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Review

Uncovering the epidemiology of bladder cancer in the Arab world: A review of risk factors, molecular mechanisms, and clinical features

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Abstract *Objective:* Bladder cancer (BC) is a significant public health concern in the Middle East and North Africa, but the epidemiology and clinicopathology of the disease and contributors to high mortality in this region remain poorly understood. The aim of this systematic review was to investigate the epidemiological features of BC in the Arab world and compare them to those in Western countries in order to improve the management of this disease.
Methods: An extensive electronic search of the PubMed/PMC and Cochrane Library databases was conducted to identify all articles published until May 2022, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. A total of 95 articles were included in the final analysis after title, abstract, and full-text screening, with additional data obtained from the GLOBOCAN and WHO 2020 databases.
Results: Most of the included articles were case-control studies examining the risk factors and molecular mechanisms of BC. These studies originated from 10 different countries, with Egypt being the most active contributor. While BC in the Arab world shares some common risk factors

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with Western countries, such as smoking and occupational exposure, it also exhibits unique features related to schistosomiasis. The high mortality rates in this region are alarming and can be attributed to various factors, including the prevalence of smoking, the impact of schistosomiasis, a combination of genetic and socioeconomic factors, treatment shortages, and limited access to care or inadequate assessment of the quality of care.

Conclusion: Despite the relatively low incidence of BC in Arab countries, the mortality rates are among the highest worldwide. BC tends to be more aggressive in the Arab world, making it essential to implement strategies to address this burden.

1. Introduction

According to the latest GLOBOCAN estimates, bladder cancer (BC) is the 10th most common cancer worldwide [1]. It is four times more common in men than in women and typically occurs in people over the age of 65 years, with 80% of cases diagnosed at this age or older [2,3]. BC ranks 13th in terms of global mortality [1], and the prognosis is worse for metastatic tumors, with a 5-year survival rate of less than 10% [4]. Common metastatic sites include the liver, lungs, bones, and adrenal glands [5].

BC is typically divided into two main types: urothelial carcinoma or transitional cell carcinoma (90%), which is associated with tobacco and environmental exposure, and squamous cell carcinoma (5%), which is often linked to *Schistosoma haematobium* (*S. haematobium*) [6,7]. Less common types include adenocarcinoma, sarcoma, and small cell carcinoma [5].

The treatment for BC depends on whether the tumor has invaded the muscle layer or not. Non-muscle-invasive BC (NMIBC) is usually well localized and can be removed through transurethral resection of the bladder (TURB) [8,9], while muscle-invasive BC (MIBC) is typically treated with radical cystectomy, radiation, and/or chemotherapy based on the patient's performance status and comorbidities [10–12].

The epidemiology of BC has been extensively studied in Western countries, but this is not the case in the Arab world. The latter consists of 22 states in Northern Africa and Western Asia [13]. Despite their differences, these countries can be considered a single epidemiological entity due to their geographical proximity, shared Arabic language, and scientific contributions [14]. BC risk factors vary by region, so the results of studies in Western countries may not necessarily be applicable to Arab countries [15–17]. There are also differences in epidemiological data between Arab countries due to variations in socioeconomic status.

This systematic review, the first of its kind, aims to collect data on the epidemiology and clinicopathology of BC in the Arab world and compare them to other regions in order to improve the management of this disease.

2. Material and methods

2.1. Search strategy and study selection

A comprehensive electronic search of the literature was conducted in the PubMed/PMC and Cochrane Library databases using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [18]. The MeSH term "Urinary Bladder Neoplasms" was combined with keywords related to the Arab world, including "Algeria", "Bahrain", "Comoros", "Djibouti", "Egypt", "Emirates", "Iraq", "Jordan", "Kuwait, "Lebanon", "Libya", "Mauritania", "Morocco", "Oman", "Palestine", "Qatar", "Saudi Arabia", "Somalia", "Sudan", "Syria", "Tunisia", "Yemen", "Arab", "East Mediterranean", and "Middle East and North Africa", to identify relevant articles.

A total of 162 articles were retrieved until May 2022, and three investigators screened the titles and abstracts, followed by full-text analysis. Of these, 95 papers met the inclusion criteria and were included in the final review. The selection process is summarized in the PRISMA diagram (Fig. 1).

English and French studies that focused on BC in the Arab world, provided original data on the epidemiological or clinicopathological characteristics of BC, were published in a peer-reviewed journal, and obtained informed consents from participants or had institutional review board approval (if applicable) were included in the review.

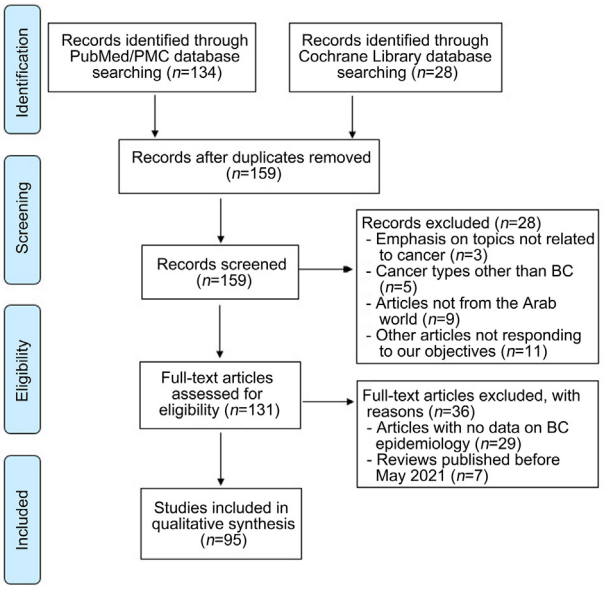

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart for the article selection process. BC, bladder cancer.

Studies that did not focus on BC or that focused on cancer types other than BC, or that were not conducted in the Arab world, were excluded.

2.2. Data extraction and quality assessment

Two independent reviewers used a standardized data extraction form and the Newcastle–Ottawa Scale to assess the quality of non-randomized studies. The Newcastle–Ottawa Scale has three domains (selection, comparability, and outcome) and a maximum score of 9, with higher scores indicating better quality.

2.3. Data sources and analysis

The characteristics of the selected studies, including study design, sample size, and main findings, were summarized in Table 1. The implications of biomarkers in BC were presented in Table 2. To illustrate the incidence and mortality of BC in Arab countries, data were extracted from the GLOBOCAN 2020 database [19] on the estimated age-standardized rates (ASRs) per 100 000 for both sexes and all ages, and represented graphically to visualize the distribution of BC in the region (Fig. 2). In addition, data about tobacco consumption in Arab countries were collected from the WHO Global Health Observatory Data Repository (Table 3). The WHO application [20] was utilized to assess the endemicity of schistosomiasis in the region, using "Status of schistosomiasis endemic countries" as the selected indicator (Table 4). Data on the distribution of Schistosoma species were also obtained from the WHO database [21] (Table S1).

Data were analyzed and synthesized using a narrative synthesis approach. The strengths and limitations of the included studies were also identified and discussed.

2.4. Ethical considerations

All included studies obtained informed consents from participants and/or had institutional review board approval, as appropriate.

2.5. Objectives and scope of the review

This systematic review aims to collect and analyze data on the epidemiology and clinicopathology of BC in the Arab world and compare them to other regions in order to improve the management of this disease. The objectives of the review are: (1) to describe the epidemiology of BC in the Arab world, including incidence, prevalence, and mortality; (2) to identify and summarize the risk factors for BC in the Arab world; (3) to investigate the genetic susceptibility and molecular mechanisms of BC in the Arab world; (4) to describe the clinicopathological characteristics of BC in the Arab world, including histological subtypes, stages at diagnosis, and tumor grades; (5) to compare the epidemiology and clinicopathology of BC in the Arab world to other regions.

