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Cancer care in areas of conflict

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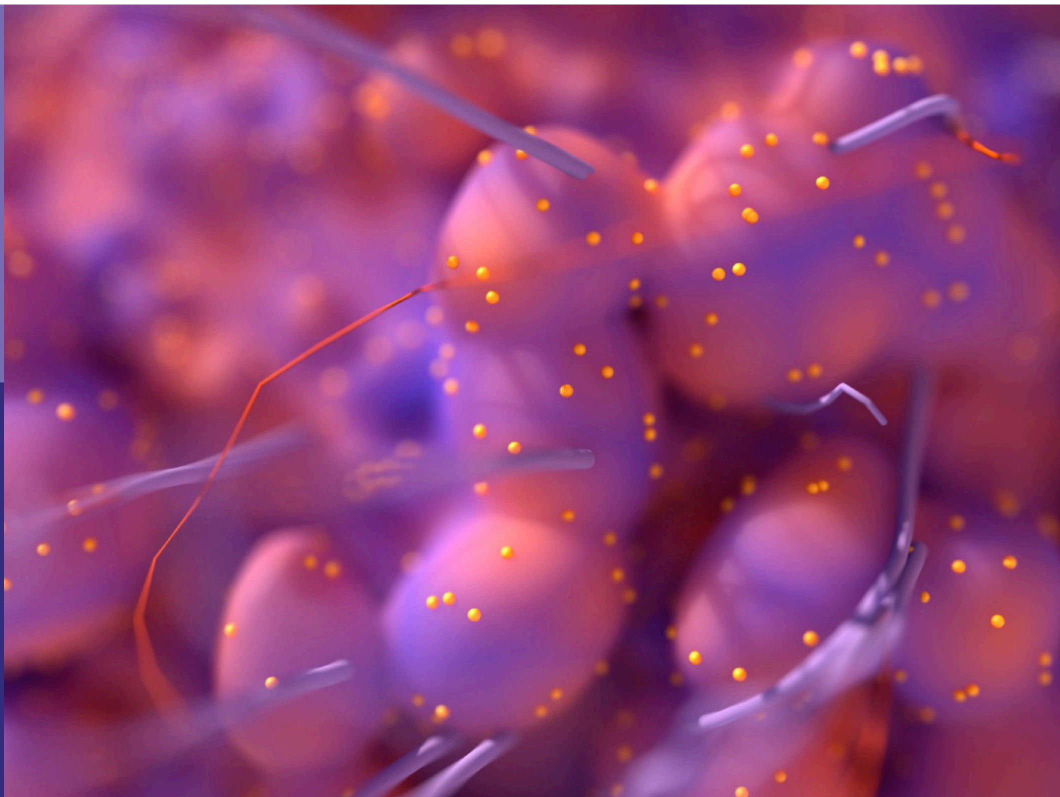

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Cancer care in areas of conflict

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Editorial: Cancer care in areas of conflict

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Editorial on the Research Topic
Cancer care in areas of conflict

The global incidence of cancer is witnessing a substantial surge within low- and middle-income countries (LMIC). Projections for the year 2035 indicate that approximately two-thirds of all cancer cases will emerge in these developing nations, with a notable concentration in the Middle East and North Africa (MENA) (1). The MENA region has faced more frequent and severe conflicts than any other part of the world (2). Already grappling with a complex landscape of acute and chronic conflicts, it faces formidable challenges in providing adequate cancer care services to its population. These challenges encompass the absence of universal healthcare coverage, the scarcity of comprehensive cancer control initiatives, a shortage of healthcare professionals, and limited access to early detection and treatment options (1, 3, 4). Furthermore, the enduring armed conflicts and insecurity that pervade the region have directly contributed to widespread migration and the disintegration of healthcare systems, resulting in a stark deficiency of high resolution, accurate healthcare data (1, 5, 6).

This editorial piece delves into the critical subject of cancer care within regions impacted by conflict, drawing insights from narrative synthesis of a compendium of 17 published articles spanning diverse corners of the globe, particularly the Middle East, North Africa, and Turkey (MENAT) area. These articles form a rich tapestry of experiences, encapsulating challenges, obstacles, needs, inequalities, and recommendations related to cancer prevention, diagnosis, treatment, quality of life, and palliative care. Through the lens of these profound contributions, a more profound comprehension of the intricate dynamics impacting cancer care in conflict-affected populations and geographies emerges. By amalgamating the collective knowledge and expertise shared within these articles, the objective is to nurture evidence-based strategies and interventions that address distinctive requisites and elevate outcomes for individuals grappling with cancer amid the adversities of conflict.

One pivotal study on this subject by Daubman et al. spotlighted individuals with cancer and other severe ailments, elucidating their heightened vulnerability during humanitarian emergencies and crises (HECs). The authors underscored the indispensability of palliative care (PC) as an integral facet of holistic care for these patients, a need that amplifies significantly during HECs. The study advocated for the inclusion of PC within humanitarian response policies and guidance, universal training of humanitarian responders in PC, and integration of PC indicators within HECs research. This study shed light on the sustained feasibility of providing the WHO essential package of PC even when other services falter.

A pioneering contribution by Al-Ibraheem et al. navigated the terrain of cancer diagnosis in conflict-afflicted territories of the Middle East, spotlighting the hurdles and limitations experienced in nations like Iraq, Syria, Yemen, and Sudan. The authors advocated surmounting these challenges and formulating tailored approaches to enrich cancer diagnosis in these contexts. Their call for a collaborative, coordinated endeavour at both national and international levels to bridge the gap in cancer diagnosis services reverberated widely across the literature.

Rihani et al. illuminate the hurdles faced by Jordan in providing high-quality cancer care to displaced children, with a specific focus on its role as a prominent host for refugees. Over the period spanning 2011 to 2022, the King Hussein Cancer Center (KHCC) extended care to 968 pediatric patients from outside of Jordan. Remarkably, a substantial 84% of these treatments were financially supported by the King Hussein Cancer Foundation (KHCF). A collaboration with St. Jude Children's Research Hospital further enhanced care from 2018-2022, benefiting 51 displaced children. This underscores the role of local-international partnerships in bridging healthcare gaps for displaced populations, emphasizing the need for sustainable, innovative care strategies.

Erashi et al. and Mansour et al. approached this topic from a different vantage point, offering insights into the characteristics of Libyan and Palestinian patients under treatment at Jordan's King Hussein Cancer Center (KHCC), situated within a middle-income MENA country. Adult patients from both populations predominantly exhibited breast, gastrointestinal, and hematolymphoid cancers, with paediatric patients frequently presenting hematolymphoid and central nervous system malignancies. Intriguingly, the presented cases manifested more advanced stages compared to their Jordanian counterparts. Obeidat et al. further contributed by delineating central nervous system tumor attributes among patients from conflict areas treated at KHCC, indicating the prevalence of gliomas, glioneuronal tumors, and neuronal tumors, with a significant proportion being grade 4 tumors.

In the context of the Syrian humanitarian crisis, Yousef et al. conducted a retrospective comparative study on retinoblastoma cases in Syrian refugees and Jordanian citizens treated at KHCC. The study highlighted disparities in age at diagnosis, treatment initiation lag, and disease stage at presentation, emphasizing the urgency of early referrals for optimal management of refugees with retinoblastoma.

Al-Hussaini et al. scrutinized the impact of the COVID-19 pandemic on patients from conflict zones treated at KHCC, uncovering fluctuations in admissions during lockdowns and their subsequent easing. Guo et al. delved into the unique needs of patients with advanced cancer and their caregivers, accentuating the significance of social support and religious considerations in refugee communities. This emphasized the importance of tailoring care to meet these nuanced requirements.

Boufkhed et al. conducted a multicenter qualitative study to uncover priorities and concerns of children and young people (CYP) with advanced cancer and their families in Jordan and Turkey. The findings underlined crucial aspects like physical pain, psychological well-being, spirituality, and social impacts, providing valuable insights into providing tailored, holistic care.Alarjeh et al. further explored communication preferences among Jordanian CYP, caregivers, and healthcare professionals, showcasing the capacity of children and parents to participate in sensitive conversations about care decisions.

Mahmood et al. analysed the demographic and treatment outcome data of Afghan cancer patients seeking treatment in Pakistan, shedding light on the challenges faced and treatment outcomes achieved, emphasizing the need for improved follow-up mechanisms. Lastly, Sater et al. presented a bibliometric analysis of cancer research within conflict-affected settings in the MENA region, identifying trends and calling for targeted research, enhanced research infrastructure, and collaboration to advance cancer outcomes.

In summary, this Research Topic encapsulates a mosaic of experiences, challenges, and advancements within the realm of cancer care amidst conflict. Through these studies, a deeper understanding emerges, offering a springboard for evidence-based interventions that can navigate the complexities of cancer care in regions beset by conflict.

Author contributions

OS: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. TK: Supervision, Writing – review & editing. FF: Supervision, Writing – review & editing. RS: Supervision, Writing – review & editing. AM: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Palestinian Patients with Cancer at King Hussein Cancer Center

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Background: The Palestinian Ministry of Health (MoH) routinely refers Palestinian patients with cancer to King Hussein Cancer Center (KHCC), the largest cancer center in the Middle East.

Aims: We aimed to describe the characteristics of Palestinian patients with cancer.

Methods: We performed a retrospective chart review of all Palestinian patients with cancer who were treated at KHCC during 2018 and 2019, of which demographic and clinical characteristics were presented.

Results: We initially started with 521 cases, out of which 41 (7.9%) cases were excluded due to misdiagnosis as malignant on pathology review. We included 480 patients with a confirmed diagnosed of cancer. Most patients were adults (88.8%) with a mean age of 50.0 ± 15.0 years ranging from 19 to 87 years. The most common cancer sites in adult men, who comprised 46.9% of the cohort were the hematolymphoid system (23.5%), followed by the digestive system (17.5%), and lung and pleura (11.5%). In women (53.1%), the most common cancer sites were the breast (46.0%), followed by the digestive system (15.0%), and the hematolymphoid system (10.2%). Children and adolescents accounted for 11.3% of the total cases, among which the hematolymphoid system was the most common cancer site (50%), followed by the brain (14.8%). About 36.0% of all patients presented with advanced-stage disease (i.e., distant metastasis).

Conclusion: The most common cancer sites in our cohort are generally similar to data from the Palestinian territories. Many patients presented with advanced-stage disease, which signals the need for awareness campaigns and screening programs. Benign tumors are misdiagnosed in many patients as cancer. The limited resources and facilities including human resources remain important challenges to the proper and timely diagnosis and management of cancer among Palestinians living in the Palestinian Territories.

KEYWORDS

Cancer care facilities, Gaza Strip, Oncology service, Palestinians, West Bank

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1 Introduction

Since its inception, the Palestinian Authority (PA) has strived to provide Palestinians with better access to health care services (1). However, limitations in infrastructure and human resources have prevented the health care system in the Palestinian territories from becoming independent (2–4). In addition, the limitations for private cancer care in the Palestinian territories include a shortage of capable cancer specialists, restricted access to medical technology and equipment, and decreased funding from international organizations such as the World Health Organization and countries such as the United States (5). Health insurance from the Palestinian Ministry of Health (MoH) is the only available coverage for cancer care in the Palestinian territories. The insurance usually covers referrals to hospitals in neighboring countries that have advanced facilities for cancer care, such as King Hussein Cancer Center (KHCC) in Jordan (6). In addition to the MoH, other sources of financial coverage include King Hussein Cancer Foundation (through the Goodwill Fund) and direct cash payments.

Cancer remains one of the leading causes of death in the Middle East and represents a significant challenge to many burdened health care systems (7–10). In the Palestinian territories, cancer is the second leading cause of death (11). According to the latest statistics reported by GLOBOCAN 2020, Gaza Strip and the West Bank hosted a total of 4,779 diagnosed cancer cases in that year (12). The age-standardized incidence rate is 158 (per 100,000 persons), and the age-standardized mortality rate is 103.5 (per 100,000 persons); both of which were higher in males compared to females. These number saw a marked increased from projections made for 2015 (13). The increasing burden of cancer, coupled with a limited health care system, represents an additional health care challenge in the Palestinian territories. The most common types of cancer diagnosed in Palestinian patients are similar to worldwide trends (14). Lung cancer is the most diagnosed type of cancer with an incidence rate of 5.2 cases (per 100,000 persons) in men, followed by leukemia and colorectal cancer. In Palestinian women, breast cancer is the most diagnosed type of cancer, followed by colorectal cancer and leukemias (5).

King Hussein Cancer Center is a comprehensive cancer center in Amman, Jordan that serves adult and pediatric patients from Jordan and other countries in the Middle East and North Africa (15). The center is crucial for the cancer care of Palestinian patients because the Palestinian territories lack a comprehensive cancer center. In this study, we describe the characteristics of all patients referred from the Palestinian MoH for cancer care at KHCC between January 2018 and December 2019. We report the demographic characteristics of the patients, their financial coverage, distribution of cancer types, and most common treatment modalities. We also discuss the challenges faced by Palestinian patients. Finally, we provide recommendations for the management and treatment of cancer in the Palestinian territories.

