), enrolment in clinical trials, or erroneous coding 18% ($n=224$) [6].

From cohort 1, two sub-cohorts were identified: cohort 2, which included patients with mUC who received systemic treatment as first-line (1 L) treatment; and cohort 3, which included patients who did not receive any systemic treatment or surgery following a diagnosis of mUC, although radiotherapy with palliative intent was allowed in this cohort.

For cohort 2, systemic treatment was defined by specific chemotherapy regimens [6]. Cystectomy prior to 1 L treatment and subsequent palliative radiotherapy (defined as a maximum of 15 radiotherapy fractions within a 2-month period, excluding radiotherapy with curative intent) were allowed. Surgery, including cystectomy, and radiotherapy with curative intent after the last 1 L systemic chemotherapy treatment were exclusion criteria in this cohort. Patients receiving neoadjuvant chemotherapy prior to cystectomy were also included in cohort 2, provided they had received additional systemic treatment following surgery.

Outcomes and statistical analyses

We compared baseline characteristics at diagnosis in the two cohorts using *t*-tests or χ^2 tests. Baseline characteristic variables included sex, education level, gross income, age, region of residence, marital status, Charlson Comorbidity Index (CCI) score, TNM status, and location of the primary tumour. The CCI score was estimated using registered diagnoses in the NPR for 10 years prior to the UC diagnosis. Based on registered T, N and M codes, we estimated the numbers of people with tumour stage T4b, N stage 2/3 or M1 status at the time of diagnosis.

To include more explanatory variables, we subsequently used a linear probability model (LPM) to identify the socioeconomic factors associated with the receipt of systemic treatment. As the receipt of treatment (or lack thereof) is associated with clinically relevant and disease-specific factors, all LPM estimations were adjusted for those factors to ensure a more accurate estimate of the association of the included socioeconomic variables. Age, T4b status, N2/3 status, M1 status, location of tumour (with "malignant neoplasm of bladder" used as reference), and CCI score (with "CCI = 0" used as reference) were included as clinically relevant control factors.

For the LPM analyses, an iterative process was used, with each socioeconomic variable included separately to examine its individual potential association with the receipt of treatment (univariate associations in addition to clinical factors, presented in supplementary materials). However, this *ceteris paribus* assumption ignores possible correlations among separately included variables. Therefore, we performed an analysis that included all socioeconomic variables to account for potential correlation between variables (multivariate associations). There are pros and cons to the application of the LPM compared to a logistic regression model. The LPM approach was chosen in the base case due to the advantageous interpretability of the parameter estimates (i.e., coefficients can be directly interpreted as the change in probability). However, in a supplementary analysis, we used a logistic regression model as an alternative.

To account for potential immortal time bias, we excluded patients in cohort 3 who did not survive the mean time from mUC diagnosis to 1 L treatment in cohort 2. This approach ensured that all included patients in cohort 3 had a chance to receive treatment. In a supplementary analysis, we included all cohort 3 patients.

Data management and statistical analyses were carried out on Statistics Denmark's research computers via a secure connection. All analyses were performed using SAS 9.4.

Results

From 2010 to 2017, 3,206 patients with locally advanced or metastatic UC were identified who, according to Danish treatment guidelines [14], were candidates for systemic treatment (cohort 1). Among them, 1,141 patients (36%) received systemic anticancer treatment (cohort 2), and 842 (26%) did not receive any treatment or surgery for advanced disease (cohort 3). Study inclusion criteria led to the exclusion of 1,223 patients (38%; Fig. 1).

In cohort 2, the mean time from the diagnosis of advanced disease to the initiation of 1 L treatment was