3. Results

A total of 95 studies on BC in the Arab world were included in the analysis, most of which were case-control studies examining risk factors and molecular mechanisms. The majority of these studies were conducted in Egypt ($n=63$), followed by Tunisia ($n=13$), Saudi Arabia ($n=6$), Lebanon ($n=4$), Jordan ($n=3$), Iraq ($n=2$), and smaller contributions from Palestine, Kuwait, Morocco, and Libya ($n=1$ each). The distribution of these studies by country is illustrated in the Supplementary Figure S1.

3.1. Incidence and mortality in the Arab world

BC is a major health issue in the Arab world. Fig. 2 illustrates the variations in BC incidence and mortality rates across Arab countries, using ASRs per 100 000 population, based on the latest data from the GLOBOCAN 2020 database [19].

3.2. Risk factors

The contribution of many factors to BC risk has been widely studied. Those factors can be categorized into modifiable and non-modifiable.

3.2.1. Modifiable risk factors

BC risk factors reported with sufficient or limited evidence by the International Agency for Research on Cancer (IARC) in the latest version [22] are illustrated in the Supplementary Table S2.

The factors associated with BC in Arab studies are illustrated below.

3.2.1.1. Tobacco smoking. Several modifiable risk factors have been identified in the Arab world. Among them, tobacco smoking has consistently shown a significant impact on BC development. For example, Zheng et al. [23] found a 1.8-time higher transitional cell carcinoma (TCC) risk among ever-smoking Egyptian males, and Makhyoun [24] reported a higher frequency of moderate or heavy smoking in BC cases (79.3% *vs.* 45.9%, $p<0.001$).

3.2.1.2. Occupational exposure. Occupational exposure to certain substances has been linked to an increased risk of BC. Farming and pesticide exposure were found to be associated with an elevated risk of BC, particularly among non-smoking Egyptian males (odds ratio [OR] 5.62; 95% confidence interval [CI] 3.75–8.36) [25].

3.2.1.3. Environmental exposure. Exposure to specific metals has also shown an association with BC. Studies conducted in Tunisia demonstrated significantly higher blood concentrations of arsenic in BC cases compared to controls ($p<0.001$), particularly among smokers [26,27].

3.2.1.4. Infections. A notable infection associated with BC development in the Arab world is *S. haematobium*. Older

Table 1 Epidemiological data about bladder cancer in North Africa and Western Asia.

Study	Country	Sample size, *n*	Age, mean, year	M:F, ratio	Smoking[a]	Bilharziasis[a]	Histological type[a]			TNM staging[a]						WHO grade[a,b]				
							TCC	SCC	Others	Ta-T1	T2	T3	T4	N^+	M1	I	II	III	LG	HG
El-Boulkany et al., 1972 [65]	Egypt	304	46.3	4.0:1	NA	NA	54 (23.4)[c]	152 (66.7)[c]	23 (9.9)[c]	NA	37 (27.4)[c]	96 (71.1)[c]	2 (1.5)[c]	34 (14.8)[c]	29 (12.8)[c]	79 (34.6)[c]	89 (38.7)[c]	61 (26.5)[c]	NA	NA
Zaghloul et al., 1992 [110]	Egypt	236	48.1	4.7:1	NA	236 (100)	49 (21.0)[c]	158 (67.5)[c]	27 (11.5)[c]	0 (0)	0 (0)	236 (100)	0 (0)	55 (23.3)	NA	62 (26.3)	86 (36.4)	88 (37.3)	NA	NA
Attallah et al., 1996 [111]	Egypt	118	NA	NA	NA	NA	33 (28.0)	71 (60.2)	14 (11.8)	NA	NA	NA	NA	NA	NA	18 (37.5)[c]	22 (45.8)[c]	8 (16.7)[c]	NA	NA
Tamimi et al., 1996 [63]	Egypt	45	NA	NA	NA	45 (100)	20 (44.4)	20 (44.4)	5 (0.1)	6 (13.3)	39 (86.7)[d]			NA	NA	12 (26.7)	25 (55.6)	8 (17.7)	NA	NA
Ali-el-Dein et al., 1997 [112]	Egypt	253	NA	4.4:1	NA	95 (37.5)	253 (100)	NA	NA	253 (100)	0 (0)	0 (0)	0 (0)	NA	NA	39 (15.4)	179 (70.8)	35 (13.8)	NA	NA
Shaw et al., 1999 [59]	Egypt	66	NA	NA	NA	66 (100)	13 (19.7)	44 (66.7)	9 (13.6)	9 (13.6)	57 (86.4)[d]			NA	NA	NA	NA	NA	NA	NA
Aly and Khaled, 1999 [60]	Egypt	31	56.0	2.8:1	NA	17 (70.8)[c]	13 (41.9)	17 (54.8)	1 (3.2)	0 (0)	1 (3.4)[c]	25 (86.2)[c]	3 (10.3)[c]	7 (25.0)[c]	NA	NA	NA	NA	NA	NA
Khaled et al., 2000 [61]	Egypt	25	60.0	2.1:1	NA	14 (70.0)[c]	9 (36.0)	16 (64.0)	0 (0)	0 (0)	1 (4.3)[c]	19 (82.6)[c]	3 (13.0)[c]	4 (18.2)[c]	NA	2 (8.0)	17 (6.0)	6 (24.0)	NA	NA
Aly and Khaled, 2002 [62]	Egypt	35	56.0	3.4:1	NA	11 (34.4)[c]	24 (68.6)	11 (31.4)	0 (0)	24 (70.6)[c]	10 (29.4)[c]	0 (0)	0 (0)	NA	NA	11 (31.4)	21 (60.0)	3 (8.6)	NA	NA
Khaled et al., 2003 [113]	Egypt	99	55.0	2.6:1	NA	77 (81.9)[c]	41 (44.6)[c]	49 (53.2)[c]	2 (2.2)[c]	1 (1.0)	2 (2.0)	96 (97.0)	0 (0)	13 (13.7)[c]	NA	12 (12.1)	62 (62.6)	25 (25.3)	NA	NA
Ali-El-Dein et al., 2003 [114]	Egypt	533	55.4	3.6:1	NA	NA	533 (100)	0 (0)	0 (0)	533 (100)	0 (0)	0 (0)	0 (0)	NA	NA	80 (15.0)	342 (64.2)	111 (20.8)	NA	NA
Aly and Khaled, 2004 [90]	Egypt	40	51.0	3.0:1	NA	29 (78.4)[c]	16 (40.0)	21 (52.5)	3 (7.5)	1 (2.7)[c]	5 (13.5)[c]	31 (83.8)[c]	NA	12 (34.3)[c]	NA	5 (12.8)[c]	21 (53.9)[c]	13 (33.3)[c]	NA	NA
Khaled et al., 2005 [79]	Egypt	180	NA	3.6:1	NA	129 (79.7)[c]	70 (38.9)	96 (53.3)	14 (7.8)	2 (1.2)[c]	10 (5.8)[c]	141 (81.5)[c]	20 (11.5)[c]	28 (16.6)[c]	NA	20 (11.1)	110 (61.1)	50 (27.8)	NA	NA
Helal et al., 2006 [80]	Egypt	114	50.8	8.5:1	NA	64 (56.1)	67 (58.8)	32 (28.0)	15 (13.2)	20 (17.5)	94 (82.5)[d]			NA	NA	NA	NA	NA	NA	NA
Khafagy et al., 2006 [115]	Egypt	60	50.5	11.0:1	NA	38 (63.3)	18 (30.0)	35 (58.3)	7 (11.7)	2 (3.3)	3 (5.0)	29 (48.3)	26 (43.4)	8 (13.3)	2 (3.3)	4 (6.7)	47 (78.3)	9 (15.0)	NA	NA
Badawi et al., 2008 [116]	Egypt	36	NA	NA	NA	NA	25 (69.4)	4 (11.1)	7 (19.4)	22 (61.1)	14 (38.9)[e]		NA	NA	NA	NA	NA	NA	27 (75.0)	9 (25.0)
Zarzour et al., 2008 [35]	Egypt	130	58.3	5.2:1	104 (80.0)	114 (87.7)	20 (15.4)	88 (67.6)	22 (17.0)	0 (0)	NA (56.3)[c]	NA (10.9)[c]	NA (32.8)[c]	NA (13.3)[c]	NA	NA	NA	NA	NA	NA
Osman et al., 2009 [117]	Egypt	60	57.2	2.2:1	NA	NA	14 (23.3)	37 (61.7)	9 (15.0)	37 (61.7)[f]		19 (31.7)	4 (6.6)	8 (13.3)	NA	13 (21.7)	10 (16.7)	37 (61.6)	NA	NA
Mahmoud et al., 2010 [89]	Egypt	51	NA	3.6:1	29 (56.9)	25 (49.0)	39 (76.5)	11 (21.6)	1 (1.9)	17 (33.3)	34 (66.7)[d]			NA	NA	NA	NA	NA	25 (49.0)	26 (51.0)
Zaghloul et al., 2010 [118]	Egypt	40	54.0	3.4:1	NA	NA	25 (62.5)	14 (35.0)	1 (2.5)	NA	NA	NA	NA	NA	40 (100)	NA	NA	NA	NA	NA
Goerlitz et al., 2011 [119]	Egypt	625	NA	4.1:1	383 (76.1)[c]	306 (52.7)[c]	389 (62.2)	236 (37.8)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Salem and Mahfouz, 2012 [30]	Egypt	1932	46.3	4.9:1	NA (56.5)	NA (65.6)	NA (42.1)	NA (49.9)	NA (8.0)	NA (3.0)	NA (17.4)	NA (72.6)	NA (7.0)	NA (36.4)	NA	NA	NA	NA	NA (31.9)	NA (68.1)
Salama et al., 2012 [87]	Egypt	65	NA	NA	NA	NA	32 (49.2)	29 (44.6)	4 (6.2)	11 (16.9)	10 (15.4)	38 (58.5)	6 (9.2)	9 (13.9)	NA	15 (23.1)	24 (36.9)	26 (40.0)	NA	NA
Shams et al., 2013 [64]	Egypt	120	49.6	4.0:1	NA	84 (70.0)	NA	120 (100)	NA	4 (3.3)	74 (61.7)	26 (21.7)	16 (13.3)	44 (36.7)	8 (6.7)	6 (5.0)	62 (51.7)	52 (43.3)	NA	NA
El-Monim et al., 2013 [120]	Egypt	100	54.9	2.3:1	NA	NA	51 (51.0)	46 (46.0)	3 (3.0)	0 (0)	11 (11.0)	85 (85.0)	4 (4.0)	14 (17.1)[c]	NA	NA	NA	NA	83 (83.0)	17 (17.0)