2 Materials and methods

We performed a retrospective chart review of all Palestinian patients with cancer who were treated at KHCC between January 2018 and December 2019, who are residents of the Palestinian territories. We sequentially included all patients registered in the institutional Cancer Registry (established July 2006). We filtered out nonunique records and excluded patients with benign tumors that were initially misdiagnosed as malignant. We retrieved the following data from the registry: date at first contact, age at diagnosis, sex, financial coverage, cancer site, histopathology, treatment, and SEER summary stage. We used IBM SPSS Statistics 23 to perform data analyses. First, we described the demographic and clinical characteristics of the full cohort. We then stratified the cohort according to age, sex, or cancer site, and described the clinical characteristics of each strata. We summarized continuous data as means and standard deviations and categorical data as absolute frequencies and percentages.

3 Results

3.1 Demographics

We screened 1,011 records for eligibility, of which 521 records (51.5%) were unique and devoid of any duplicates. Of the 521 patients, we excluded 41 (7.9%) with benign tumors who were previously misdiagnosed. The most common sites of the misdiagnosed tumors were the breast (22.0%), central nervous system (19.5%), pituitary gland (12.2%), digestive system (12.2%), and soft tissues (9.8%). We included, in the final analysis, all remaining 480 patients, 186 (38.8%) and 294 (61.3%) of whom presented to the center in 2018 and 2019, respectively (Refer to Figure 1). Of the total, 248 patients were female (51.7%) and 232 (48.3%) were male. The mean age at diagnosis was 45 ± 19 years; 54 patients (11.3%) were children or adolescents (<18 years old) and 426 (88.8%) were adults (≥18 years old). Most patients were financially covered by the Palestinian MoH (n = 435, 90.6%). This cohort of Palestinian patients represented 5.3% of all patients treated at KHCC during 2018 and 2019.

3.2 Clinical characteristics

The most common cancer sites, in order, were the breast, hematolymphoid system, and digestive system. Table 1 describes the site-specific frequencies of cancers among Palestinian

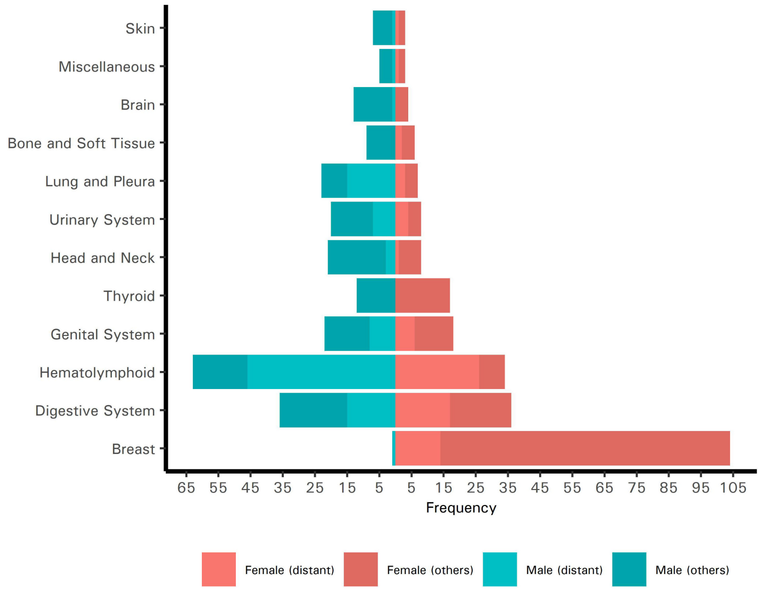

FIGURE 1
Pyramid plot of the site-specific frequencies of cancers in Palestinian patients who presented to King Hussein Cancer Center in 2018 and 2019 (*N* = 480) stratified by sex. The frequencies of cancers with distant metastases are indicated.

TABLE 1 Site-specific frequencies of cancers in Palestinian patients who presented to King Hussein Cancer Center in 2018 and 2019 (N = 480) stratified by age and biological sex.

Site	Total (n = 480) *n* (%)	Female (n = 248) *n* (%)	Male (n = 232) *n* (%)	Adults (n = 426) *n* (%)	Women (n = 200) *n* (%)	Men (n = 226) *n* (%)	Children and adolescents (n = 54) *n* (%)	Girls and female adolescents (n = 22) *n* (%)	Boys and male adolescents (n = 32) *n* (%)
Breast	105 (21.9)	104 (41.9)	1 (0.4)	105 (24.6)	104 (46.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hematolymphoid System	97 (20.2)	34 (13.7)	63 (27.2)	70 (16.4)	23 (10.2)	47 (23.5)	27 (50.0)	11 (50.0)	16 (50.0)
Digestive System	72 (15.0)	36 (14.5)	36 (15.5)	69 (16.2)	34 (15.0)	35 (17.5)	3 (5.6)	2 (9.1)	1 (3.1)
Lung and Pleura	30 (6.3)	7 (2.8)	23 (9.9)	30 (7.0)	7 (3.1)	23 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Head and Neck	29 (6.0)	8 (3.2)	21 (9.1)	28 (6.6)	8 (3.5)	20 (10.0)	1 (1.9)	0 (0.0)	1 (3.1)
Thyroid	29 (6.0)	17 (6.9)	12 (5.2)	27 (6.3)	16 (7.1)	11 (5.5)	2 (3.7)	1 (4.5)	1 (3.1)
Urinary System	28 (5.8)	8 (3.2)	20 (8.6)	26 (6.11)	7 (3.1)	19 (9.5)	2 (3.7)	1 (4.5)	1 (3.1)
Male Genital System	22 (4.6)	0 (0.0)	22 (9.5)	21 (4.9)	0 (0.0)	21 (10.5)	1 (1.9)	0 (0)	1 (3.1)
Female Genital System	18 (3.8)	18 (7.3)	0 (0.0)	17 (4.0)	17 (7.5)	0 (0.0)	1 (1.9)	1 (4.5)	0 (0)
Brain	17 (3.5)	4 (1.6)	13 (5.6)	10 (2.3)	2 (0.9)	8 (4.0)	8 (14.8)	1 (4.5)	7 (21.9)
Bone and Soft Tissue	15 (3.1)	6 (2.4)	9 (3.9)	9 (2.1)	3 (1.3)	6 (3.0)	5 (9.3)	4 (18.2)	1 (3.1)
Skin	10 (2.1)	3 (1.2)	7 (3.0)	9 (2.1)	3 (1.3)	6 (3.0)	1 (1.9)	0 (0.0)	1 (3.1)
Miscellaneous	8 (1.7)	3 (1.2)	5 (2.2)	5 (1.2)	2 (0.9)	3 (1.5)	3 (5.6)	1 (4.5)	2 (6.3)

patients stratified by age and biological sex. Together, these sites accounted for 274 cancers (57.1%). We describe the SEER summary stage of all cases in Table 2. Of all patients, 239 (49.8%) received chemotherapy, 210 (43.8%) underwent surgery, 114 (23.8%) received radiotherapy, 92 (19.2%) received palliative therapy, 39 (8.1%) received hormonal therapy, 16 received immunotherapy (3.3%), and 16 (3.3%) underwent bone marrow transplantation.

TABLE 2 The SEER summary stage at presentation of Palestinian patients with cancer who presented to King Hussein Cancer Center in 2018 and 2019 (N = 480) stratified by age and biological sex.

Stage	**Total (n = 480) *n* (%)**	**Women (n = 200) *n* (%)**	**Men (n = 226) *n* (%)**	**Girls and female adolescents (n = 22) *n* (%)**	**Boys and male adolescents (n = 32) *n* (%)**
In situ	10 (2.1)	7 (3.1)	3 (1.5)	0 (0.0)	0 (0.0)
Localized	99 (20.6)	44 (19.5)	41 (20.5)	2 (9.1)	12 (37.5)
Regional by direct extension	29 (6.0)	13 (5.8)	14 (7.0)	0 (0.0)	2 (6.3)
Regional to lymph nodes	67 (14.0)	53 (23.5)	12 (6.0)	1 (4.5)	1 (3.1)
Regional both by direct extension and lymph nodes	45 (9.4)	18 (8.0)	26 (13.0)	1 (4.5)	0 (0.0)
Distant	173 (36.0)	59 (26.1)	83 (41.5)	16 (72.7)	15 (46.9)
Unknown	57 (11.9)	32 (14.2)	21 (10.5)	2 (9.1)	2 (6.3)

3.3 Clinical characteristics according to age and sex

3.3.1 Adults

Of 426 adult patients, 226 (53.1%) were women and 200 (46.9%) were men. The most common cancer sites in women, in order, were the breast, digestive system, and hematolymphoid system. In men, the most common cancer sites, in order, were the hematolymphoid system, digestive system, and lung and pleura. The mean age at diagnosis was 49 ± 14 years for women and 51 ± 16 years for men. At the time of presentation, 59 women (26.1%) and 83 men (41.5%) had distant metastases.

3.3.2 Children and adolescents

Of 54 children and adolescents, 22 (40.7%) were female and 32 (59.3%) were male. The most common cancer sites in girls and female adolescents were the hematolymphoid system and bone and soft tissue. In boys and male adolescents, the most common cancer sites were the hematolymphoid system and brain. The mean age at diagnosis was 11 ± 6 years for girls and female adolescents and 8 ± 5 years for boys and male adolescents. At the time of presentation, 16 girls and female adolescents (72.7%) and 15 boys and male adolescents (46.9%) had distant metastases.

3.4 Clinical characteristics according to the most common cancer sites

3.4.1 Cancers of the breast

The most common cancer site overall was the breast (*n* = 105, 21.9%). The patients were exclusively adults, and all except one were women (*n* = 104, 99.0%). The mean age at diagnosis was 50 ± 13 years. According to the SEER summary stage, the disease was *in situ* in six patients (5.7%), localized in 24 (22.9%), regionalized in 44 (41.9%), distant in 15 (14.3%), and unknown in 16 (15.2%). The predominant type, by histology, was invasive ductal carcinoma (*n* = 101, 96.2%). The remaining cases were invasive lobular carcinoma and mucinous adenocarcinoma (each *n* = 2, 1.9%). Overall, 50 patients (47.6%) underwent surgery, 49 (46.7%) received chemotherapy, 29 (27.6%) received hormone therapy, 17 (16.2%) received radiotherapy, seven (6.7%) received palliative therapy, and four (3.8%) received immunotherapy.

3.4.2 Cancers of the hematolymphoid system

Cancers of the hematolymphoid system were the second most common overall (*n* = 97, 20.2%). The number of adults (*n* = 70, 72.2%) was more than twice the number of children and adolescents (*n* = 27, 27.8%). In addition, the number of male patients (*n* = 63, 64.9%) was almost twice the number of female patients (*n* = 34, 35.1%). The mean age at diagnosis was 32 ± 18 years. According to the SEER summary stage, the disease was localized in six patients (6.2%), regionalized in 12 (12.4%), distant in 72 (74.2%), and unknown in seven (7.2%). The most common type, by histology, was non-Hodgkin lymphoma (*n* = 30, 30.9%), followed by chronic lymphocytic leukemia (*n* = 21, 21.6%), Hodgkin lymphoma (*n* = 19, 19.6%), acute myeloid leukemia (*n* = 9, 9.3%), chronic myeloid leukemia (*n* = 5, 5.2%), multiple myeloma (*n* = 5, 5.2%), and acute lymphocytic leukemia (*n* = 1, 1.0%). Overall, 77 patients (73.3%) received chemotherapy, 20 (19.0%) received palliative therapy, 14 (13.3%) received radiotherapy, 13 (12.4%) underwent transplantation, four (3.8%) underwent surgery, and four (3.8%) received immunotherapy.

3.4.3 Cancers of the digestive system

Cancers of the digestive system were the third most common overall (*n* = 72, 15.0%). Most patients were adults (*n* = 69, 95.8%), and the sexes were equally affected (each *n* = 36, 50.0%). The mean age at diagnosis was 54 ± 17 years. According to the SEER summary stage, the disease was localized in seven patients (9.7%), regionalized in 26 (36.1%), distant in 32 (44.4%), and unknown in seven (9.7%). The most common type was colorectal carcinoma (*n* = 39, 54.2%), followed by gastric carcinoma (*n* = 14, 19.4%), pancreatic adenocarcinoma (*n* = 12, 16.7%), hepatocellular carcinoma (*n* = 4, 5.6%), carcinoid (*n* = 1, 1.4%), cholangiocarcinoma (*n* = 1, 1.4%), and carcinoma of the small intestine (*n* = 1, 1.4%). Overall, 41 patients (56.9%) received chemotherapy, 29 (40.3%) underwent surgery, 21 (29.2%) received palliative therapy, six (8.3%) received radiotherapy, and two (2.8%) received immunotherapy.