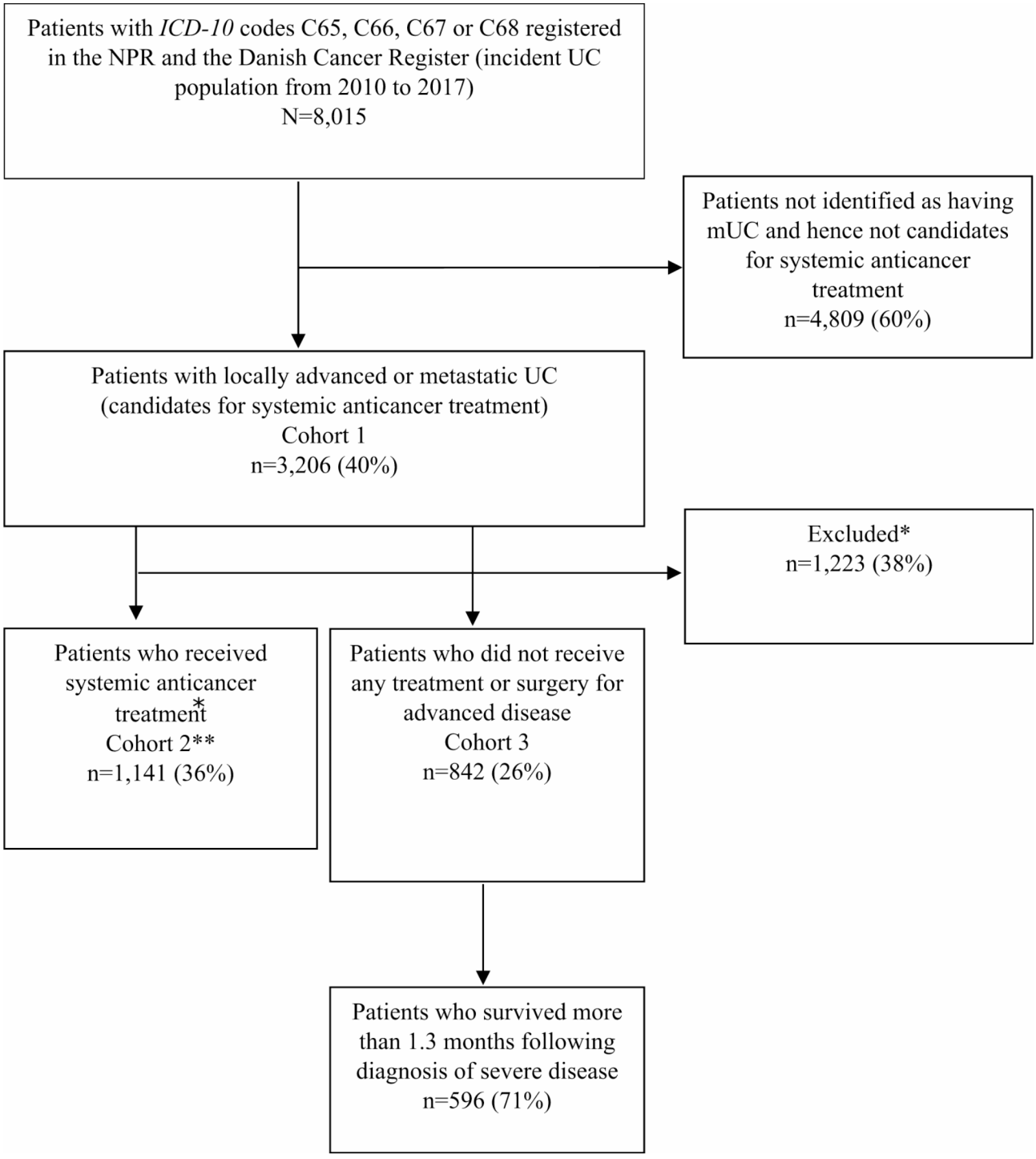

Fig. 1 Flow chart of the study population

*Exclusion criteria: did not receive prespecified treatments ($n=477$), last systemic treatment was before surgery ($n=510$), received curative-intent radiotherapy after neoadjuvant chemotherapy ($n=12$), enrollment in clinical trials or erroneous coding ($n=224$)

**Systemic treatment received: carboplatin + gemcitabine: $n=273$ (24%), cisplatin + gemcitabine: $n=538$ (47%), gemcitabine monotherapy: $n=172$ (15%), unspecified chemotherapy: $n=158$ (14%)

ICD-10, *International Classification of Diseases*, *Tenth Revision*; mUC, metastatic urothelial carcinoma; NPR, National Patient Register; UC, urothelial carcinoma

1.3 months. In cohort 3, 246 patients died within 1.3 months, leaving 596 patients for further analysis.