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Table 1 (*continued*)

Study	Country	Sample size, *n*	Age, mean, year	M:F, ratio	Smoking[a]	Bilharziasis[a]	Histological type[a]			TNM staging[a]						WHO grade[a,b]				
							TCC	SCC	Others	Ta-T1	T2	T3	T4	N^+	M1	I	II	III	LG	HG
El-Sharkawi et al., 2014 [74]	Egypt	70	61.3	2.9:1	NA	36 (51.4)	NA	NA	NA	33 (47.1)[f]		37 (52.9)[g]		NA	NA	NA	NA	NA	NA	NA
Harraz et al., 2014 [121]	Egypt	102	52.9	5.4:1	NA	NA	62 (60.8)	25 (24.5)	15 (14.7)	17 (16.7)	49 (48.1)	34 (33.3)	2 (2.0)	15 (14.7)	NA	NA	NA	NA	NA	NA
Khaled et al., 2014 [122]	Egypt	114	55.3	3.6:1	NA	NA	50 (43.9)	59 (51.7)	5 (4.4)	0 (0)	2 (1.8)	82 (71.9)	30 (26.3)	11 (9.6)	NA	18 (16.1)[c]	65 (58.0)[c]	29 (25.9)[c]	NA	NA
Haggag et al., 2014 [123]	Egypt	120	61.0	3.3:1	NA	NA	87 (72.5)	28 (23.3)	5 (4.2)	NA	NA	NA	NA	21 (17.5)	45 (37.5)	NA	NA	NA	NA	NA
Wang et al., 2015 [57]	Egypt	224	61.3	6.5:1	175 (78.1)	NA	224 (100)	0 (0)	0 (0)	53 (31.4)[c]	116 (68.6)[c,d]			NA	NA	NA	NA	NA	NA	NA
Spradling et al., 2016 [78]	Egypt	879	54.0	3.7:1	NA	557 (63.4)	519 (59.0)	360 (41.0)	0 (0)	137 (15.6)	337 (38.3)	336 (38.2)	69 (7.8)	288 (32.8)	137 (15.6)	NA	NA	NA	225 (25.6)	654 (74.4)
Martin et al., 2018 [95]	Egypt	1238	54.0	3.7:1	NA	802 (64.8)	751 (60.7)	398 (32.1)	89 (7.2)	175 (14.1)	480 (38.8)	469 (37.9)	114 (9.2)	341 (27.6)	NA	NA	NA	NA	272 (22.0)[c]	848 (68.0)[c]
Owyong et al., 2019 [82]	Egypt	151	51.8	1.8:1	NA	122 (80.8)	0 (0)	151 (100)	0 (0)	10 (6.6)	75 (49.7)	57 (37.7)	9 (6.0)	46 (30.5)	NA	NA	NA	NA	80 (53.0)	71 (47.0)
Harraz et al., 2019 [124]	Egypt	74	61.8	9.6:1	47 (63.5)	NA	74 (100)	0 (0)	0 (0)	48 (64.8)	7 (9.5)	19 (25.7)	0 (0)	1 (16.7)[c]	NA	NA	NA	NA	NA	NA
Al-Sharaky et al., 2020 [92]	Egypt	80	62.0	9.0:1	NA	26 (32.5)	72 (90.0)	5 (6.2)	3 (3.7)	NA	NA	NA	NA	25 (50.0)[c]	NA	NA	NA	NA	18 (22.5)	62 (77.5)
Esawy et al., 2020 [88]	Egypt	75	63.0	5.3:1	NA	NA	NA	NA	NA	34 (45.3)	16 (21.4)	7 (9.3)	18 (24.0)	NA	NA	16 (21.3)	42 (56.0)	17 (22.7)	NA	NA
Ben Selma et al., 2010 [125]	Tunisia	125	70.0	6.8:1	75 (60.0)	NA	119 (95.2)	5 (4.0)	1 (0.8)	70 (58.8)[c]	28 (23.5)[c]	17 (14.3)[c]	4 (3.4)[c]	NA	NA	37 (31.1)[c]	49 (41.2)[c]	33 (27.7)[c]	NA	NA
Rouissi et al., 2011 [44]	Tunisia	193	65.2	10.4:1	154 (79.8)	NA	193 (100)	0 (0)	0 (0)	149 (77.2)	44 (22.8)[d]			NA	NA	NA	NA	NA	NA	NA
Ben Wafi et al., 2018 [52]	Tunisia	218	64.8	5.6:1	176 (80.7)	NA	218 (100)	0 (0)	0 (0)	146 (67.0)	72 (33.0)[d]			NA	NA	76 (34.9)	73 (33.5)	69 (31.6)	NA	NA
Hadami et al., 2018 [126]	Morocco	30	65.0	6.5:1	NA	NA	NA	NA	NA	22 (73.3)	8 (26.7)	0 (0)	0 (0)	NA	NA	NA	NA	NA	12 (40.0)	18 (60.0)
Saheb Sharif-Askari et al., 2018 [68]	Libya	835	63.7	8.8:1	594 (71.1)	NA	730 (87.4)	74 (8.9)	31 (3.7)	NA	NA	NA	NA	NA	NA	NA	NA	NA	696 (83.4)	139 (16.6)
Nedjadi et al., 2016 [91]	Saudi Arabia	160	60.0	4.9:1	NA	NA	160 (100)	0 (0)	0 (0)	NA	NA	NA	NA	18 (17.3)[c]	17 (17.0)[c]	NA	NA	NA	68 (44.4)[c]	85 (55.6)[c]
El-Siddig et al., 2017 [66]	Saudi Arabia	116	62.4	4.8:1	NA	NA	111 (95.7)	2 (1.7)	3 (2.6)	78 (70.5)[c]	33 (29.5)[c,d]			NA	NA	NA	NA	NA	72 (65.0)[c]	39 (35.0)[c]
Mokhtar et al., 2017 [77]	Saudi Arabia	328	58.0	4.5:1	NA	80 (24.4)	235 (71.7)	79 (24.1)	14 (4.2)	29 (8.8)	91 (27.7)	159 (48.5)	49 (14.9)	82 (25.0)	NA	NA	NA	NA	11 (2.3)	317 (96.7)
Al-Maghrabi et al., 2019 [83]	Saudi Arabia	123	65.0	4.9:1	NA	NA	123 (100)	0 (0)	0 (0)	46 (37.4)	47 (38.2)	17 (13.8)	13 (10.6)	25 (20.3)	13 (10.6)	NA	NA	NA	31 (25.2)	92 (74.8)
Al-Maghrabi, 2019 [85]	Saudi Arabia	122	65.0	4.8:1	NA	NA	122 (100)	0 (0)	0 (0)	59 (48.4)	44 (36.1)	8 (6.6)	11 (9.0)	24 (19.7)	13 (10.7)	NA	NA	NA	32 (26.2)	90 (73.8)
Alghafees et al., 2022 [67]	Saudi Arabia	3750	62.3	4.6:1	NA	NA	3371 (89.9)	208 (5.5)	171 (4.6)	NA	NA	NA	NA	185 (4.9)	448 (11.9)	406 (13.1)[c]	796 (25.7)[c]	1898 (61.2)[c]	NA	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Sample size, *n*	Age, mean, year	M:F, ratio	Smoking[a]	Bilharziasis[a]	Histological type[a]			TNM staging[a]				WHO grade[a,b]				
							TCC	SCC	Others	Ta-T1	T2	T3	T4	N^+	M1	I	II	III	LG	HG
Kobeissi et al., 2013 [50]	Lebanon	54	67.1	All males	NA	NA	50 (94.3)[c]	NA	1 (1.9)[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA	26 (51.0)[c]	25 (49.0)[c]
Labban et al., 2021 [93]	Lebanon	37	72.1	6.4:1	16 (66.7)[c]	NA	37 (100)	0 (0)	0 (0)	0 (0)	13 (48.1)[c]	14 (51.9)[c,g]		25 (67.6)	31 (83.8)	NA	NA	NA	NA	NA
Matalka et al., 2008 [105]	Jordan	110	60.6	9.0:1	NA	NA	110 (100)	0 (0)	0 (0)	79 (71.8)	22 (20.0)	8 (7.3)	1 (0.9)	NA	2 (1.8)	NA	NA	NA	66 (60.0)	44 (40.0)
Bodoor et al., 2010 [94]	Jordan	121	63.0	7.1:1	92 (76.0)	NA	121 (100)	0 (0)	0 (0)	93 (76.9)	24 (19.8)	4 (3.3)	NA	NA	NA	54 (44.6)	32 (26.4)	35 (28.9)	NA	NA
Bani-Hani et al., 2022 [127]	Jordan	119	61.1	12.2:1	99 (83.2)	NA	119 (100)	0 (0)	0 (0)	119 (100)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA	77 (64.7)	42 (35.3)
Al-Abbasi et al., 2009 [53]	Iraq	54	65.5	3.2:1	NA	NA	54 (100)	0 (0)	0 (0)	18 (33.3)	9 (16.7)	12 (22.2)	15 (27.8)	NA	NA	11 (20.4)	23 (42.6)	20 (37.0)	NA	NA
Avitan et al., 2017 [97]	Palestine	68	62.6	5.8:1	NA	NA	63 (92.6)	NA	NA	51 (75.0)	17 (25.0)[d]			NA	5 (7.4)	NA	NA	NA	27 (39.7)	41 (60.3)