4 Discussion

We performed the first study of Palestinian patients with cancer seeking care and treatment in Jordan. We described the demographic and clinical characteristics of 480 Palestinian patients treated at KHCC in 2018 and 2019. The most common cancer sites were the breast in female patients and the hematolymphoid system in male patients. Cancers of the digestive system were the second most common in both male and female patients.

Cancer is a leading cause of death in both developed and developing countries (14). Cancer care is challenging even in the best of conditions and becomes exceedingly so in areas of conflict in the Middle East with compromised health care systems (16). Barriers to high-quality cancer care include scarce medical resources, limited access, financial difficulties, absent screening programs, and poor awareness (10, 17).

We found that breast cancer was the most common cancer in Palestinian women treated at KHCC (41.9%). This finding is similar to data from the Palestinian MoH; the rate of breast cancer was 31.3% in the Palestinian territories in 2016 (18). Notably, we also found that 14.3% of Palestinian women with breast cancer treated at KHCC had distant metastasis and 6.7% received palliative therapy. In the Palestinian territories, the 5-year overall survival of women with breast cancer is almost 50% (19). In comparison, the 5-year overall survival of women with breast cancer in the United States, Jordan, and Israel is almost 85% (20, 21). The difference may be attributed to poor breast cancer awareness, lack of screening programs for breast cancer, and limited access to and poor utilization of health care (22). To address the high rate of advanced-stage disease at presentation, we recommend awareness campaigns be held in the Palestinian territories. Awareness campaigns may improve early detection of the most common cancers and lead to better outcomes. Moreover, the implementation of affordable screening programs, especially for cancers of the breast and colorectum, can also improve early detection.

The distribution of cancer sites in our cohort was similar to data from the Palestinian territories for female patients but not male patients. In our study, the most common cancer sites in male patients were the hematolymphoid system, followed by the digestive system and lung and pleura. In the Palestinian territories, the most common cancer sites in men were the lung, followed by the prostate and colorectum (13). The rate of hematolymphoid cancers in our cohort is likely higher because the Palestinian MoH routinely refers patients to KHCC for bone marrow transplantation; only one hospital in the Palestinian territories (namely An-Najah National University Hospital, located in the West Bank) provides bone marrow transplantation and the service is limited (19). It should be noted that the burden of lung cancer among Palestinian may be linked to the Palestinian territories' lack of a preventive national program for cancer risk. This is best exemplified in the rates of smoking within the Palestinian territories as they are among the highest in the world reaching as high as 26.3% and 56% among the general population and university students, respectively (23). Moreover, Palestinian male students were 10 times more likely to smoke than their female counterparts. Despite the high rates of smoking, the Palestinian MoH did implement WHO tobacco control strategies, raised taxes on tobacco products, and banned their promotion (5). Nonetheless, evidence for the effectiveness of such strategies is yet to emerge.

All patients who present to KHCC undergo baseline diagnostic testing, and all available tissue material and radiographs are reviewed in-center. Interestingly, we found that 7.9% of patients with benign tumors were initially misdiagnosed. Tumors of the central nervous system and soft tissues are often reported by specialists, and pathologists with that expertise are lacking in the Palestinian territories. The shortage of specialists is a significant barrier to optimal cancer care in the Palestinian territories. This barrier may be addressed by virtual multidisciplinary team meetings, twinning between KHCC and hospitals in the Palestinian territories, and other telemedicine solutions. Initiatives to train Palestinian physicians offer numerous advantages. First, the psychosocial outcomes of patients may improve because of the decreased financial burden as well as increased social support. Second, the physical health outcomes of patients may also improve because cancer care is less likely to be interrupted and patients can be followed up for longer durations.

Lack of ancillary testing, which aids in diagnosis and helps distinguish malignant tumors from mimics, may also contribute to misdiagnosis. Many studies have investigated the rate of medical errors in the Palestinian territories, but no specific data are available for misdiagnosis in oncology (24–26). Misdiagnoses may be attributed to the lack of comprehensive cancer care as well as the limited availability of advanced diagnostic equipment. For example, positron emission tomography/computed tomography (PET/CT scan) is not available in the Palestinian territories, there are no nuclear medicine specialists, and patients who require the scan are referred to hospitals in Israel (19). Further studies are required to identify the causes of misdiagnosis, and these causes may be addressed by non-punitive interventions.

The infrastructure of cancer care in the Palestinian territories is deficient and requires investment; there is an urgent need for advanced diagnostic equipment and specialist care. Capacity-building is needed to address the shortage of laboratories, diagnostic equipment, radiation oncology units, bone marrow transplantation units, cancer rehabilitation units, and palliative care wards. For example, with respect to radiation oncology equipment, only two linear accelerators are available to serve the oncologic needs of all Palestinians (1 machine per 1,000,000 inhabitants). These machines are only available in East Jerusalem, thus subjecting patients from Gaza and the West Bank to transportation-related delays (27).

The Palestinian territories lack a comprehensive cancer center that offers specialized, essential cancer care services, such as targeted therapies, multidisciplinary care, palliation, and rehabilitation. Surgery and chemotherapy are generally available, but only one hospital (namely Augusta Victoria Hospital, located in East Jerusalem) offers radiotherapy (19). There are only one radiation oncologist and two medical oncologists per one million population (5). Moreover, to our knowledge, palliative care is generally not available to date in the Palestinian territories. Cancer care is expensive, especially if modalities such as bone marrow transplantation or immunotherapy are indicated. We found that 90.6% of Palestinian patients at KHCC were covered by the Palestinian MoH. However, the MoH only covers the direct costs of Palestinian patients, which presents additional challenges to patients with cancer and their companions, who are not included in the coverage.

Moreover, when analyzing the status of cancer care within the Palestinian territories within a proper geopolitical context, it appears that care defects are not solely oriented around resource scarcity but rather due to asymmetrical racial policies and logistics which originate in the deep historical context of the region (27). Patients with cancer from Gaza and the West Bank may experience significant diagnosis and treatment delays due to the state of inaccessibility set by these policies. These patients are subjected to a myriad of military checkpoints, administrative approvals (e.g., security paperwork and checkups), and permanent roadblocks; all of which may affect the quality of care delivered to and accessed by those patients (28).

We acknowledge two limitations in our study. First, Palestinian patients are followed up for six months following discharge from KHCC, so we could not perform outcome analyses. Second, the Cancer Registry did not restage patients using the 2018 version of the SEER summary staging system if they were initially staged as code 5 using the 2000 version. This largely contributed to missing staging data in 11.9% of patients.

4.1 Conclusion

In conclusion, KHCC provides comprehensive cancer care to Palestinian patients referred from the Palestinian MoH. The distribution of cancer sites is similar to data from the Palestinian territories. However, awareness campaigns and screening programs are substandard relative to other countries in the region, which may explain the high rate of advanced-stage disease at presentation. Further studies are required to study the outcomes of Palestinian patients with cancer and the challenges they face during treatment.

Data availability statement

All data/data sets associated with this project can be requested from the corresponding author at a reasonable request.

Ethics statement

Studies involving human participants are reviewed and approved by the Institutional Review Board of KHCC. This study was approved under number 20KHCC29. The IRB at KHCC works in accordance with the declaration of Helsinki and its amendments. The IRB granted a waiver of informed consent since the data collected was existing and no patients' identifiers were collected. Written informed consent from participants or legal guardian/ next of kin was not required in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MA-H and AM. Methodology: JZA. Formal analysis: JZA and MA-H. Writing – original draft: RM, and JZA. Writing – review & editing: AA-A, MA-H, and AM. Supervision: MA-H and AM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cancer registration in the Middle East, North Africa, and Turkey (MENAT) region: A tale of conflict, challenges, and opportunities

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Cancer registration is a core component of national and regional cancer control strategies. In the Middle East, North-Africa and Turkey (MENAT) region, capacity and resources for cancer registration is variable and shaped by multiple contextual challenges. This viewpoint maps out practical recommendations around cancer registration, in an attempt to inform cancer control planning, policy, and implementation. The recommendations laid out in this viewpoint are informed by the discussions held at the Initiative for Cancer Registration in the MENAT (ICRIM) virtual workshop, which convened registry managers, policy makers, and international agencies from 19 countries in the MENAT region. The discussions were distilled in four categories of recommendations, revolving around cancer registration procedures, collaborative governance, putting cancer registration on the map, and capacity building. This viewpoint provides a much-needed mapping of practical recommendations around cancer registration, informed by direct key stakeholders in the region. These practical recommendations offer a road map for policy making, cancer control planning, and future regional capacity strengthening initiatives.

KEYWORDS

cancer registration data, cancer control, population based cancer registries (PBCRs), cancer surveillance, Middle East & North Africa (MENA)

Introduction

The global burden of cancer is disproportionately greater in low- and middle-income countries (LMICs), including many countries in the Middle East, North Africa, and Turkey (MENAT) region (Table 1) (1). An increase of more than 60% in cancer burden is projected in LMICs by 2030 (2). Due to multiple factors, including recurrent and endemic conflicts, changing demographics, and increased environmental contamination, the MENAT region is expected to witness the highest increase in cancer burden worldwide (3). The burden of cancer in the MENAT is multifaceted. In the Gulf Cooperation Council (GCC) countries, which include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates, colorectal and lung cancers are the most prevalent in men, and breast and thyroid cancers are most prevalent in women. In the rest of the MENAT region, lung, liver, and prostate cancers are the most common in men, whereas breast, colorectal, and cervical cancers are the most common in women (4). This rising burden of cancer in the region necessitates clear and well-developed national and regional cancer control plans. Accurate cancer registration is an instrumental component of any cancer control strategy (5). However, in the MENAT region, cancer registration, especially population-based, is underdeveloped, varies immensely across countries, and faces multiple logistical, political, financial, and conflict-related challenges (2, 6, 7).

While countries in the MENAT region share sociocultural attributes and history, they have very diverse socioeconomic and political contexts that impact their health and the health systems in place (Table 1). Rich countries like Qatar, Saudi Arabia, and the United Arab Emirates invest heavily in health infrastructure and developing medical cities and complexes, which raised the quality of healthcare services (8). Countries like Algeria, Egypt, Iraq, Jordan, and Lebanon have made significant progress in improving health outcomes but are still facing multiple political, economic, and social challenges that render their health systems fragile and unable to cope with rising healthcare demands (9). Countries with medium and low Human Development Index (HDI), including Syria, Yemen, and Sudan, have the highest infant mortality rates and maternal mortality ratios in the MENA region. These countries have been plagued by recurrent and chronic conflicts, further degrading their already fragile health systems (10).

Historically, the role of cancer registration was to identify standard descriptive epidemiological parameters—incidence and prevalence—which were suggested to form the basis of understanding prevention, screening, early diagnosis strategies,

TABLE 1 The socioeconomic and demographic diversity in the MENA region.

Country	Population	HDI	HDI tier	GNI per capita (US$)
Bahrain	1,472,233	0.875	Very high	39,497
Kuwait	4,268,873	0.831	Very high	52,920
Oman	4,576,298	0.816	Very high	27,054
Qatar	2,695,122	0.855	Very high	87,134
Saudi Arabia	3,640,882	0.875	Very high	46,112
Turkey	85,341,241	0.838	Very high	31,033
United Arab Emirates	9,441,129	0.911	Very high	62,574
Algeria	44,903,225	0.745	High	10,800
Egypt	110,990,103	0.731	High	11,732
Iran (Islamic Republic of)	8,855,057	0.774	High	13,001
Jordan	11,285,869	0.72	High	9,924
Lebanon	5,489,739	0.706	High	9,526
Libya	6,812,341	0.718	High	15,336
Palestine	5,250,072	0.715	High	6,583
Tunisia	12,356,117	0.731	High	10,258
Iraq	44,496,122	0.686	Medium	9,977
Morocco	37,457,971	0.683	Medium	7,303
Syrian Arab Republic	22,125,249	0.577	Medium	4,192
Mauritania	4,736,139	0.556	Medium	5,075
Djibouti	1,120,849	0.509	Low	5,025
Sudan	46,874,204	0.508	Low	3,575
Yemen	33,696,614	0.455	Low	1,314
Somalia	17,597,511	—	Not rated	1,018

HDI, Human Development Index; GNI, gross national income; MENA, Middle East and North Africa.

and treatment: survival and mortality (11, 12). This, along with national audits, could then be utilized for wider services and systems analysis (13). Additionally, cancer registries play a significant role in the evidence-based management of cancer in some high-income countries, through the analysis of health system capacities to inform planning (14). Importantly, cancer registries can provide high-quality data for epidemiological research studies and feasibility assessment for prospective interventional clinical trials, as well as quality indicators for healthcare outcome monitoring.