Baseline characteristics of cohorts 2 and 3

Baseline characteristics of cohorts 2 and 3 are presented in Table 1. Most patients with mUC were men, and the percentage of men was similar in both cohorts (cohort 2, 71%; cohort 3, 68%; $p = 0.134$). The mean age was 67.4 years in cohort 2 compared to 75.8 years in cohort 3; however, this difference was not significant ($p = 0.189$). Among patients in cohort 2 compared to cohort 3, the mean income was higher ($p < 0.0001$), more patients had

Table 1 Baseline characteristics of patients in cohorts 2 and 3

	Cohort 2 (received treatment)	**Cohort 3 (did not receive treatment)**	
	***n* = 1,141**	***n* = 596**	**P-value**
Time to initiation of 1 L therapy, mean (95th percentile), months			
From diagnosis,	8.33 (29.5)	-	
From diagnosis of advanced disease	1.29 (11.34)	-	
Sex, male, n (%)	813 (71)	404 (68)	0.134
Education, n (%)			
High school education	722 (63)	283 (47)	**< 0.01**
Income, mean (SD), €			
Gross income, mean (SD), €	37,699 (63,482)	28,244 (36,304)	**< 0.0001** (SMD**: 0.18)
Age, mean (SD), y	67.4 (8.6)	75.8 (9.1)	
< 60, n (%)	196 (17)	27 (5)	0.189
60–75, n (%)	757 (66)	231 (39)	(SMD**: 0.96)
> 75, n (%)	188 (16)	338 (57)	
Region of residence, n (%)			
Region North	94 (8)	69 (12)	**< 0.05**
Region Mid	251 (22)	126 (21)	
Region South	289 (25)	150 (25)	
Capital Region	324 (28)	139 (23)	
Region Zealand	183 (16)	112 (19)	
Marital status, n (%)			
Married	735 (64)	303 (51)	**< 0.0001**
Never married	108 (9)	56 (9)	
Divorced	177 (16)	83 (14)	
Widow/widower	117 (10)	154 (26)	
Registered partnership	< 5	NA	
Dissolved registered partnership	< 5	NA	
CCI, n (%) *			
0	485 (43)	147 (25)	**< 0.0001**
1–3	492 (43)	282 (47)	
> 3	164 (14)	167 (28)	
Unique persons with stage T4b, N2/3 or M1, n (%)	576	330	
T4b	89 (15)	67 (20)	**< 0.05**
N2/3	186 (32)	89 (27)	0.458
M1 (any of the variables indicating metastatic disease)	427 (74)	260 (79)	**< 0.05**
Prior cystectomy	311 (27)	NA	
Neoadjuvant chemotherapy prior to cystectomy	65 (6)	NA	
Location of primary tumour, n (%)			
Malignant neoplasm of renal pelvis (C65)	173 (15)	64 (11)	**< 0.01**
Malignant neoplasm of ureter (C66)	72 (6)	15 (3)	
Malignant neoplasm of bladder (C67)	877 (77)	509 (85)	
Malignant neoplasm of other and unspecified urinary organs (C68)	19 (2)	8 (1)	

* CCI score was estimated using registered diagnoses in the NPR for 10 years prior to UC diagnosis

1 L, first line; CCI, Charlson Comorbidity Index; NA, not available; NPR, National Patient Register; UC, urothelial carcinoma

** SMD: standardized mean difference

at least a high school education (63% vs. 47%; $p < 0.01$), and more patients were married (64% vs. 51%; $p < 0.0001$). In cohort 3, more patients lived in Region Zealand and Region North, with fewer patients living in the Capital Region ($p < 0.05$). Patients in cohort 2 compared to cohort 3 had fewer comorbidities ($p < 0.0001$) and relatively fewer tumours originating in the urinary bladder. Overall, differences in tumour location between the two cohorts were observed ($p < 0.01$). Finally, stage T4b and M1 tumours were found more frequently in cohort 3 than in cohort 2 ($p < 0.05$).

Factors associated with receipt of systemic anticancer treatment

The descriptive statistics and comparison of baseline characteristics (Table 1) suggested an association between socioeconomic factors and the receipt of systemic treatment. Table 2 presents the results of the LPM estimates. The socioeconomic factors included were region of residence (with the Capital Region used as reference), level of education, income, sex and marital status.

In the first analysis, only clinically relevant factors were included in the LPM, and the parameter estimates showed that increasing age, T4b and M1 stage, and the presence of comorbidities were associated with a lower probability of receiving systemic treatment. The probability of receiving systemic treatment was 1.9% lower for each year of increased age. Furthermore, compared with patients with a CCI score of 0, patients with a CCI score of > 3 had a 16.8% lower probability of receiving systemic treatment ($p < 0.0001$). In contrast, an initial diagnosis of UC originating in the ureter (*ICD-10* code C66) compared to the bladder (*ICD-10* code C67) was associated with a higher probability of receiving treatment (18.5%; $p = 0.0001$).