HG, high grade; LG, low grade; M:F, male-to-female; N^+, positive lymph node involvement (N1–N3); NA, not available; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma; TNM, tumor, node, and metastasis.

[a] Values are presented as *n* (%).

[b] The classification of bladder tumors into grades I–III or into categories of HG and LG was based on the 1973 and 2004/2016 WHO grading systems [129].

[c] The corresponding variables were not assessed for the entire samples due to missing data.

[d] The value represents combined categories for T2, T3, and T4.

[e] The value represents combined categories for T2 and T3.

[f] The value represents combined categories for Ta-T1 and T2.

[g] The value represents combined categories for T3 and T4.

Egyptian data indicated that *S. haematobium* infection is an important risk factor for squamous cell carcinoma (SCC) [28–30]. The association between urinary schistosomiasis (bilharziasis) and BC was stronger in cases infected at a younger age [31].

3.2.2. Non-modifiable risk factors

3.2.2.1. Demographic factors. Various studies highlighted age and gender as significant demographic risk factors for BC. The incidence of BC tends to rise with increasing age [32].

Furthermore, BC shows a higher prevalence in males compared to females. Two studies examined BC in women. Low estrogen exposure (early menopause or late pregnancy) significantly increased BC risk, while oral contraceptives decreased risk [33]. Among married Egyptian women, non-occupational exposure to agricultural work also elevated BC risk [34].

3.2.2.2. Family history and consanguinity. Zarzour et al. [35] found that family history of BC and parents' consanguinity played a significant role in BC development in Egypt ($p<0.001$).

3.2.2.3. Molecular mechanisms and genetics. The influence of the various risk factors is modulated by genetic susceptibility.

3.2.2.3.1. CYP1A1, NQO1, and SOD2 polymorphisms, and K-ras mutations. The TT genotype of *CYP1A1* was associated with a higher risk of tobacco-related BC ($p<0.0001$) [36]. The same was true for the TT genotype of *SOD2* (OR 4.41; 95% CI 1.86–10.42), while the CC genotype increased the risk associated with *S. haematobium* infection (OR 3.59; 95% CI 2.21–5.84) [37].

A combination of low *NQO1* (TT or TC) and high *SOD2* (CC or TC) was associated with a higher risk of pesticide-related BC [38]. *K-ras* mutations were also strongly correlated with pesticide exposure, and they were associated with higher acetylcholinesterase levels ($p<0.001$) [39].

3.2.2.3.2. NAT, GST, MTR, and MTHFR polymorphisms. BC risk related to *NAT2* slow acetylator genotype (especially *NAT2**5) was highlighted in several articles [40–42]. An Egyptian study identified the *NAT2**5/*5 genotype as a potential risk factor for bilharzial BC (BBC) ($p=0.026$) [41].