The Initiative for Cancer Registration in the MENAT virtual workshop

The Lancet series on global oncology emphasized the need for capacity strengthening in cancer registration across the MENAT region, for involving stakeholders in the process of cancer surveillance and for facilitating networking activities (2, 15–17). In harmony with this call and the established challenges around cancer registration, the Global Health Institute at AUB (AUB GHI), in partnership with the Naef K. Basile Cancer Institute (NKBCI) and the Research for Health in Conflict (R4HC-MENA) consortium, organized the Initiative for Cancer Registration in the MENAT (ICRIM) virtual workshop. The workshop gathered more than 30 cancer registry managers, academics, researchers, and clinicians from the MENAT region, including conflict-affected countries, to discuss challenges and propose recommendations around cancer registration.

Prior to the workshop, a survey was sent (in 2019) to 26 national and institutional cancer registry managers and administrators from 19 countries in the MENAT region (Algeria, Bahrain, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Tunisia, Turkey, United Arab Emirates, and Yemen) to understand the current landscape of cancer registration across these very different health systems. The self-administered online survey, in both English and Arabic languages, was composed of 25 questions related to cancer registration status in the respective country (10 questions) and cancer registry-specific questions (15 questions) (Supplementary Material). The results highlighted the divide in cancer registration resources and capacities in the MENAT. While GCC countries reported well-developed population-based cancer registries, countries like Syria, Yemen, Libya, and Iraq reported severely hindered cancer registration due to chronic and recurrent conflicts and displaced populations. The challenges around incomplete medical records, inaccurate death records, lack of trained staff, absence of legislation mandating cancer registration, lack of funds, weak healthcare infrastructure, and poor communication between stakeholders were also reported (6). The ICRIM Workshop took place remotely on the 3 and 4 February 2022, where the participants engaged in two rounds of discussions, framed around the results of the survey, to formulate contextualized recommendations for improving cancer registration in the MENAT.

Recommendations for improving cancer registration in the MENAT

The ICRIM discussions around improving cancer registration in the MENAT region can be distilled into the following recommendations:

1. Cancer registration procedures: To reduce the variability in registries and under-reporting and ensure the high quality of vital statistics and mortality data, cancer registration procedures and related data systems should be standardized, linked, and digitalized.

a) Establish standard operating procedures (SOPs) for cancer registries in the region, which include standardized registration forms, in addition to training, operation, ethics, and confidentiality manuals and guidelines conforming with international standards (International Agency for Research on Cancer (IARC)).

"Filing system at data sources need to be improved"—*Libya*

"Different systems for cancer data entry in the West Bank and Gaza"—*Palestine*

"Committee to standardize cancer registration methodology for the region; "Development of a standardized report form for cancer registration"—*Egypt*

"Design a Standard Procedure Manual for cancer registries"—*Oman*

b) Connect cancer registration records with civil and death registries to ensure proper data linkage.

"Link cancer registry with civil registration for demographic data"—*Palestine*

"Linkages of PBCR with other data sets, and promote data use in cancer control plans (patient satisfaction, medical expenditures, quality of life)"—*Turkey IARC Hub*

2 Collaborative governance: regional networks must be mobilized to establish a collaborative governance structure that includes key stakeholders in the region. This was a cross-cutting theme highlighted by most attendees.

a) Create a common legal framework for reporting and registration. In our survey, 8 out of 22 registries (from 19 countries) reported an absence of legislation mandating cancer registration in their country.

"Legislations mandating cancer registration: Cancer is not a notifiable disease"—*Libya*

"Create a legal framework for reporting and registration"—*Yemen*

"Decree that mandates cancer registration for each country"—*Egypt*

"Decree to notify cancer cases by all stakeholders, aiming to achieve a population-based cancer registry and quality network at national level"—*Syria*

b) Establish formal governmental linkages with cancer registration agencies under the World Health Organization (WHO), including International Association of Cancer Registries (IACR) and Global Initiative for Cancer Registry Development (GICR). Alternatively, IARC may reach out directly to national cancer registry departments to support logistical improvements while avoiding arduous red tape in heavy bureaucratic pathways.

"Lack of Major international initiatives aiming at developing or improving cancer registration (e.g., ARC/GICR site visits, training workshops, cancer registration initiatives, etc.)"—*Tunisia*

"Collaborate with IARC/GICR (WHO) to conduct more training for cancer registrars on data quality and cancer staging"—*Oman*

"Establishment of a professional collaboration with WHO, IARC on cancer registration and research"—*United Arab Emirates*

c) Introduce registry twinning programs, linking MENAT registries with established regional and global registries. This would facilitate the effective exchange of expertise, skills, and knowledge.

"More interaction between the registries in different countries, meetings for cancer registrars, site visits; Registry twinning programs"—*Turkey*

"Networking and twining"—*Jordan*

d) Establish a regional cancer registration expert group for sharing expertise and knowledge. The registry expert group would form a cancer registry scientific coordination committee that aims to ensure the proper governance, implementation, and financial sustainability of cancer registration in the region.

"Establish a Cancer Registry Scientific Coordination Committee"—*Yemen*

"Set up a MENA Scientific Committee"—*Algeria*

"Regional networking, and advocacy to increase cancer awareness and political commitments to cancer surveillance"—*Morocco*

3. Putting cancer registration on the map: a bold approach must be adopted to increase visibility, awareness, and productive collaboration on cancer registration in the MENAT and its impact on practice and policy.

a) Establish an online knowledge exchange and convening platform to bring together relevant multi-sectoral stakeholders in cancer registration to develop a "community of practice". The platform would organize regular regional webinars and workshops that approach, in a contextualized manner, topics including staff retention strategies, technical aspects, economic evaluation, and awareness around cancer registration. This platform may help maximize the dissemination and use of data and knowledge by engaging different stakeholders, including communities, and using various communication channels that can be tailored and contextualized to different audiences.

"Lack of trained staff and difficulty in trained staff retention"—*Turkey IARC Hub*

"Scientific collaboration: studies, publications"—*Turkey*

"Meeting for the key officials to explain importance of cancer registration"—*Egypt*

"Advance workshops and hands on training in specific areas on cancer registration, such as data analysis and scientific writing, quality control, cancer staging"—*United Arab Emirates*

"Regional workshops to share experience and lessons learnt"—*Lebanon*

b) Institute an annual "Day of Cancer Registration" in the MENAT. This day would be attached to an event, where cancer registrars, epidemiologists, policymakers, researchers, and clinicians convene to discuss cancer registration needs, challenges, and recommendations. Such events would include technical, policy, and dissemination meetings to create a translation pipeline from knowledge to policy.

"Plan an annual International Day of MENA cancer registries"—*Algeria*

"Look for pathways to influence decision-makers"—*Turkey*

c) Develop social media campaigns on cancer registration in Arabic, English, French, and Turkish languages. In addition, documentation should be produced to raise awareness on cancer registration targeting the general population and policymakers in the MENAT region.

"Increase awareness advocacy and marketing of cancer registration"—*Jordan*

"Raising awareness to the indispensability of accurate cancer surveillance for cancer control"—*Morocco*

4. Capacity building: capacity building for cancer registration should be expanded to train more data entry staff to utilize electronic systems and ensure proper data capture (using CanReg5 at minimum).

This theme was particularly pertinent to LMICs in the MENAT region, including Palestine and Iraq. Cancer registration capacity was noted to

a) Implement regular capacity-strengthening trainings by the GICR to all registries in the region. Such training should be expanded to include all registry staff, in addition to training of other key stakeholders including staff at the ministries of health and at sources of data (i.e., centers where cancer is diagnosed and treated).

"Training of focal points on CanReg5 and abstracting data"—*Palestine*

"Continuous visits and evaluation by International Agency for Research on Cancer (IARC)/(GICR)"—*Iraq*

"Expand cancer registration capacity of the existing centers through the training of personnel and upgrading of facilities"—*Yemen*

"We need workshops at all levels, at Ministry level and at medical level"—*Yemen*

"Provide regular training on cancer registration"—*Algeria*

b) Organize an easily accessible and contextualized certification program for cancer registrars. Advanced training for key staff would be undertaken to establish peer to peer "trainers" team within the region.

"None of the cancer registry personnel is a Certified Tumor Registrar"—*Palestine*

"Provide advanced training for the key staff to establish a 'trainers team'"—*Iraq*

"Training workshops to train registers and improve the quality of reporting"—*Sudan*

c) Develop an online course for cancer registration, taking into account local and regional challenges. The course would be asynchronous and would provide the basis for developing a cancer registration certificate.

"Provide basic Cancer Registration Training Programs for all staff. A structured certification program might be organized"—*Iraq*

In conclusion, the workshop revealed a profound need among those involved in cancer registration in MENAT for increased visibility, training opportunities, and political support from international entities and for developing regional collaboration and cooperation. In the discussions, it was clear that the needs and challenges were most severe in countries impacted by conflict. Further convening events, including workshops, meetings, and conferences, are needed to garner the necessary support and buy-in from cancer registration stakeholders to materialize the recommendations that were laid out in this article. ICRIM has been mandated to continue its leading role on these issues in collaboration with all stakeholders in the region.

ICRIM

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Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

ZA-S: conceptualizing, writing-original draft, supervision, writing-review and editing, project administration. DM: conceptualizing, writing-review and editing, supervision; SA: conceptualizing, writing-review and editing, supervision; AS: conceptualizing, writing-review and editing, supervision; GA-S: conceptualizing, writing-review and editing, supervision; IF: conceptualizing, writing-review and editing, supervision; RS: conceptualizing, writing-review and editing, supervision, funding acquisition; AA: conceptualizing, writing-review and editing, supervision; SS: conceptualizing, writing-review and editing, supervision, funding acquisition; AT: conceptualizing, writing-review and editing, supervision, funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cancer diagnosis in areas of conflict

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To date, many Arab countries within the Middle East are facing political, financial, and social instability from war and conflicts. These conflicts have led to severe resources shortages and sometimes complete breakdowns in cancer care and diagnosis. Cancer diagnosis at early stages is the most vital step in achieving optimal cancer care and outcomes. Shortages in cancer diagnostic services have meant that many people within areas of conflict are ultimately deprived of these services in their own countries. Therefore, many of these cancer sufferers must bear travel expenses to neighboring countries in order to seek these services. A lack of prevention, screening, and diagnostic services for this population is known to deepen the cancer care deficit within these areas. Additionally, the financial burden of traveling abroad alongside the need to secure childcare and time off work can be overwhelming. As a result, patients within areas of conflict are frequently diagnosed at later stages and are less likely to receive optimal management plans. Though conflict-affected regions encounter many similar challenges in delivering quality cancer care, pronounced region-specific differences do exist. Therefore, it is important to build a roadmap that can provide tailored solutions to deficits in instruments, manpower, and facilities for each and every region involved. Keeping in mind the importance of collaboration and coordination on national and international levels to address the ground disparity in cancer diagnostic services, the main objective of this review article is to examine the significant problems, shortages, and difficulties in providing cancer diagnosis with a focus on imaging to conflict-affected populations in the Middle East (mainly Iraq, Syria, Yemen, and Sudan). Finally, we discuss how access to cancer diagnostic imaging services has been impacted by these conflicts.

KEYWORDS

cancer diagnosis, imaging, war, conflict, refugees, Middle East, resources

1 Introduction

Critical cancer diagnostic care, including the synergistic benefit of combined diagnostics and appropriate treatments, has been adversely impacted by conflicts within many Arab countries. At the time of conflicts, many hospitals, centers, or private sector providers were destroyed, rendered non-functional, or variably compromised (1). Concurrently these sites experienced a shift of focus toward military services, with less stable financial support for health services. These and other factors have contributed to a regression in achieving developmental milestones for cancer diagnostic services.

The burden of cancer diagnosis extends beyond the affected nations to many of their bordering neighbors, compelled to rally additional efforts to provide healthcare services insofar as possible. Many cancer patients, including refugees, cannot afford the costs of cancer diagnosis and are not covered by insurance companies. This can lead to significant, often catastrophic health expenditures for these patients and their families. Common to this patient population are cancer diagnoses at advanced stages, too late to hope for cures. Life-prolonging and/or palliative management can be considered. Meanwhile many others are forced to endure their cancers without any interventions offered or received.

In parallel fashion, cancer care has been significantly impacted by conflicts and wars (2). This was reflected in the lack of access to optimal cancer surgery, radiation therapy, and chemotherapy services, as well as cancer diagnosis (2). Long-term conflicts are known to paralyze many aspects of cancer care, including demands, supplies, equipment, infrastructure, and personnel (1). Many cancer care seekers are forced to travel abroad for better cancer care delivery (3). The majority of cross-border cancer care seekers will end up experiencing financial and economic hardship in addition to the psychological burden of the disease itself (3).