After adjusting for clinically relevant factors, the inclusion of all socioeconomic factors (multivariate association) showed that residence in Region Zealand or Region North was associated with a lower probability of receiving treatment compared with the Capital Region, while completing at least a high school education and being married were associated with a higher probability of receiving treatment. Specifically, residents in Region

Table 2 Regression estimates on different factors' association with receipt of systemic treatment*

	Association with clinical factors		Multivariate association	
	Estimate	*P-value*	*Estimate*	*P-value*
Region of residence				
Region Zealand			**−0.068**	**0.031**
Region South			−0.034	0.237
Region Mid			−0.014	0.651
Region North			**−0.128**	**0.001**
Capital Region			0	.
Education				
High school			**0.0914**	**< 0.0001**
Gross income, **€10,000**			0.0024	0.188
Female			0.019	0.407
Married			**0.099**	**< 0.0001**
Clinically relevant factors				
Age	**−0.019**	**< 0.0001**	**X**	
T4b	**−0.111**	**0.003**	**X**	
N2/3	0.002	0.940	**X**	
M1 (any of the variables indicating metastatic disease)	**−0.059**	**0.0074**	**X**	
Malignant neoplasm of renal pelvis (C65)	**0.082**	**0.008**	**X**	
Malignant neoplasm of ureter (C66)	**0.185**	**0.0001**	**X**	
Malignant neoplasm of bladder (C67)	.	.	**X**	
Malignant neoplasm of other and unspecified urinary organs (C68)	−0.064	0.4509		
CCI 1–3	**−0.047**	**0.034**	**X**	
CCI > 3	**−0.168**	**< 0.0001**	**X**	
CCI 0	.	.	**X**	

Xs indicate that the analysis also included adjustment for the clinically relevant factors. However, the parameter estimates for the clinically relevant factors are not presented

*Analysis of patients in cohort 2 ($n = 1141$) vs. patients in cohort 3 who were alive after 1.3 months from mUC diagnosis ($n = 596$)