In Tunisia, *NAT2**5/*7 was associated with a seven-fold increase in BC risk (OR 7.14; 95% CI 1.30–51.40) [42]. Slow *NAT2* variants further increased tobacco-related BC when combined with *GSTT1* wild-type ($p=0.001$), *GSTM1* null-genotype ($p=0.0002$), *XPC*(CC) ($p=0.0001$), or *XPG*(CC) ($p=0.001$); and there was a strong cumulative effect when all these factors were combined (OR 61; 95% CI 5.25–1711.89) [43–46]. The same was found when slow *NAT2* was combined with *MTR* 2756*G ($p=0.0008$), or *MTHFR* 667*T alleles ($p=0.0003$) [47,48] by disrupting folate metabolism. Additionally, *RFC* mRNA expression was significantly higher in bladder tumors ($p<0.0001$), particularly the urothelial type [49].

Among the Lebanese population, the *NAT1**14A genotype increased BC risk, while *NAT1**10 reduced the risk ($p<0.001$) [50].

3.2.2.3.3. COMT and VEGF. *COMT* genotypes encoding for low- (Met/Met) or intermediate- (Val/Met) activity

Table 2 Biomarkers and genes found in BC and their potential clinical utility.

Study	Country	BC type	Biomarker and gene	Finding
Abul-Fadl and Metwalli, 1963 [69]	Egypt	BBC	Urinary β-glucuronidase; urinary acid phosphatase	• Increased in BC -5 folds (urinary β-glucuronidase) • Decreased in BC -10% (urinary acid phosphatase)
Khalafallah and Abul-Fadl, 1964 [70]	Egypt	BBC	Tryptophan metabolites: 3-hydroxyanthranilic acid, anthranilic acid, kynurenic acid, and xanthurenic acid	• Increased in BC -8 folds (3-hydroxyanthranilic acid) -6 folds (anthranilic acid) • Decreased in BC -50% (kynurenic acid) -50% (xanthurenic acid)
El-Sewedy et al., 1978 [72]	Egypt	BBC	Urinary α-esterases	• Increased in BC ($p<0.001$); diagnostic accuracy of 95.9%
Tricker et al., 1989 [71]	Egypt	BBC	Urinary nitrate, nitrite, and N-nitroso-compounds	• Increased in BC
El-Sharkawi et al., 2014 [74]	Egypt	NA	Urinary MMP-3 and urinary MMP-9	• Increased in BC - early and late stage (urinary MMP-3) - late stage only (urinary MMP-9) • Diagnostic accuracy of about 94% (excluding early-stage MMP-9)
Salama et al., 2012 [87]	Egypt	NA	NMP22, E-cadherin, cathepsin D	• Increased in BC • Correlated to recurrence (NMP22 and E-cadherin)
Kapila et al., 2008 [75]	Kuwait	NA	NMP22 (with urine cytology)	• Increased sensitivity (to 96%) but decreased specificity (to 30%)
Ismail et al., 2016 [76]	Egypt	NA	*mRNA-S100A* genes (with urine cytology)	• Increased sensitivity (to 87%–96%)
Esawy et al., 2020 [88]	Egypt	NA	Serum irisin	• Decreased in BC ($p<0.001$); negative correlation with mortality and stage ($p<0.001$)
Mahmoud et al., 2010 [89]	Egypt	NA	Serum interleukin-8	• Increased in BC ($p<0.0001$); sensitivity 71%, specificity 98% for a cut-off of 35 pg/mL; invasiveness ($p<0.01$)
Warren et al., 1995 [54]	Egypt	BBC	*p53* mutation	• Increased CpG dinucleotide transitions
Osman et al., 1997 [81]	Egypt	BBC	*p53* mutation	• Invasiveness, LNI ($p<0.04$)
Khaled et al., 2003 [113]	Egypt	BBC	*p53* mutation	• High stage and grade ($p<0.0001$)
Helal et al., 2006 [80]	Egypt	BBC	*p53* mutation	• High grade ($p=0.03$)
Owyong et al., 2019 [82]	Egypt	SCC	*PD-L1* negative	• High stage ($p=0.04$) and grade ($p=0.01$), LNI ($p<0.01$), and recurrence ($p=0.03$)
Moussa et al., 2009 [84]	Egypt	NA	*COX2*	• Increased in BC
Al-Maghrabi et al., 2019 [83]	Saudi Arabia	TCC	*COX2*	• High grade ($p<0.001$) and LNI ($p=0.011$)
Al-Maghrabi, 2019 [85]	Saudi Arabia	TCC	*SIRT1*	• Local recurrence and poor survival
Aboushousha et al., 2020 [86]	Egypt	TCC	*STAT3*	• High grade and muscle-invasiveness
Aly and Khaled, 2004 [90]	Egypt	BBC	*HER2*	• High grade ($p=0.01$)
Nedjadi et al., 2016 [91]	Saudi Arabia	TCC	*HER2*	• High stage ($p=0.002$) and LNI ($p<0.04$)
Al-Sharaky et al., 2020 [92]	Egypt	NA	*ROC1*, *P21*, and *CAIX*	• Invasiveness and high grade

Table 2 (*continued*)

Study	Country	BC type	Biomarker and gene	Finding
Labban et al., 2021 [93]	Lebanon	NA	Coexpression of *GATA3* and cytokeratin 5/6 or 14	• Reduced progression-free survival compared to *GATA3* alone
Bodoor et al., 2010 [94]	Jordan	NA	*FGF23*	• Good prognosis, low stage and grade

BC, bladder cancer; BBC, bilharzial BC; *CAIX*, carbonic anhydrase IX; *COX2*, cyclooxygenase 2; *FGF23*, fibroblast growth factor 23; *GATA3*, GATA binding protein 3; *HER2*, human epidermal growth factor receptor 2; LNI, lymph node involvement; MMP, matrix metalloproteinase; NA, not available; NMP22, nuclear matrix protein 22; *PD-L1*, programmed death-ligand 1; *ROC1*, regulator of cullins 1; SCC, squamous cell carcinoma; *SIRT1*, sirtuin 1; *STAT3*, signal transducer and activator of transcription 3; TCC, transitional cell carcinoma.

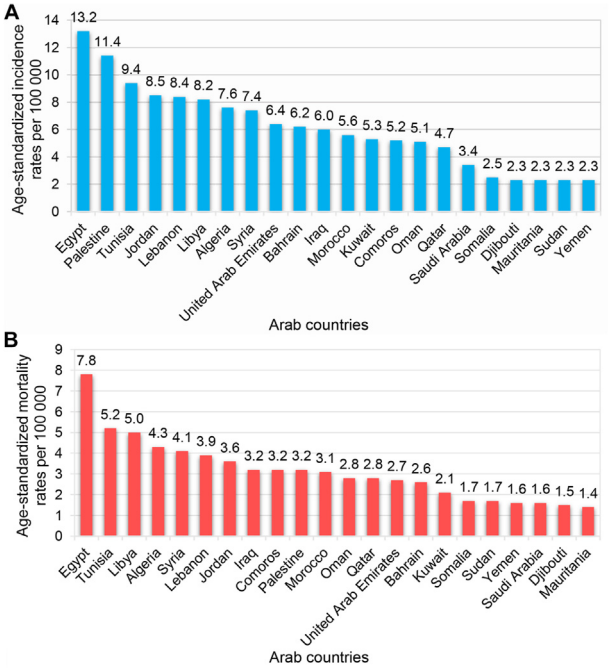

Figure 2 Estimated age-standardized rates per 100 000 of bladder cancer in the Arab world, in 2020, for both sexes and all ages. (A) Incidence; (B) Mortality. Data obtained from GLOBOCAN 2020 [19].

enzymes were associated with lower incidence of SCC among men only (OR 0.57; 95% CI 0.34–0.96) [51].

Similarly, for *VEGF* variants, the A allele of −2578C/A was associated with a lower BC risk ($p=0.002$), and the C_{-2578}-I_{-2549}-C_{+936} haplotype seemed to be an important risk factor for TCC ($p=0.005$), in Tunisian population [52]. Al-Abbasi et al. [53] found an overexpression of *VEGF* in TCC (77.77% of cases, $p<0.05$).