The outbreak of war led to the termination of training programs in many countries, largely due to a lack of experienced personnel. Iraq is one of the countries where nuclear medicine training has ended due to the conflict in the region. In addition, many advanced diagnostic services are still not available in Arab countries that have been affected by war. The departure of many scientists, physicians, and physicists in search of a safer way of life has constituted a major barrier. Staff members who have remained currently deal with a wide range of issues, including a lack of modern services, a lack of local support networks, and a lack of steady financial support. Revision plans must be developed to improve diagnostic services in conflict zones. The goal of the international oncologic community should be to optimize cancer diagnostic and therapeutic services. Potential advantages of this optimization strategy include early cancer detection and establishing cultural and economic solutions to enhance the overall plan (4). This would require cooperation between societies, associations, and private cancer institutions.

The primary goal of this review article is to discuss difficulties experienced during conflicts in Arab countries (mainly Iraq, Syria, Yemen and Sudan). Addressing the known barriers and concerns in cancer diagnosis, with a particular focus on cancer imaging capability. Considering elaborating on comparable and nation-specific issues. Finally, develop a revival strategy for every country in order to offer the best diagnostic care possible.

2 Cancer diagnosis in Iraq

Iraq has experienced significant hardship due to various wars, sanctions, and embargoes. The significant impact of multiple wars, the 2003 invasion, and subsequent conflicts have severely affected the delivery of cancer diagnostic services. Since 1980, overall local healthcare delivery has declined remarkably. A possible link has been drawn between the use of depleted uranium-tipped ammunition and white phosphorus munitions in warfare and the development of cancer in Iraqi cancer patients (5). Over the last four decades, the government has been more interested in the security issues by nourishing its military service than in caring for medical demands. Simultaneously, cancer incidence increased by 50% during the last decade (6). The high incidence of cancer, coupled with inadequate healthcare infrastructure, is definitively impeding cancer diagnosis and treatment services (7). In order to revive cancer diagnostic services, a plan must be put in place to address and circumvent all known problems. It's also necessary to establish a lasting infrastructure in order to control cancer on both local and global scales (8).

2.1 The current status of manpower in Iraq

There are relatively few qualified doctors, technicians and scientists in Iraq for cancer diagnosis. The lack of manpower is known to have a severe impact on diagnostic service capacity. The number of experts able to provide accurate pathologic diagnoses for childhood cancers is very limited, and they are often very busy (9). There is an insufficient number of female radiologists specialized in breast imaging. Similarly, there is a severe shortage of male radiologists in the field of breast imaging. This is further complicated by patient conservatism and religious fervor that are known to paralyze the delivery of this essential service. The number of such highly specialized specialists, such as radiation oncologists, interventional radiologists, and pediatric onco-radiologists, is also inadequate (Table 1). Other specialties, such as nuclear medicine (NM) physicians and technicians, as well as endoscopists, are primarily found in tertiary hospitals and large cities (Table 1). One of the valid

TABLE 1 Manpower facts and problems in Iraq.

Specialty	Amount of manpower	Known problems
Paediatric oncology	10	- Limited numbers - Busy schedules
Radiologists	570	- Defect in female radiology service - Limited interventional radiologists - Inadequate numbers of paediatric onco-radiologists
Nuclear medicine	21	- Limited numbers of board-certified nuclear physicians
Nuclear technologists	6	- Inadequate numbers of nuclear technologists
Endoscopists	35	- Sub-optimal numbers

solutions to this problem is to build a local network of specialists with similar scientific interests. This would help physicians to work together more effectively and efficiently and make it easier for new training programs to be adopted. The result, a new generation of specialists would emerge and hopefully fill the relevant gaps.

2.2 Infrastructures, supplies, demands, and systematization

The use of diagnostic imaging services is essential for correctly diagnosing, staging, and monitoring the treatment and progression of cancers. As well, imaging is used to guide procedures such as the placement of ports (central venous catheters) for systemic administration of medicines per evidence-based protocols. Imaging also diagnoses complications or co-morbidities, such as pneumonia. In Iraq, cancer diagnostic services would benefit from systematic reviews, especially in the public sector. After the Gulf War, material shortages became more evident (10). The imposed sanctions have banned a range of cancer services, including linear accelerators, PET machines, some chemotherapy drugs, and radioisotopes (11). In order to restrict Iraq's capability to manufacture weapons of mass destruction, the country experienced a 13-year deficit in cancer diagnosis. During that timeframe, many Iraqi cancer patients were forced to travel abroad to access advanced diagnostic services. One of the main challenges is the lack of availability of equipment for diagnostic imaging such as mammography, endoscopy, and pediatric imaging. The lack of equipment was evident for some time and was accompanied by a 50% cancer incidence surge in the last decade (6), which made the problem worse (Table 2). During wars, the contamination resulted from depleted uranium and other toxic wastes are among justified observations for the resultant cancer diagnosis to incidence discordance (12). For example, there are a maximum of 180 CT units and 125 MR units in the country. These values translate to only 4.5 and 2.3 unites per million people (13). These values are still insubstantial when plotted against the capacity of services achieved in neighboring countries like Saudi Arabia which has achieved values of about 25.1 and 15.8 respectively (14). A recent microsimulation model by Ward et al. suggested that countries with few imaging units could benefit significantly from optimizing and expanding their resources (15). It is important to note that the biggest improvement in cancer diagnostic care would come from improving MRI and CT equipment (15).

To date, many public sector hospitals have relied on physical archiving for patients' data. However, this method is becoming increasingly outdated and inefficient. Physical archiving is considered to be the least secure and most primitive method of archiving. A large number of data sets previously stored physically are either missing or difficult to recover, and many more were destroyed during previous conflicts. Electronic information systems, such as Picture Archiving and Communication Systems (PACS), Radiology Information Systems (RIS), or Health Information Systems (HIS), are needed to store and access patient data easily.

2.3 IRAQI training program: Achievements and drawbacks

During the time of conflict in 1985, the Iraqi training program was established (9). The goal of this program is to meet the increased demand for expert professionals in various fields. The program has been successful in providing specialists for many medical and diagnostic branches for several years. There are several advanced diagnostic fields that are, however, not addressed in the current plan, including molecular cytogenetic immunopathology, next generation sequencing (NGS) training, and nuclear medicine (NM) board program. These fields lack senior specialists able to adopt the new training programs. Noteworthy and promising, the Iraqi Ministry of Health has implemented a program to address the identified problems in coordination with the Iraqi Board for Medical Specialties. This resulted in the establishment of a board-certified radiotherapy training program to address the shortage in this field (16).

TABLE 2 Current status of diagnostic services among Iraqi Provinces.

Kurdistan Including (Erbil, Sulaymaniyah and Duhok)		
X-ray units	234	
Ultrasound units	92	
CT units	15	
MR units	8	
Gamma Camera units	3	
PET/CT units	3	
Rest of Iraq Including (Baghdad, Mosul, Basra, Dhi Qar, Babil, Anbar, Diyala, Kirkuk, Salah Al-Din, Najaf, Wasit, Qadisiya, Karbala, Maysan, and Muthanna)		
X-ray units	1585	
Ultrasound units	1356	
CT units	165	
MR units	117	
Gamma Camera units	11	
PET/CT units	9	
Total number of resources		Units per million
X-ray units	1819	45.5
Ultrasound units	1448	36.2
CT units	180	4.5
MR units	125	3.2
Gamma Camera units	14	0.35
PET/CT units	12	0.3
Current Observation		
Severe limitations are currently observed in nuclear medicine field followed by conventional imaging (CT and MR units). Future vision should provide effective plan to invest in these two major services to fortify cancer diagnostic service delivery in the country.		

2.4 The current status of the nuclear medicine service in Iraq

The NM field had provided the most advanced diagnostic services among all neighboring countries up until 1980. Multiple NM governmental centers in large provinces provided diagnostic and therapeutic services (17). Before 1990, Iraq relied on local sources of radioiodine to meet the needs of each nuclear medicine center. After the establishment of sanctions, the country was no longer able to produce radioiodine and became reliant on international suppliers (Table 3). The war also had a profound impact on the Iraqi training program for NM. The training program for NM specialists was stopped in 1996, resulting in a limited number of specialists in the following years. To date, many of the available specialists in NM have been forced to complete their residency and training programs in Jordan to gain the experience required to serve their country. There is a high demand for NM technicians, but there is a shortage of qualified professionals. A concurrent lack of radio-pharmacists and radiochemists exists, likely due to a lack of certified education and training programs in these disciplines. There is not yet an established local society for NM in Iraq. NM practice in 2003 was limited by a lack of equipment, with only 5 gamma cameras and no SPECT/CT or PET/CT available (Table 3). This translates into a ratio of 0.2 units per million people (13). Despite increasing investment in infrastructure, Iraq is still ranked among the least-resourced Arab countries in terms of the number of equipment units per million people. The current number of SPECT/CT devices, gamma cameras, and PET/CT machines is still not adequate, at only 0.4 units per million (13). Regions that are free from conflict usually have much better infrastructure delivery. For example, Kuwait and Jordan have a total of 10.3 and 2.0 per million, respectively (18).

TABLE 3 Table demonstrating the effects of UN Sanctions on Nuclear Medicine services and program in Iraq.

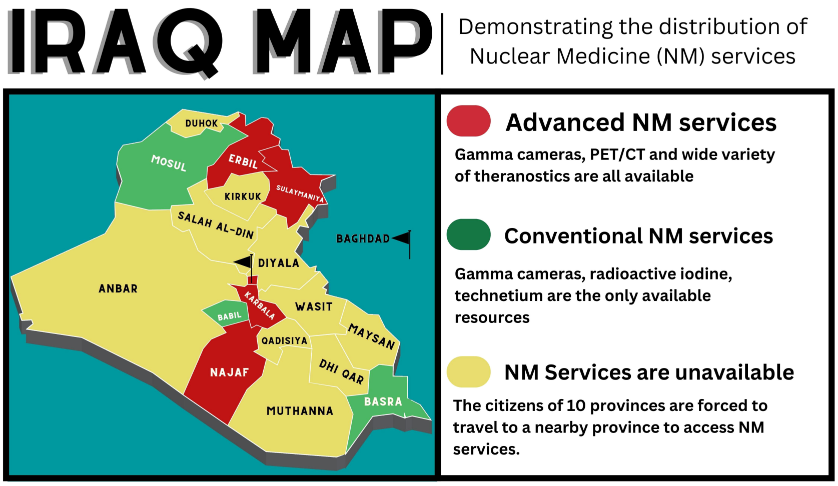
Items	Before Sanction	During Sanction	After Sanction
No. of Gamma camera units	5	0	+7
No. of PET/CT units	0	0	+14
No. of Private sectors providing nuclear medicine services	0	0	+11
RAI^{131} Supply Source	Local	Prohibited	Imported
Nuclear Medicine training Program	Established	Stooped	Not Adopted

2.5 Overcoming the triple: Non-homogeneity, bungling, and workforce shortages

The war against Islamic State in Iraq and Sham (ISIS) has left some of Iraq's provinces (i.e., Mosul) with destroyed health care centers. Many of Mosul's hospitals were severely damaged during the conflict and are currently not operational. At the same time, many of the southern provinces were involved in mismanagement of resources, which deprived locals of access to cancer diagnostic services. In addition, the lack of certain medical specialties and subspecialties is evident in many rural areas and major provinces. The current map of cancer diagnostic services in Iraq shows a non-uniform distribution (Figure 1). The current distribution of cancer care services in Iraq implies that residents of the majority of northern provinces, along with a few southern provinces as well as western provinces, have to travel to Baghdad, Erbil, Karbala, or Najaf to access the latest services in cancer diagnosis. Additionally, most of the advanced centers and hospitals are located within the private sector (7). These hospitals are increasingly offering their services without any insurance program to cover the expenses (7). This trend is likely to continue as the costs of health care continue to rise. Many patients will experience financial hardship in order to access current medical services. To ensure cancer diagnostic services are effective, it is necessary to overcome the challenges mentioned above. Assessing and strategically prioritizing service needs, based on population size, infrastructure, and manpower deficits, are vital to achieving the best possible patient outcomes.

2.6 The current impact of addressed problems on cancer diagnosis

There is a substantial disparity in the quality of cancer diagnostic services available in Iraq, when compared to its more stable neighboring countries. It has been observed that Iraq is one of the Middle Eastern nations wherein cancer incidence has increased significantly despite inadequate cancer diagnosis (6). During times of war and turmoil, Iraq is unable to maximize its potential in the development of its diagnostic and therapeutic sectors. This problem is further complicated by the



Gamma cameras, PET/CT and wide variety of theranostics are all available

Gamma cameras, radioactive iodine, technetium are the only available resources

The citizens of 10 provinces are forced to travel to a nearby province to access NM services.

FIGURE 1
The distribution of NM services among Iraqi provinces.

lack of security and financial instability that are known to hugely impact cancer diagnosis.