CCI, Charlson Comorbidity Index

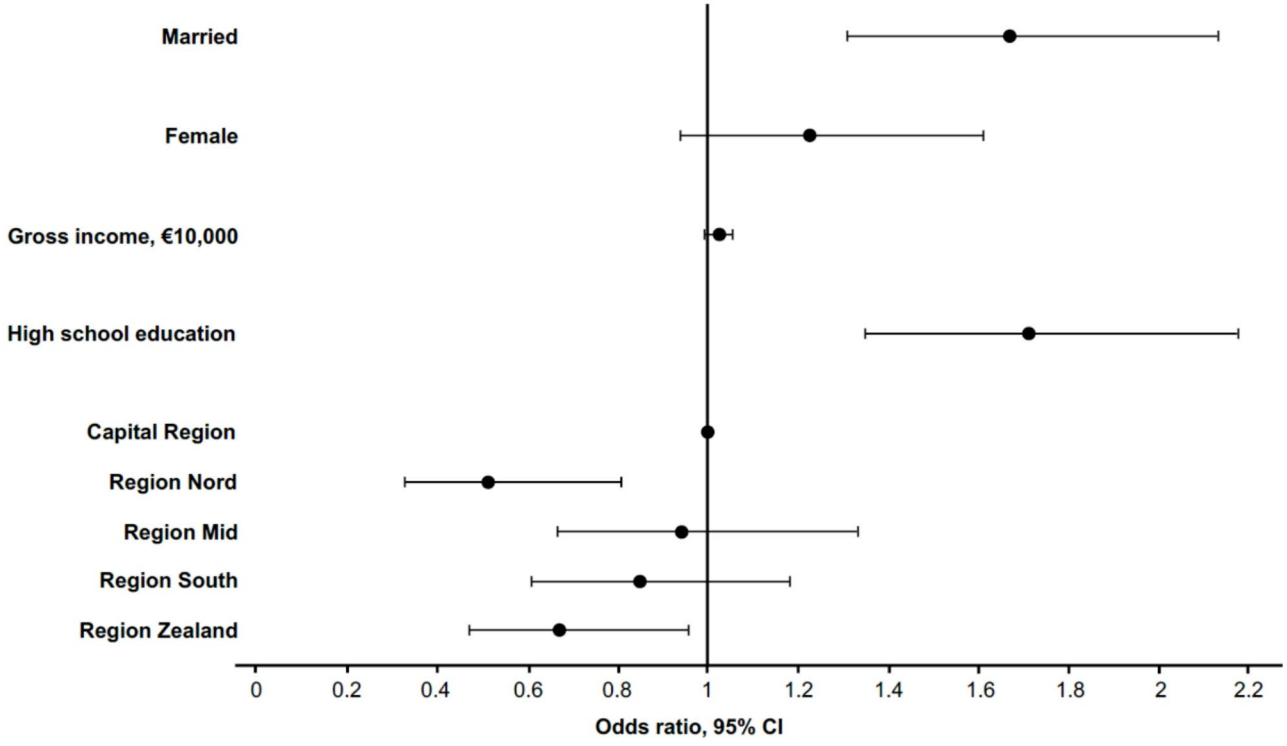

Fig. 2 Forest plot, logistic regression on socioeconomic factors' association with receipt of systemic treatment (cohort 2 vs. patients in cohort 3 who survived more than 1.3 months)

Zealand had a lower probability of receivng systemic treatment (6.8%; $p = 0.031$), as did residents in Region North (12.8%; $p = 0.001$) compared with residents in the Capital Region. Having at least a high school education and being married were associated with a higher probability of receiving treatment (9.14% and 9.9%, respectively; $p < 0.0001$). Level of income (analysis IV) and sex were not associated with a change in the probability of receiving systemic treatment ($p = 0.188$ and $p = 0.407$, respectively).

The multivariate associations presented in Table 2 are confirmed by the univariate associations presented in Supplementary Table 1 (columns II-VI), confirming that the results of the multivariate analysis are robust.

Analysis using a logistic regression model confirmed the results of the LPM (Fig. 2). That is, residence in two specific regions was associated with a lower probability of receiving treatment (odds ratio, < 1), while completion of at least high school and being married were associated with a higher probability of receiving treatment (odds ratio, > 1).

With few deviations, the baseline characteristics in the full cohort 3 ($n = 842$) were identical to those in the reduced cohort 3 ($n = 596$). In the comparison with cohort 2, the same significant differences were observed (Supplementary Table 2).

LPM analyses with the full cohort 3 ($n = 842$) led to the same conclusions as the original LPM analyses, with the exception that higher income was associated with a higher probability of receiving treatment (Supplementary Table 3). However, the parameter estimate (mean marginal effect) was relatively low (0.53% per €10,000 gross income increase; $p = 0.004$). Application of the logistic regression model confirmed the results of the LPM (Supplementary Fig. 1).

Discussion

In this study we identified 3,206 patients diagnosed with UC who, according to guidelines, were eligible for systemic treatment for advanced disease or in the neoadjuvant setting. Of these, 842 patients (26%) with mUC who did not receive any systemic treatment or surgery were identified. By comparing these patients with those who received systemic treatment ($n = 1,141$), we identified socioeconomic factors contributing to the probability of receiving systemic treatment for advanced disease. Specifically, when adjusting for clinical factors, we found that in addition to increasing age, residence in Region Zealand or Region North—two relatively rural regions—was associated with a lower probability of receiving treatment. In contrast, having completed at least high school and being married were associated with a higher probability of receiving systemic treatment. Of the 842 patients in the

untreated cohort, 246 (29%) died within 1.3 months after the diagnosis of mUC. It can be speculated that these patients were diagnosed very late with advanced disease.

As stated, the Danish healthcare system offers free and universal access to treatment and care, and cancer treatment is provided exclusively at public hospitals. Naturally, for patients living in remote areas and more rural regions the distance to hospitals may be longer implying a more resource- and time-consuming access to treatment and monitoring visits. However, compared to other countries the distances in Denmark are relatively short and to our knowledge no Danish studies have found distance to be a barrier to cancer treatment. Nevertheless, studies from other countries suggest that increased travel requirements may lead to inappropriate treatment [15].

This study does not establish a causal relationship. However, the findings of this study are not unexpected considering other research in the field. A systematic literature review by Wilke et al. presented at the ESMO Congress 2022 found clinical factors such as age, performance status and renal function to be associated with undertreatment [16]. At the same congress, Knott et al. [17] presented data based on patients identified in the National Cancer Registration Dataset. They concluded that approximately 70% of (mainly geriatric) patients with mUC were untreated and that patients who received systemic treatment were younger, healthier and less socioeconomically disadvantaged [17].

Socioeconomic differences in relation to survival have been examined in patients with other cancers. In a Danish study, Dalton et al. [2] estimated an increased relative 5-year survival rate in patients with cancer; however, the increase in survival was significantly greater in the high-income group than in the lowest-income group. Pruthi et al. [18] and Gore et al. [19] evaluated the impact of marital status (married versus unmarried) on outcomes in a US setting to understand the survival differences in patients undergoing cystectomy for bladder cancer. They concluded that marriage was associated with improved survival in patients with bladder cancer, most likely due to differences in cancer screening, risk behaviors, and access to medical care.