3.2.2.3.4. Other genetic findings and chromosomal aberrations. Patients with BBC presented more transitions at CpG dinucleotides ($p=0.003$) [54] and more CpG island hypermethylation in several genes ($p=0.027$) [55].

The frequency of micronuclei in exfoliated oral cells correlated to a higher BC risk in Tunisia ($p<0.001$) [56]. Long heterogeneous telomere and chromosomal aberrations in blood lymphocytes also increased BC risk [57,58]. Loss of heterozygosity in BBC was much more frequent in 9p (65%; presence of *CDKN2* gene) and 17p (58%; presence of *p53* gene). 9q loss of heterozygosity was less critical in BBC (39%) [59]. Chromosome 9 deletion was highly reported, followed by chromosome 17 [60]. Also, loss of chromosome Y strongly correlated with schistosomiasis ($p=0.007$) [61,62]. *P16* alterations correlated with BBC and were found in 53% of cases [63].

c-KIT overexpression was seen in 78.3% of SCC with a strong positivity in schistosomiasis ($p<0.0001$) [64].

3.3. Clinical presentation and diagnosis

3.3.1. Clinicopathologic features

Epidemiological data about BC age distribution, sex composition, risk factors, types, stages, and grades were gathered from the different studies, and presented in Table 1. The articles were classified by country (from the most to the least contributing) and by year of publication (from the oldest to the most recent), in North Africa and Western Asia, respectively. Articles that did not have sufficient data were removed.

El-Boulkany et al. [65] described the clinicopathological characteristics of BBC in Egypt in 1972. The mean age was 46.3 years; the male-to-female ratio was 4.0:1; 66.7% were SCC; and MIBC was more common. The tumors were predominantly nodular fungating (68.5%), mainly located in the posterior wall (44.6%), and only 8.8% were multicentric. The chief complaint was burning micturition (65.1%) rather than hematuria (47.9%) [35,65].

In recent Saudi studies, most tumors had a papillary configuration (64.9%) [66]; 85.6% of tumors were multifocal; and unifocal lesions were more frequently located in the lateral wall (6.2%) than in the posterior wall (2.7%). The male-to-female ratio was 4.6:1, but the mean survival rate was higher among men (5.49 years *vs.* 4.99 years, $p<0.001$) [67].

In Libya, lesions were most commonly located in the lateral wall (62.5%) [68].

3.3.2. Diagnostic markers

Various biomarkers discussed in this research were collected in Table 2.

Abul-Fadl and Metwalli [69] studied the impact of several enzymes on BC risk and found that urinary β-glucuronidase increased with schistosomiasis (2 folds) and even more with BC (5 folds). Meanwhile, urinary acid phosphatase decreased with schistosomiasis and decreased even more with BC (1/10).

Khalafallah and Abul-Fadl [70] conducted a study on the urinary excretion of different tryptophan metabolites in various malignancies and found a marked increase in 3-hydroxyanthranilic acid (about 8 times) and anthranilic acid (about 6 times) in BBC, as well as a characteristic

Table 3 Prevalence and ranking of tobacco smoking, BC incidence and mortality, and HDI in the Arab World in 2020 [106,128].

Arab country	Prevalence of tobacco smoking[a], %	Tobacco smoking ranking worldwide[a]	BC incidence ranking in the Arab world	BC mortality ranking in the Arab world	HDI
Algeria	21.0	#75	#7	#4	0.736 (H)
Bahrain	14.9	#99	#10	#15	0.877 (VH)
Comoros	20.3	#78	#14	#9	0.562 (M)
Djibouti	NA	NA	#19	#21	0.510 (L)
Egypt	24.3	#50	#1	#1	0.734 (H)
Iraq	18.5	#86	#11	#8	0.679 (M)
Jordan	34.8	#14	#4	#7	0.723 (H)
Kuwait	17.9	#88	#13	#16	0.822 (VH)
Lebanon	38.2	#7	#5	#6	0.726 (H)
Libya	NA	NA	#6	#3	0.703 (H)
Mauritania	10.7	#127	#20	#22	0.556 (M)
Morocco	14.5	#100	#12	#11	0.679 (M)
Oman	8.0	#144	#15	#12	0.827 (VH)
Palestine	21.2	#72	#2	#10	0.716 (H)
Qatar	11.8	#119	#16	#13	0.854 (VH)
Saudi Arabia	14.3	#105	#17	#20	0.870 (VH)
Somalia	NA	NA	#18	#17	NA
Sudan	NA	NA	#21	#18	0.510 (L)
Syria	NA	NA	#8	#5	0.577 (M)
Tunisia	24.6	#48	#3	#2	0.737 (H)
United Arab Emirates	NA	NA	#9	#14	0.912 (VH)
Yemen	20.3	#80	#22	#19	0.460 (L)

BC, bladder cancer; H, high; HDI, Human Development Index; L, low; M, moderate; NA, not available; VH, very high.
[a] From WHO Global Health Observatory Data Repository (apps.who.int/ghodata).

Table 4 Global distribution of schistosomiasis endemicity in the different WHO regions, according to the WHO 2020 [20].

WHO region	Number of individuals receiving PC for schistosomiasis
Africa	211 470 992
Eastern Mediterranean	20 582 722
Western Pacific	2 939 845
Americas (South America)	1 620 830
South-East Asia	21 815
Europe	Not applicable
Global	236 636 204

PC, preventive chemotherapy.

reduction in the excretion of kynurenic and xanthurenic acid (about 50%), which was not seen in any other malignancy examined.

Urinary nitrate, nitrite, and N-nitroso-compounds were particularly elevated in schistosomiasis and BBC [71]. In addition, significantly higher urinary α-esterase levels were detected in BBC ($p<0.001$), with an important degree of diagnostic accuracy (95.9%) [72]. A study in Iraq found that 52.6% of BC cases had positive serum alpha-fetoprotein, and all of these cases presented with bilharziasis, suggesting that alpha-fetoprotein may have a potential role in BBC [73].

Urinary matrix metalloproteinase-3 (MMP-3) and MMP-9 seemed promising as diagnostic biomarkers for BC, especially for non-BBC. MMP-3 increased in early-stage BC and remained high in late-stage disease, whereas MMP-9 was only high in advanced-stage BC. The diagnostic accuracy was 94% on average (excluding early-stage MMP-9) [74].

A study in Kuwait concluded that combining urine cytology with NMP22 increased the sensitivity from 30% to 96%, at the expense of decreased specificity from 87% to 30%, compared to urine cytology alone. This combination could potentially help for early detection of cases that require further cystoscopy [75]. *mRNA-S100A* genes could also be combined with urine cytology to improve its sensitivity [76].

3.4. Prognosis

3.4.1. Prognostic index

BC prognosis was strongly correlated with the stage of the disease and lymph node involvement [77,78], and to a lesser extent with the grade [79].

3.4.2. Prognostic markers

Several biomarkers and genetic mutations have been linked to poor prognosis in BC. For example, *p53* mutations [80,81] and negative *PD-L1* expression [82] were associated with invasiveness, high grades, and lymph node involvement.

Upregulated COX2 immunostaining was linked to a worse prognosis in TCC [83], and higher levels of COX2 were observed in BC cases, with a homogeneous distribution in SCC and a heterogeneous distribution in TCC [84].

SIRT1 expression has been identified as a predictor of local recurrence and lower survival in TCC [85]. *STAT3* expression was also significantly increased in high-grade and muscle-invasive TCC [86].