3 Cancer diagnosis in Syria

In Syria, prior rapid progress in cancer diagnostic capacity was halted and has regressed considerably since the outset of civil war. As a result of the conflict, several previously active diagnostic fields have suffered shortages of personnel, destruction of infrastructure, or neglect. The economic constraints and shift in focus to military and weaponry fields have left many medical and oncologic services underdeveloped. The departure of many well-known scientific figures, specialists, and physicists from the country was driven by them seeking a more stable environment. A comprehensive and long-term solution is necessary to effectively address cancer diagnosis in Syria.

3.1 The current status of manpower in Syria

The findings of a recent study indicate that many diagnostic cancer departments are facing significant shortages, neglect, and workload issues (19). The problem of an imbalanced workload/workforce has become increasingly prevalent in recent years, particularly in the aftermath of the war. The unavailability of many specialized medical services has had a detrimental effect on besieged areas. According to recent surveys given to cancer specialists, only Damascus among the seven regions offers preventive measures such as mammograms, colonoscopies, and pap smears (Table 4) (20). In East Aleppo, there are no oncologists or pathologists to serve the population of 500,000 people (20). There is a lack of trained technicians in the field of nuclear medicine, which includes medical physicists, specialists in hybrid imaging, and radiopharmacists/radiochemists (Table 5). This lack of trained personnel limits the advancement of nuclear medicine technology. This is especially the case for PET/CT, where there are only a few specialists and technologists.

3.2 Infrastructure, supplies, demands, and systematization

Since the conflict in 2011, Syria has been under economic sanctions that have had a negative impact on its cancer diagnostic system (Table 4). Sanctions prevented the import of essential supplies, such as non-domestic manufactured radioisotopes and equipment parts, preventing important cancer diagnostic equipment from being repaired. All clinics currently have access to basic diagnostic tools, such as laboratory blood tests, biopsies, and basic imaging studies (20). There is a lack of access to conventional imaging modalities in besieged areas as compared to major cities (Table 4). Positron emission tomography (PET) scanners are only available in Damascus, and patients have to pay for them (12). To date, advanced cancer diagnostic services, such as genetic testing and interventional radiology, are not available in many areas (20). These vital services are currently not adopted and remained unexplored in both pre-conflict and post-conflict times. Patients who can afford to pay for advanced services are often referred to neighboring countries for care. But many cancer patients cannot afford to travel or pay for expensive treatment, so they do not receive the care they need. The lack of funding creates difficulties in managing equipment, including maintaining it properly and ensuring its quality. There is a lack of PACS, RIS,

TABLE 4 Summary of available infrastructures for cancer diagnosis in Syria. Modified from the source "Cancer Care in Times of Crisis and War: The Syrian Example, Table 2".

Resources	Major Provinces	Besieged Provinces
Pathology	Available	Limited*
Conventional Imaging	Available	Limited
Mammography	Limited	Extremely limited*
Nuclear Medicine Services	Limited	Not available
Screening	Not available	Not available
Genetic testing	Not available	Not available
Clinical Trials	Not available	Not available
Teleradiology	Not available	Not available

***Limited:** Services that are clustered in city capital of all besieged provinces but lacking in peripheral areas. Resources capabilities, infrastructure and manpower are suboptimal in these areas.

***Extremely limited:** Services that are confined to city capital of only few provinces but lacking in many other provinces. Resource capabilities, infrastructure and manpower are suboptimal in these areas.

TABLE 5 Past and current status of manpower and infrastructure in Syria demonstrating pattern of slow growth, no growth and degradation in certain resources and personnel during war.

Resource	Total Number of Diagnostic units			Observation
	Before War	Current Status	Current units per million	
X-ray	992	1001	58.8	Slow Growth
CT	297	300	17.6	Slow Growth
MRI	152	152	8.9	No growth
SPECT	4	7	0.4	Slow Growth
PET/CT	2	2	0.12	No growth
Mammography	200	207	12.1	Slow Growth
Cyclotron	1	1	0.06	No growth
Personnel	Total Number of available Staff in charge			Observation
	Before War	Current Status		
NM Physicians	11	5		Degradation
NM Technologists	12	11		Degradation
Medical Physicists	24	25		Slow Growth
Radiologists	98	73		Degradation
Future Recommendation				
The current observation necessitate investment in nuclear medicine field to ensure even and adequate delivery of this vital service. Additionally, revival plan must be created to account for current problems in each and every department.				

or HIS. Currently, teleradiology is unavailable due to insufficient IT infrastructure (PACS, RIS, HIS).

3.3 Syrian refugees: A new problem since the war

The Syrian conflict has resulted in the displacement of millions of Syrians, who have fled to neighboring countries like Turkey, Iraq, Jordan, Egypt, and Lebanon (Figure 2) (21–26). The Syrian refugee crisis has also led to an influx of refugees into Europe, with many making the dangerous journey across the Mediterranean Sea to countries like Greece, Germany, and Sweden in search of safety and refuge. Many host countries have experienced financial difficulties as a result of providing cancer diagnostic care for many cancer sufferers among refugees. The King Hussein Cancer Center (KHCC) in Jordan has reported that a total of 356 Syrian refugees have received full cancer care (27). The King Hussein Cancer Foundation Goodwill Fund was responsible for paying all patients' costs, which amounted to around USD $11 million (27). Many Syrian refugees and cancer patients are currently accessing cancer diagnostic services at KHCC (27). The Nuclear Medicine Department at KHCC has been providing advanced cancer diagnostic and therapeutic services since 2013 (28). Additionally, Abdul-khalek et al. carried out a broad-range population study on the total cost of cancer diagnostic and therapeutic services among Syrian refugees in neighboring countries (29). This study found that the total cost of cancer diagnosis and treatment services for refugees was approximately 140.23 million euros (29). There are many Syrian refugees who have not had access to cancer diagnostic services. It is important for countries that host cancer patients to cooperate with charities and other organizations that can provide financial assistance. Making this change will ease the financial burden for both cancer patients and the countries hosting them.

3.4 The current impact of addressed problems on cancer diagnosis

When assessing the current status of cancer diagnosis in Syria, one can discern a division of the country into two major subgroups. The country is currently divided into besieged areas and governmental areas. The major cities and provinces are currently under the control of the government, while other cities are not (Table 4). The disparities in the provision of cancer diagnosis between the two groups have been attributed to the consequences of these conflicts (20) (Table 4). At present, regions under regulation are finding it challenging to meet requirements, though they may have attained triumph in particular disciplines or areas. Conversely, areas under siege

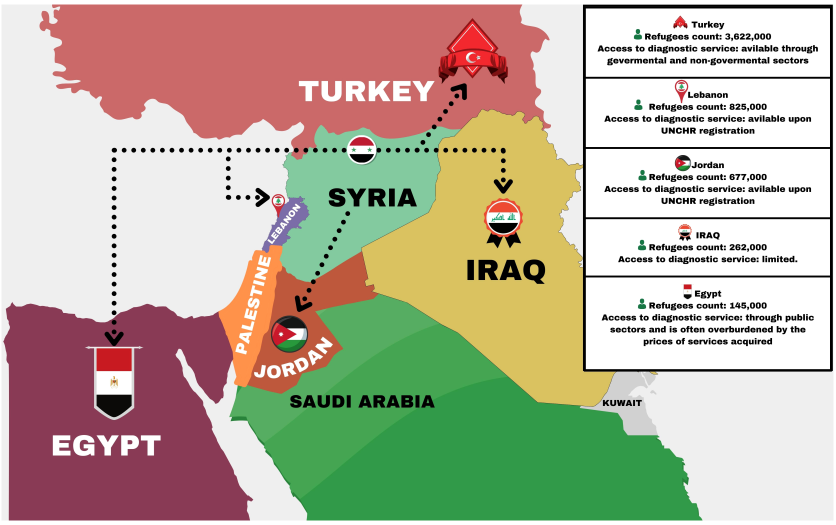


FIGURE 2
The current situation of Syrian refugees in surrounding nations in terms of numbers and access to services for cancer diagnosis. Modified from the Source "Syria Regional Refugee Response 2022".

are deprived of major diagnostic services, either unavailable or severely restricted. In response, effort must be duplicated to account for this non-uniformity that's known to affect cancer diagnosis in this country.

4 Cancer diagnosis in Yemen

Yemen is facing significant challenges in terms of political unrest and economic underdevelopment. According to a recent study, nearly two-thirds of the population are living in poverty, and over half are food-insecure (30). Collectively, the population is struggling to advance itself in an increasingly globalized world. This has had a significant impact on patients' ability to pay for cancer diagnostic services, making cancer care and overall healthcare facilities less affordable (31). According to the latest estimates, Yemen has the lowest health spending in the world, as well as in the Middle East (32). This is a major problem for the country, as it strives and toils to provide adequate healthcare for its citizens. Cancer diagnostic deficits are caused by a variety of problems that persist today.

4.1 The current status of infrastructure in Yemen

The seven-year conflict in Yemen has had a significant adverse effect on the nation's health sector, especially in terms of cancer treatment. Cancer patients experience difficulties in accessing basic cancer diagnostic services as well as comprehensive cancer care. Cancer patients in Yemen face two main challenges: their personal battle against cancer and the fight to get access to cancer diagnostic and therapeutic services. The cancer diagnosis rate in Yemen is significantly lower than average due to the extremely low number of cancer imaging equipment, especially evident in NM and MR imaging (33). As a result, cancer incidence is greatly underestimated and does not reflect the true picture of cancer trends on a national level. According to data, there are currently fewer than 100 CT scanners, 30 MRI units, and 50 mammography devices in use (33). NM is least of all diagnostic services in terms of existing equipment numbers with only 5 gamma cameras available locally (0.2 units per million people) but unfortunately, they are predominantly nonfunctional due to lack of manpower and radiopharmaceuticals. It is noteworthy that Yemen is the only Arab country that does not provide advanced nuclear diagnostic services such as SPECT, SPECT/CT or PET/CT, which are not available in the country (18).

4.2 The burden of financial instability

Currently, the only local cancer centers that provide most of the diagnostic services required for many Yemeni cancer patients are located in Hadramout and Sana'a. Established in 2013, the National Oncology Center in Hadramawt is a non-profit cancer center known for providing cancer diagnostic and treatment services (30). Even though the center plays a vital role, the salaries of the working team are not always covered by the government. This is a problem that needs to be addressed in order to ensure that the center can continue to function properly

(30). The organization's working staff are financially dependent on donations from charitable foundations and small-town organizations in order to maintain the operating budget and offer nonprofit services (30). This dependence means that the center is limited in its ability to provide services and meet its operating budget (30). The center has recently faced significant challenges in continuing to provide free services due to the political unrest in Yemen, the shifting economic climate, and the lack of external funding (30). This refers to clinics, chemotherapies, medications, lab work, and mammograms. Because it doesn't have enough money, the center will have to shut down and stop giving its services (30). The lack of health insurance reflects lower access to care, and the financial burden is known to limit the patient's adherence to cancer diagnosis and care (34). This is why cancer sufferers are often diagnosed at advanced stages.

4.3 The effects of war on nuclear medicine centers

Prior to the outbreak of war in Yemen, nuclear medicine services were already inadequate. Through that time, only primitive nuclear medicine tests were carried out through the use of gamma cameras, which were the sole operational units in the nation. Yemen's conflict has had a significant impact on NM services and centers. Despite the fact that the country has a sufficient number of nuclear medicine physicists, the country's lack of NM physicians has resulted in the discontinuation of limited and primitive NM diagnostic services. According to a recent report, the import of radioisotopes has been discontinued at Al-Thawra Hospital in Sana'a, rendering the gamma camera useless (33). The other nuclear medicine department in Aden has been unable to provide any services since they failed to install a gamma camera. Yemen doesn't have enough high-tech medical imaging services, so many people, who can afford it, have to leave the country to get care.

4.4 Seeking treatment abroad

The lack of financial stability and qualified medical staff, as well as the absence of necessary diagnostic and therapeutic options, have forced many cancer sufferers to travel abroad (33). Cancer patients often receive care at a later stage when the disease is more advanced. Patients who cannot afford to travel for medical care are not getting optimal care in their home country. Providing financial stability, and progressively establishing new basic and advanced healthcare facilities of high standards, are lofty goals; but these may be the best initial infrastructural steps toward sustainably improving oncologic healthcare for the Yemeni people.

4.5 The current impact of addressed problems on cancer diagnosis

Cancer diagnosis, incidence, and care in Yemen have been undervalued since the outbreak of conflict. Financial instability, personnel departure and insecurity have complicated the access to cancer diagnosis. Many patients are seeking treatment and care outside the country in hopes of obtaining a more effective treatment plan. The provision of cancer services is often suboptimal, resulting in an impediment to effective cancer diagnosis and treatment.