It could be hypothesised that differences in outcomes might be a result of inequalities in the timing of diagnosis or receipt of treatment. Researchers of other types of cancer have examined whether socioeconomic status has any relationship to patients' access to treatment. A systematic review and meta-analysis by Forrest et al. [20] examined access to lung cancer treatments based on patients' socioeconomic status. They primarily included UK- and US-based studies and found that patients living in more socioeconomically deprived circumstances were less likely to receive any type of treatment, surgery or chemotherapy.

In an international context, it is interesting that significant and measurable inequality in access to healthcare was found in a country like Denmark, which has universally free access to healthcare. This might indicate that these underlying mechanisms play a role in other healthcare systems as well. Importantly, our results do not provide reasons for not receiving treatment and thus it is impossible to evaluate whether the treatment decision is based purely on clinical reasons or if it also includes other rfactors. A Danish study on reasons for not receiving neoadjuvant chemotherapy treatment for muscle-invasive urothelial cancer suggests that patient refusal of treatment was a predominant reason among patients with no apparent contraindication [21]. A recent Danish single-centre cohort study at Rigshospitalet in Copenhagen involving 100 patients with metastatic or unresectable urothelial carcinoma who did not receive treatment found that the most prevalent reason for not receiving treatment was poor physical condition, followed by decreased renal function and patient preferences. Interestingly, only 41% of patients in this cohort had been evaluated at the Department of Oncology [22], indicating that the majority were not referred. The median overall survival in this cohort was 1.9 months, which aligns with our finding that many patients with unresectable/metastatic UC who do not receive systemic treatment have a short survival.

Study limitations

This population-based, retrospective study is based on exhaustive and comprehensive nationwide registers, including all patients diagnosed with mUC in Denmark between 2010 and 2017. This is a strength compared with other studies that do not include complete patient populations [17]. However, despite the assessed high quality of Danish registers [9, 10], missing data and misclassification do occur. Given the relatively large study population, however, data are assumed to be missing at random and are not believed to impact the results of the study.

In the analyses of factors associated with the receipt of systemic treatment, we applied an LPM and a logistic regression model framework. The latter is equivalent to the approach used by Knott et al. [17], but other approaches (e.g. the probit model) could have been included. Furthermore, the identification of factors associated with the receipt of systemic treatment was limited to analyses of the available data and variables.

Conclusions

We found that 26% of patients in our mUC cohort in Denmark did not receive any systemic anticancer treatment or radical surgery in the pre-immuno-oncology era from 2010 to 2017. A comparison of patients in Denmark who did or did not receive systemic treatment for

advanced disease showed that greater age and residence in two relatively rural regions were associated with a lower probability of treatment while having completed at least a high school education and being married were associated with a higher probability of treatment. In a country with free and universal access to healthcare, further research is needed to investigate the factors contributing to the decision not to provide systemic treatment to these patients.

Abbreviations

CCI	Charlson Comorbidity Index
ICD-10	*International Classification of Diseases, Tenth Revision*
LPM	linear probability model
mUC	metastatic urothelial carcinoma
NPR	National Patient Register
UC	urothelial carcinoma

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22467-z.

Supplementary Material 1

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Author contributions
MHP and JO retrieved the data and performed the analyses. All authors (DSH, MDH, MHP, JO, PN, MA, and JBJ) contributed to writing and proofreading the paper and can vouch for its completeness and accuracy.

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Data availability
The data that support the findings of this study are available from Statistics Denmark's Research Service. However, restrictions apply to the availability of these data, which were used under license/authorisation for the current study and so are not publicly available. Additional data analyses are available from the authors upon reasonable request and with permission of Statistics Denmark's Research Service.

Declarations

Ethics approval and consent to participate
The study was register based and complied with the regulations and instructions established by Statistics Denmark. We used only anonymised data and present data only in aggregate and anonymous form. We did not contact or require any active participation from study participants. Ethics committee approval and written informed consent are not required for register-based research, according to Danish law.

Consent for publication
Not applicable.

Competing interests
MHP and JO are employees of EY, a paid vendor to the alliance between Merck and Pfizer in the present study. DSH and MDH are employees of Pfizer Denmark. MA and JBJ were clinical consultants as part of the present study. PN is an employee of Merck A/S, Denmark, an affiliate of Merck KGaA.

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