NMP22, E-cadherin, and cathepsin D were all found to be significantly higher in BC, with the first two correlating with recurrence [87]. Lower serum irisin was detected among BC cases ($p<0.001$) and was associated with higher mortality rates (38.2% *vs.* 5%) [88]. Higher serum interleukin-8 was detected in BC ($p<0.0001$) and was linked to invasiveness ($p<0.01$) [89]. In aggressive tumors, higher expressions of *HER2* [90,91], *ROC1*, *P21*, and *CAIX* [92] were also observed.

Labban et al. [93] tested the role of triple-marker immunohistochemical assessment of MIBC in Lebanon and concluded that the coexpression of *GATA3* and cytokeratin 5/6 or cytokeratin 14 reduced progression-free survival compared to *GATA3* expression alone.

In contrast, *FGF23* expression was an shown to be a good prognosis marker, as it was correlated with lower tumor stage in Jordan ($p<0.001$) [94].

3.4.3. BC types with poor prognosis

SCC is more aggressive than TCC, as it is often associated with muscle-invasive tumors and tends to occur at a younger age, with a greater male predilection [86].

TCC variants also have a worse prognosis than pure TCC [95]. Neuroendocrine carcinoma, even when not mixed with TCC, was typically diagnosed at an advanced stage and had a median survival of about 15 months in Tunisian populations [96].

Women tend to have a higher proportion of SCC [67] or non-pure TCC [97].

3.5. Treatment

The established guidelines of the American Urological Association (AUA) and the European Association of Urology (EAU) provide valuable recommendations for managing BC [8,10]. These guidelines offer guidance on treatment options based on the stage and grade of the cancer. NMIBC is commonly treated with tumor removal using TURB, while radical cystectomy is considered the primary treatment approach for MIBC, supported by surveillance protocols and follow-up care. In the case of NMIBC, tumors are stratified into risk levels, with high-risk tumors exhibiting features such as high-grade, carcinoma *in situ*, or T1 tumors. For high-risk NMIBC, adjuvant Bacillus Calmette-Guérin (BCG) immunotherapy has demonstrated significant benefits in reducing tumor recurrence and progression. Intermediate-risk NMIBC tumors may also benefit from BCG therapy; however, its administration can be affected by the shortage of BCG supply [98]. In certain instances, very high-risk NMIBC cases may be considered for radical cystectomy [10].

Nevertheless, the current practices regarding BC treatment in the Arab world remain relatively unclear. Limited data availability and variations in healthcare systems among Arab countries make it challenging to determine the extent to which these established guidelines are followed and implemented in the region.

4. Discussion

The present review analyzed the current state of knowledge on BC in the Arab world, highlighting the epidemiological, clinicopathological, and molecular characteristics of the disease.

4.1. Global perspective on incidence and mortality

When considering the regions with the highest incidence of BC worldwide (ASR>8.6/100 000), Arab countries are not at the top of the list, with the exception of Egypt and Tunisia [19]. The highest incidence rates are observed in the WHO Europe and WHO Americas regions (Figure S2). Studies have shown a positive correlation between BC incidence and Human Development Index [16,99], likely due to higher exposure to industrial chemicals. The ASR per 100 000 is 13.2 in Egypt versus 21.2 in Greece [19].

Although Lebanon is not considered a developed country, its incidence of BC has been among the highest in the world in recent years [32], ranking first in 2018 according to the American Institute of Cancer Research [17,100]. This may be due to the high prevalence of smoking in Lebanon, as well as pollution and environmental exposure [32]. In addition, genetic susceptibility to BC in Lebanese patients has been reported by Kourie et al. [101].

In terms of mortality, the highest rates are observed in the Eastern Mediterranean WHO region (Figure S2), with Egypt ranking first in mortality worldwide (7.8/100 000), followed by Tunisia (5.2/100 000) (Fig. 2B).

While Egypt and Tunisia have significant incidence and mortality rates, some countries with a high impact of the disease have limited data, such as Jordan and Lebanon, or no data at all, like Algeria and Syria (Figure S1 and Fig. 2).

4.2. Risk factors and contributors to high mortality rates

4.2.1. Tobacco smoking

Tobacco smoking is widely recognized as the primary risk factor for BC, making it the second most tobacco-related cancer following lung cancer [2]. Not only does smoking significantly increase the incidence of BC, but it also contributes to various comorbidities. A study investigating short-term mortality risks among patients with non-metastatic BC revealed that only 50% of the mortality cases were directly attributed to BC itself [102]. The remaining deaths were associated with other coexisting cancers, or more frequently, non-malignant causes such as cardiovascular diseases and chronic obstructive pulmonary disease, which are strongly linked to tobacco smoking. When comparing tobacco consumption patterns with BC incidences and mortality rates (Table 3), notable alignments can be observed. For instance, in 2020, Lebanon ranked 7th globally in tobacco smoking, while it held the 5th position in BC incidence and the 6th position in BC mortality rates within the Arab world. Similarly, countries like Jordan, Tunisia, and Egypt displayed high rankings in both tobacco consumption and BC incidence and mortality

rates. It is worth mentioning that the use of waterpipes, which is prevalent in Arab cultures, appears to contribute, alongside tobacco smoking, to the increased disease burden [103].

Studies have indicated a notable global decline in smoking rates, particularly in higher-income countries. However, this trend has not been reflected in the Arab world, where tobacco smoking has continued to rise significantly over the past half-century [104]. This concerning pattern of increasing tobacco use has been observed in 16 Arab countries, including Egypt, Lebanon, Jordan, Libya, Algeria, among others. Despite the efforts made worldwide to reduce smoking rates and implement effective tobacco control measures, the persistent increase in tobacco consumption in Arab countries poses a significant challenge that should be addressed.

4.2.2. *S. haematobium*

Schistosomiasis is a widespread blood fluke infection that affects around 250 million people annually, particularly in impoverished communities with poor sanitation. The infection is transmitted through contact with contaminated water and is found in 78 countries, with over 90% of the burden in Africa [20,21]. In 2020, more than 211 million individuals in Africa required preventive chemotherapy for schistosomiasis, compared to a global total of 236 million (Table 4).

There are two main forms of schistosomiasis: intestinal and urogenital. The main species of schistosomiasis and their regional distribution are shown in Table S1. Urinary schistosomiasis, caused by *S. haematobium*, has been linked to BC, particularly SCC, and was found in Africa, the Middle East, and Corsica (France) [21].

Among the five Arab countries considered endemic and requiring chemotherapy for schistosomiasis, only Egypt was represented in the present research, while the disease status in four other Arab countries remains undefined (Table 5). BC characteristics in the context of schistosomiasis (BBC) differ from those without this association. SCC, which is associated with schistosomiasis, typically occurs at a younger age compared to TCC (40—50 years *vs.* 65—75 years) and exhibits a relatively higher male-to-female ratio. Moreover, SCC is significantly more muscle-invasive [7,86]. These characteristics are reflected in the epidemiological data in Table 1.

This pattern holds true when comparing Arab and Western countries, or even Arab and non-Arab populations in the same country [97]. Similarly, after controlling for schistosomiasis, Egypt has seen a transition from SCC to TCC, with a subsequent change in BC profile [28]. This shift may be due to improved living conditions, resulting in a decrease in exposure to schistosomiasis, and the adoption of a Western lifestyle and diet. Additionally, a shift from solid nodular to papillary configuration of BC was also noted [30], which increases the risk of bleeding and hematuria.

S. haematobium control measures, primarily through preventive praziquantel mass chemotherapy, have proven to be an affordable and effective approach to combat BC in endemic regions. These measures have also played a significant role in controlling the disease in countries such as Oman, Morocco, Tunisia [21].

In Jordan, where schistosomiasis is not endemic, the vast majority of BC cases are TCC, with age and stage characteristics similar to Western countries, but a significantly higher male-to-female ratio (9:1 *vs.* [3—4]:1) [105]. These findings suggest that environmental and lifestyle factors may play a role in the development of BC in Arab countries.