5 Cancer diagnosis in Sudan

Sudan, officially the Republic of Sudan, is a country in Northeast Africa. It shares borders with the Central African Republic to the southwest, Chad to the west, Egypt to the north, Eritrea to the northeast, Ethiopia to the southeast, Libya to the northwest, South Sudan to the south, and the Red Sea to the east. It has a population of about 45 million people as of 2022 and occupies 1,8 million square kilometers, making it Africa's third-largest country by area, and the third-largest by area among Arab countries (35). It was the largest country by area in Africa and the Arab countries until the secession of South Sudan in 2011, since which both titles have been held by Algeria (36). Its capital is Khartoum, and its most populous city is Omdurman (part of the metropolitan area of Khartoum).

5.1 The past and current status of overall diagnostic services in Sudan

Sudan ranked among the first African countries to forge ahead in the areas of diagnosis and treatment of cancer. The first comprehensive cancer center opened there in the early 1960s, the Radiation and Isotope Centre in Khartoum (RICK) (37). Thereafter Sudan initiated establishment of their first National Cancer Registry (NCR) in 1967 (36). Unfortunately, currently there is no active national cancer registry in the country. However, Sudan, like the rest of the world, has seen an increase in the incidence of cancer over the last few decades (38). In March 2021, the Global Cancer Observatory (GLOBOCAN of the WHO/International Agency for Research on Cancer (IARC) estimated 27,382 new cancer cases among both sexes in the year 2020 in the capital of Sudan (Khartoum) compared to 6,771 new cases in 2010 (39, 40).

5.2 Current status of manpower and infrastructure

To date, there are fourteen (governmental and private) health facilities that provide cancer care in Sudan (Table 6). Of

TABLE 6 Treatment facilities in Sudan in the governmental and private sectors. Adapted from the Source "Cancer Care in Arab World, Chapter 16, General Oncology Care in Sudan, Table 16.3".

No.	Name of the facility	Established	Location	Sector	Services
1	Khartoum Oncology Hospital (RICK)	1962	Khartoum state Capital of Sudan	Governmental	- Radiation - Nuclear medicine - medical oncology services
2	National Cancer Institute	1997	Wad Madani city Second city of Sudan Middle Sudan	Governmental	- Radiation - Nuclear medicine medical oncology services
3	Tumor Therapy and Cancer Research—Shendi	2008	Nile Valley state North Sudan	Governmental	- Radiation - Nuclear medicine medical oncology services
4	Khartoum Oncology Specialized Center	2010	Khartoum state Capital of Sudan	Private	Medical oncology services
5	Khartoum Breast Care Center	2010	Khartoum state Capital of Sudan	Private	Medical oncology services
6	Dongola Cancer Center	2012	North state North Sudan	Governmental	Medical oncology services
7	Taiba Cancer Center	2013	Khartoum state Capital of Sudan	Private	Medical oncology services
8	Shafi Specialized Oncology Center	2015	Khartoum state Capital of Sudan	Private	Medical oncology services
9	East Oncology Center	2015	Qadarif state East Sudan	Governmental	Medical oncology services
10	Port Sudan Oncology Center	2015	Red Sea state East Sudan	Governmental	Medical oncology services
11	Kordofan Cancer Center	2015	North Kordofan state West Sudan	Governmental	Medical oncology services
12	Merowe Oncology Center	2017	North state North Sudan	Governmental and Private	Radiation Nuclear medicine medical oncology services
13	Nyala Cancer Center	2019	South Darfur state West Sudan	Governmental	Medical oncology services
14	Al-Fashir Cancer Center	2020	North Darfur state West Sudan	Governmental	Medical oncology services
15	Universal Hospital Sudan	2021	Khartoum state Capital of Sudan	Private	Radiation Nuclear Medicine Medical oncology Services

these, only three governmental facilities provide comprehensive cancer care in Sudan, and they are located in the center of the country. Others either lack at least one major diagnostic/treatment discipline (pathology, radiology, NM, radiotherapy) or provide only chemotherapy-based anticancer treatment. Furthermore, although there are national training programs in some of the aforementioned cancer-related specialties, there is still a tangible lack of professionals and personnel dealing with the significant rise in cancer incidence. This is superimposed upon the fact that well-qualified and experienced staff leave the country for better prospects abroad. As well, because of the political and economic instability, there is a lack of a comprehensive national vision to address such shortcomings in this health sector. A compounding factor is the impact of sanctions imposed on Sudan following the takeover of a prior regime in power, which has affected the reach of state-of-the-art equipment and software in the field. Currently, there are a total of seven (active) NM centers in the country (governmental and private) (Table 7). Interestingly, only two centers established outside the capital city provide conventional nuclear diagnostic services through available SPECT devices (Figure 3). On the other hand, the remaining five NM centers are all situated in the capital city and offer radioactive nuclides like technetium and fluorine. Since there are no cyclotrons, reactors, or generators in the country, all of the radioactive materials are brought in from other countries. To put this shortage of diagnostic services in context, and when comparing NM services in neighboring countries, Egypt for example, there are 88 PET/CT centers in the country, 55 in Cairo alone, 11 in Alexandria, and 22 centers in the rest of the country. Not to mention the presence of 3 Cyclotrons, 1 PET/MR and 3 PEM units in Cairo, in addition to a radiopharmaceutical factory that covers 60% of the country needs from radiopharmaceuticals.

Since its independence, Sudan has endured a series of violent conflicts and political instability in terms of being the country with the most coup attempts on the continent, with a tally of 17 attempts (6 of which led to a successful takeover of power). Conflicts started with the civil war in the southern part of the country (ended by the secession of South Sudan) at the east-central borders with Ethiopia and Eritrea, and finally the war in Darfur, west of the country. As a result, the country went through decades of decline in infrastructure and a lack of basic supplies of water and sanitation, power, and transportation in areas of conflict. This situation has produced a humanitarian crisis that burdens not only the areas of conflict but the whole country. For example, the internally displaced people (IDPs) from the region of Darfur are estimated to be around 3 million as of January 2022, according to the United Nations High Commissioner for Refugees (UNHCR). For these reasons, the health services, including cancer diagnosis, in the regions of conflict as well as in the relatively peaceful neighboring regions have been significantly affected as an inevitable sequela. For example, there is only one area in the west of the country with radiology services, one pathology lab, and no NM services, even though about 9 million people reside there.

5.3 The lack of cancer diagnostic services

Prior to 2003, when the Darfur conflict began, there was no cancer care in the region at all. However, as Table 6 shows, the region has recently seen the opening of multiple centers that

TABLE 7 Nuclear medicine centers in Sudan in the governmental and private sectors.

No.	Name of the facility	Location	Sector	Equipment	Workforce
1	Khartoum Oncology Hospital (RICK)	Khartoum state Capital of Sudan	Governmental	SPECT SPECT/CT	18
2	National Cancer Institute	Jazirah state Second city of Sudan Middle Sudan	Governmental	2 SPECT	8
3	Tumor Therapy and Cancer Research—Shendi	Nile Valley state North Sudan	Governmental	SPECT	5
4	Alneelain Center	Khartoum state Capital of Sudan	Private	SPECT	10
5	Ahmed Gasem center	Khartoum state Capital of Sudan	Private	SPECT	3
6	Royal Care Hospital	Khartoum state Capital of Sudan	Private	SPECT	4
7	Universal Hospital Sudan	Khartoum state Capital of Sudan	Private	PET/CT SPECT/CT	11
8	Merowe Oncology Center	North state North Sudan	Governmental and Private	SPECT	0

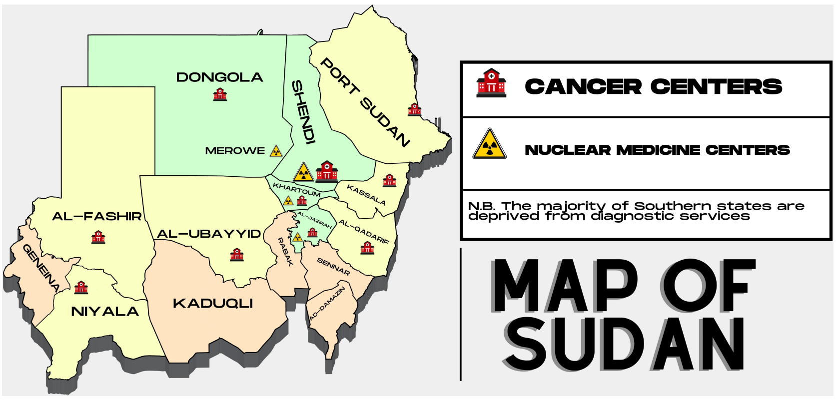


FIGURE 3
The availaby of cancer diagnostic service providers in Sudan.

provide at least one chemotherapy clinic with an on-site oncologist. Nevertheless, the other services related to diagnosis and treatment are still missing in an area yet to cope with the aftermath of the conflict and the lack of basic services as explained above. The case is not quite different in other areas of the country where multiple states still lack well-established pathology labs and NM services, and all patients are sent to the capital insofar as possible.

When we look at the radiology services, we find that there are only 6 mammography units in the whole country in just two regions (Khartoum “5 machines” and Wad Madani “1 machine” cities). 17 CT machines in Khartoum the capital, 6 in Wad Madani city and 1 device in all of Senar, Kasala, Gadarif, Merowe, Kosti, Halfa, Shendi, Alobied and Tangesi cities. 10 MRI machines in the capital, 3 in Wad Medani and only one machine in rest of the country found in Merowe.

Currently all radiopharmaceuticals are imported from outside the country with no domestic production. Furthermore, theranostic applications are limited to I^{131} therapeutic clinics, provided in only two centers in the country. These clinics are not open on a regular basis, with interrupted services due to logistic issues, including that all radioactive iodine supplies are also brought from outside the country.

5.4 The current impact of addressed problems on cancer diagnosis

Regarding cancer care services, all services in governmental centers are provided either free of charge or with only minimal fees through a national insurance company. However, not all services are available; some services need to be done in the private sector or outside the country. For example, immunohistochemistry services are exclusively offered in private sector while PET/CT imaging is currently unavailable locally. All of these factors and when compared to neighboring countries depict how of an impact war can produce on the health care system and to the economy in general.

6 The vital role of international oncologic community in prosperity of cancer diagnosis and care delivery

Local, Arabic and international communities is one of the established programs to provide solution to many addressed problems in regards to cancer diagnosis. Establishment of local societies for each and every field in cancer diagnosis is vital to achieve optimal harmonization and outcome. Arabic-wise, the amalgamation of many cancer care providers under the umbrella of the pediatric oncology east and Mediterranean group (POEM) have been witnessed in the last decade. This group is currently interested in providing solution and coordination between Arab countries. Internationally, collaboration between the union for international cancer control (UICC) and the World Health organization (WHO) are already underway to address all the barriers encountered in conflict affected regions and beyond (41).

7 Conclusion

The damage to the infrastructure and loss of many cancer diagnostic field workers will continue to impede the ability to rebuild a comprehensive cancer diagnostic system after the conflicts have resolved in the aforementioned featured countries. The ability to understand the long-term effects of war is complicated by a lack of communication, the departure of scientific figures, and the discontinuation of training programs and research. There are local and global efforts to mitigate the harm and destruction associated with impaired cancer diagnostic and treatment capacities. In order to create an effective revival program, a clear plan must be developed that identifies obstacles and establishes a roadmap for addressing each issue, one at a time and in a sustainable, phased approach.

Author contributions

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Presentation and management outcomes of Retinoblastoma among Syrian refugees in Jordan

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Purpose: The humanitarian crisis in Syria has had a profound impact on the entire region. In this study, we report the patterns of presentation and management outcomes of Syrian patients with Retinoblastoma (Rb) treated at a single tertiary cancer center in Jordan.

Methods and Materials: This is a retrospective comparative study of Syrian refugees and Jordanian citizens who had Rb between 2011 and 2020. Collected data included patient demographics, presentation, tumor stage, treatment modalities, eye salvage rate, metastasis, and mortality.

Results: Thirty Syrian refugees (16 (53%) had bilateral disease) and 124 Jordanian citizens (51(41%) had bilateral disease) were diagnosed with Rb during this period. The median age at diagnosis for refugees was 10 and 32 months for patients with bilateral and unilateral Rb consecutively, compared to 6 and 28 months for citizens. The median lag time between signs of disease and initiation of treatment was 3 months for refugees, compared to 1 month for citizens.Refugees were more likely to present with a more advanced stage (p=0.046). Out of 46 affected eyes in refugees; 32 (70%) eyes were group D or E, while out of 175 affected eyes among citizens; 98 (56%) eyes were group D or E. Therefore, refugees with Rb were more likely to mandate primary enucleation (48%) compared to citizens (25%) (p=0.003). However, out of 24 eyes among refugees who received conservative therapy, 15 (62%) eyes were successfully salvaged, while out of 131 affected eyes among citizens who received conservative therapy, 105 (80%) eyes were successfully salvaged (p=0.06). Two (7%) of the refugees and four (3.2%) of the citizens with Rb died from metastasis.