BC associated with schistosomiasis (BBC) displays certain genetic and molecular characteristics (Table 2) that set it apart from non-BBC. According to the AUA and EAU guidelines, biomarkers studies remain inconclusive and cannot replace cystoscopy and urine cytology [8,10] in the diagnosis of BC. However, the use of biomarkers for detecting BC recurrences and risk of progression should be further investigated in this region to reduce the cost of illness.

Agricultural work has been identified as a potential risk factor for BC in several studies due to its association with the spread of schistosomiasis and the use of pesticides. Certain pesticides used in agriculture, such as orthotoluidine, have been classified as confirmed carcinogens by the IARC (Table S2). However, the prevalence of pesticide use in the Arab world is generally lower [106] compared to other countries like China, the USA, and Argentina. Therefore, the impact of pesticide exposure on BC mortality rates in the Arab region remains unclear. Furthermore, while the IARC presents other occupational exposures as contributing factors for BC risk, their discussion and exploration in Arab studies are limited.

4.2.3. Genetics and Mediterranean race

The observation of high mortality rates from BC in both the Arab world and non-Arab countries with geographical proximity, such as Mali [19] and several European states (Figure S2), suggests a potential role of genetics and Mediterranean race in disease susceptibility and aggressiveness. The presence of predisposing genetic factors, possibly amplified by high consanguinity levels in Arab countries [35], may contribute to increased risk and severity of BC.

However, it is important to acknowledge that these regional patterns of BC mortality can also be attributed to other influential factors, including shared environmental exposures and socioeconomic conditions.

4.2.4. BCG shortages and limited access to care

Limited access to healthcare and treatment shortage in Arab countries can significantly contribute to the high mortality rates of BC [98]. Many Arab countries have underdeveloped healthcare systems or face socioeconomic challenges, leading to disparities in healthcare resources and infrastructure. To assess the comparability between socioeconomic status and mortality, the Human Development Index rankings of Arab countries in 2020 were collected, revealing the discrepancies among these nations (Table 3) [106]. Additionally, even in highly developed countries like Saudi Arabia, treatment shortage can be an issue. For instance, in 2020, Alshyarba et al. [98] highlighted the shortage of BCG immunotherapy, a standard treatment for NMIBC, in Saudi Arabia, and proposed solutions to address this problem. Furthermore, there appears to be high levels of air pollution, a known carcinogen with

Table 5 Regional distribution of schistosomiasis endemic countries in the Arab world, according to the WHO 2020 [20].

Arab country	Schistosomiasis endemicity status
Egypt[a]	Endemic, requiring PC
Somalia	Endemic, requiring PC
Mauritania	Endemic, requiring PC
Sudan	Endemic, requiring PC
Yemen	Endemic, requiring PC
Libya[a]	Status of transmission to be determined
Syria	Status of transmission to be determined
Iraq[a]	Status of transmission to be determined
Oman	Status of transmission to be determined
Tunisia[a]	Interruption of transmission to be confirmed
Jordan[a]	Interruption of transmission to be confirmed
Lebanon[a]	Interruption of transmission to be confirmed
Morocco[a]	Interruption of transmission to be confirmed
Djibouti[a]	Interruption of transmission to be confirmed
Algeria	No PC required
Saudi Arabia[a]	No PC required
Palestine[a]	Non-endemic
United Arab Emirates	Non-endemic
Bahrain	Non-endemic
Kuwait[a]	Non-endemic
Comoros	Non-endemic
Qatar	Non-endemic

PC, preventive chemotherapy.
[a] Countries with published studies about bladder cancer epidemiology.

limited evidence for BC in humans according to the IARC monographs (Table S2), in the six Arab countries with very high Human Development Index [106].

Considering that radical cystectomy is the mainstay treatment for MIBC, strategies such as referring radical cystectomy to high-volume centers have demonstrated potential in reducing morbidity. The Egyptian National Cancer Institute serves as an example of a centralized approach to BC treatment, illustrating the potential benefits of specialized centers. However, the centralization of care might exacerbate limited access to treatment in some regions, as indicated by Arora et al. [107], who found a plateau for the complication rate at 50–55 cases per year.

Moreover, despite well-established guidelines for BC treatment from organizations like the AUA and EAU, the actual implementation of these guidelines remains limited in practice. A collaborative review by Leow et al. [108] in 2020 emphasized the importance of performance indicators in assessing the quality of care provided to BC patients in preoperative, intraoperative, and postoperative settings. Specific protocols, including smoking cessation, counseling, administration of prophylactic antibiotics in some patients with high risk of postoperative sepsis, and standardized TURB procedures with checklist-based quality assurance, are crucial for the management of NMIBC. For MIBC, a multidisciplinary approach and consideration of bladder preservation in select cases should be implemented, with a protocol of surveillance and follow-up. Although specific instruments used in several countries were referenced in this article, the adoption and use of quality indicators remain unclear in the Arab world, underscoring the need for improved adherence to established guidelines and protocols.

Furthermore, the low incidence and high mortality rates of BC in Arab countries raise concerns about disease detection and reporting. Late-stage disease detection and underreporting may contribute to the observed patterns. It is imperative to raise awareness about the significance of BC and improve knowledge and understanding of the disease burden in Arab countries. This is particularly evident in countries like Lebanon, where high smoking rates and a lack of awareness about BC persist [109]. Comprehensive efforts should be made to address the challenges of limited access to care, treatment shortages, and disease awareness to reduce mortality and improve outcomes.

4.3. Study strengths and limitations

One of the key strengths of this review is its broad scope and thorough approach to analyzing the epidemiology of BC in Arab countries. By accessing data from two major databases (PubMed/PMC and Cochrane) and including all literature published up until May 2022, this review is able to provide a comprehensive overview of the prevalence, risk factors, molecular mechanisms, and clinical features of BC in these countries, as well as the role of *S. haematobium* infection. Additionally, the fact that all the articles obtained from the original search were in English or French ensures that no relevant information was missed due to language barriers. Overall, this review offers a detailed and up-to-date look at the current state of knowledge on BC in the Arab world, and explores different causes of the high mortality rates observed in this region, suggesting some solutions that can be adopted.

However, it is important to acknowledge several limitations. Firstly, the reliance on only two research databases may have resulted in the omission of relevant publications from other sources. Secondly, while there was a fair number of articles on the topic, they were predominantly derived from only 10 out of the 22 Arab countries, with Egypt ($n=63$; 66%) and Tunisia ($n=13$; 14%) being the most represented. This uneven distribution may restrict the generalizability of the findings to other Arab nations. Moreover, the predominance of retrospective case-control studies within the available literature introduces potential biases. Finally, the lack of information on several important aspects of BC, such as cyclophosphamide, Lynch syndrome, and the potential protective role of the Mediterranean diet, highlights areas where further research is warranted.

5. Conclusion

This systematic review sheds light on the significant public health challenge posed by BC in the Arab world. Despite lower incidence rates compared to Western countries, this region has the highest mortality rates worldwide. Several key factors lead to this alarming trend, including the high prevalence of smoking in many Arab countries, coupled with the associated comorbidities. Additionally, cultural practices such as waterpipe smoking, the lingering effects of schistosomiasis, low socioeconomic status in certain countries leading to limited access to care, elevated pollution levels in developed Arab countries, treatment shortages even in developed nations, low knowledge about the disease, and unclear management practices all contribute to increased BC mortality rates. To address this issue, strict policies against tobacco smoking should be implemented, along with schistosomiasis control in endemic regions, and increased awareness campaigns to educate the public about the disease burden. Furthermore, the use of quality indicators to assess healthcare performance and improve outcomes, as well as further research on biomarkers for surveillance and follow-up, should be prioritized. These interventions hold the potential to mitigate the impact of BC in the Arab region and reduce mortality rates.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2023.10.001.

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