Conclusion: Syrian refugees with Rb presented with more advanced disease due to delay in diagnosis and referral that increased the treatment burden by decreasing the chance for eye globe salvage. However, patients who received the timely intervention had a similar outcome to citizens with Rb; probably a reflection of the management of all patients at a single specialized center. We advocate for the timely referral of refugees with this rare life-threatening tumor to a specialized cancer center for the best possible outcome.

KEYWORDS

enucleation, eye salvage, refugees, Retinoblastoma, survival

1 Introduction

Timely diagnosis and prompt management of Retinoblastoma (Rb), the most common primary intraocular malignancy in children linked to mutations in the *RB1* gene, are critical for the cure (1, 2). Globally, the incidence of RB is one in 15-20 thousand live births (3, 4). Although disease-specific mortality has markedly improved over the past years (5), global disparities in regional mortality rates remain a burning issue (6, 7). For example, the mortality rate in Asia and Africa, is as high as 40% to 70%, compared to less than 5.0% in Europe, Canada, and the United States (8–12). The incidence of Rb among the Jordanian population is estimated as one in 15620 newborns per year. Over the past few years, the mortality rate decreased from 38% to 5.0% because of the strict centralization of care for all Rb patients to a single specialized tertiary cancer center, in addition to the increased awareness among families and health caregivers in the country about this disease (13–16).

The humanitarian crisis in Syria, which started in 2011, has had a profound impact on the entire region. An estimated 5.6 million Syrians have fled their country, mainly to Turkey, Jordan, and Lebanon (17). Jordan hosts over 1 million Syrians; most of whom reside in host communities rather than in Refugee camps, where they have access to existing public health services (18). In 2018, cancer affected more than 18 million people worldwide, and more than 9.0 million died from the disease (19), and refugees are not immune (20, 21). Between 2011 and 2019, 917 Syrian cancer patients were registered at the King Hussein Cancer Center (KHCC) hospital-based cancer registry. A lack of sufficient funding from either host countries or international refugee aid organizations is expected to result in the suboptimal treatment of patients with cancer (22, 23).

Rb is a rare form of cancer, where a delayed diagnosis is considered the single most important poor prognostic factor in terms of survival and eye salvage rates (22–25). In a retrospective international study of 692 patients from 11 RB centers around the world, the long lag time between the first symptom for RB and visiting the RB treatment center was significantly associated with higher chances of an advanced tumor at presentation, presence of high-risk histopathology features, systemic metastasis and death (26). Refugees are challenged with difficulties in accessing adequate health care, which may result in delays in diagnosis and management of Rb, therefore are expected to have a worse outcome compared to citizens in the host countries. In this study, we evaluate the patterns of presentation and management outcomes among Syrian refugees living in Jordan, diagnosed with Rb who received treatment at King Hussein Cancer Center, in Amman, Jordan.

2 Materials and methods

This study was approved by the Institutional Review Board at King Hussein Cancer Center (IRB number = 22KHCC140). It was a retrospective, clinical case series of 124 Jordanian patients (citizens) and 30 Syrian patients (refugees) with 175 and 46 eyes affected with Rb, respectively, who had been managed at KHCC. Data from patients managed between 2011 and 2020 was analyzed. Inclusion criteria included Jordanian citizens and Syrian Refugee patients who had clinical and/or pathological diagnosis of Rb and were treated at KHCC and followed for at least 2 years after diagnosis. Syrian patients who are not refugees were excluded from this study.

Data collected included age at diagnosis, sex, laterality, affected site, International Intraocular Retinoblastoma Classification stage (IIRC) at diagnosis (26), presenting signs and symptoms, the lag time between the presenting sign and starting treatment, modality of treatment, eye salvage, metastasis, and mortality. Selection and data collection required access to patients' medical records and Ret-Cam images.

2.1 Treatment modalities

We used a combination chemotherapy regimen of CVE (carboplatin, vincristine, and etoposide). Each CVE cycle was repeated every 4 weeks for a total of 6-8 cycles according to the patient's condition and tumor status. Ocular oncology follow-up was provided with examination under anesthesia before every cycle of chemotherapy and every 4 weeks thereafter. Fundus photos were taken using a RetCam II (Clarity Medical System, Pleasanton, CA, USA). Combination focal therapy was applied as needed as Trans pupillary thermotherapy (TTT) and/or triple freeze-thaw cryotherapy (MIRA CR 4000). External beam radiation therapy was administered when needed consistently by applying 45 Gy in 25 fractions.

2.2 Statistical analysis

Descriptive analysis was carried out using mean, median, and range. Comparative analysis was carried out between refugees and citizens, and the P value was measured using Fisher's exact test to analyze each factor's predictive power.

3 Results

Over 10 years (2011-2020), 124 citizens and 30 refugees met our inclusion criteria.

3.1 Refugees Rb patients

Out of 30 refugees with Rb, 12 (40%) were males, and 18 (60%) were females. Sixteen (53%) patients had bilateral Rb, and 14 (47%) had unilateral Rb. The median age at diagnosis was 10 months for patients with bilateral disease and 32 months for patients with unilateral disease. The median lag time between signs of disease and starting treatment was 3 months. The most common presenting sign was leukocoria in 16 (53%) patients, followed by strabismus in 6 (20%) patients, poor vision in 3 (10%), buphthalmos in 3 (10%) patients, 1 (3%) patient was diagnosed by screening (based on family history of Rb), and 1 patient presented with extraocular disease. Out of 46 affected eyes, 13(28%) eyes were collectively IIRC group A, B, or C, 32 (70%) eyes were group D or E, and 1 (2%) had an extraocular disease at the time of diagnosis (Figure 1 and Table 1).

Treatment and outcome: Twenty-two (48%) eyes were treated by primary enucleation. In comparison, 24 (52%) eyes received conservative therapy (combined systemic chemotherapy and focal consolidation therapy), and 15 (32%) eyes in this group were successfully salvaged by the last date of follow-up, while secondary enucleation was the outcome for 9 eyes (overall, enucleation was the treatment for 31 (67%) of the total affected eyes). Two patients (7%) had metastasis and died by the last follow-up date (Table 1).

3.2 Citizens' Rb patients

Out of 124 affected patients, 69 (56%) patients were males and 55 (44%) patients were females. Fifty-one (41%) patients had bilateral disease, and the rest had unilateral disease. The median age at diagnosis was 6 months for patients with bilateral disease and 28 months for patients with unilateral disease, and the median lag time between signs of disease and starting treatment was 1 month. The most common presenting sign was leukocoria in 88 (77%) patients, followed by strabismus in 25 (20%) patients, poor vision in 5 (4%), buphthalmos in one (1%) patient, and five (4%) patients were diagnosed by screening (based on family history of Rb). Out of 175 affected eyes, 77 (44%) eyes were IIRC group A, B, or C, collectively, while 98 (56%) eyes were group D or E at the time of diagnosis (Table 2). None of the patients had an extraocular disease.

Treatment and outcome: Forty-four (25%) eyes were treated by primary enucleation, while 131 (75%) eyes received conservative therapy (combined systemic chemotherapy and focal consolidation therapy), and 105 (60%) eyes in this group were successfully salvaged by the last date of follow-up while secondary enucleation was the outcome for 26 eyes (overall, enucleation was the treatment for 70 (40%) of the total affected eyes). Four patients (3.2%) had metastasis and died by the last date of follow-up (Table 2).

3.3 Comparison between citizen and refugees Rb patients

There was no difference between citizens and refugees in terms of sex, laterality, and incidence of familial diseases. The median age at diagnosis for citizens with Rb was 6 and 28 months for patients with bilateral diseases and unilateral disease, consecutively, while it was 10 and 32 months for refugees (Table 3). Although there was no statistically significant difference between both groups in terms of presenting symptoms, the refugees showed a tendency to more advanced signs as 10% of refugees with Rb had buphthalmos (compared to

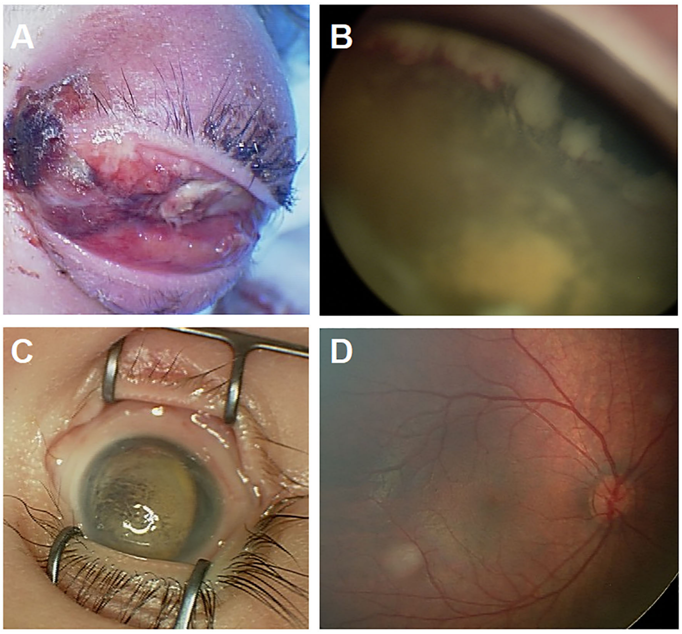

FIGURE 1
(A) Represents one of the refugees who came after 6 months of having leukocoria as a sign of ocular disease in the left eye and did not seek care until the patient developed extraocular disease extension. She passed away with bone marrow metastasis. **(B, C)** This patient is a refugee who presented with bilateral advanced intraocular Retinoblastoma. The right eye **(B)** showed extensive tumor that is extending to the ciliary body, and the left eye **(C)** had phthisis bulbi due to advanced disease, and unfortunately ended with bilateral enucleation. **(D)** This child was diagnosed by screening and had right group A tumor.

TABLE 1 Demographics, Tumor features, and management outcomes for 30 Syrian refuges with retinoblastoma treated between 2011-2020.

		Number	%
Median age at diagnosis (Bilateral, Unilateral)		10 months, 32 months	
Gender	Male	12	40%
	Female	18	60%
Laterality	Unilateral	14	47%
	Bilateral	16	53%
Side	Right	10	33%
	Left	4	13%
	Both	16	54%
Familial RB			
Presenting signs	Leukocoria	16	53%
	Squint	6	20%
	Poor vision	3	10%
	Buphthalmos	3	10%
	By screening	1	3%
	Extraocular disease	1	3%

(Continued)

TABLE 1 Continued

			Number	%	
Median age at diagnosis (Bilateral, Unilateral)			10 months, 32 months		
The median lag time between signs of the disease and starting treatment			3 months		
	Number (%)	1ry enucleation (%)	Conservative treatment	Salvage for amended treatment.	Overall Eye Salvage
Number of eyes	46	22 (48%)	24 (48%)	15 (62%)	15 (32%)
IIRC stage					
A	4 (9%)	0 (0%)	4 (17%)	4 (100%)	4(100%)
B	3 (7%)	0 (0%)	3 (12.5%)	3 (100%)	3(100%)
C	6 (13%)	0 (0%)	6 (25%)	5 (80%)	5 (80%)
D	17 (37%)	8 (36%)	9 (37%)	4 (44%)	4 (24%)
E	15 (33%)	13 (59%)	2 (8%)	0 (0%)	0 (0%)
Extraocular*	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Metastasis	2 (7%)				
Secondary malignancy	0 (0%)				
Mortality	2 (7%)				

*This eye with the extraocular disease was treated by enucleation after neoadjuvant chemotherapy.

TABLE 2 Demographics, Tumor features, and management outcomes for 124 Jordanian patients with retinoblastoma treated between 2011-2020.

		Number	%
Median age at diagnosis (Bilateral, Unilateral)		6 months, 28 months	
Gender	Male	69	56%
	Female	55	44%
Laterality	Unilateral	73	59%
	Bilateral	51	41%
Side	Right	35	28%
	Left	38	31%
	Both	51	41%
Familial RB		18	15%
Presenting signs	Leukocoria	88	71%
	Squint	25	20%
	Poor vision	5	4%
	buphthalmos	1	1%
	By screening	5	4%
	Extraocular disease	0	0%
The median lag time between signs of the disease and starting treatment		1 month	

(Continued)

TABLE 2 Continued

			Number	%	
Median age at diagnosis (Bilateral, Unilateral)			6 months, 28 months		
	Number (%)	1ry enucleation (%)	Conservative treatment	Salvage for amended treatment.	Overall Eye Salvage
Number of eyes	175	44 (25%)	131	105 (80%)	105 (60%)
IIRC stage					
A	12 (7%)	0 (0%)	12	12 (100%)	12 (100%)
B	24 (14%)	0 (0%)	24	23 (96%)	23 (96%)
C	41 (23%)	0 (0%)	41	38 (93%)	38 (93%)
D	75 (43%)	22 (29%)	53	32 (60%)	32 (43%)
E	23 (13%)	22 (96%)	1	0 (0%)	0 (0%)
Extraocular	0 (0%)				
Metastasis	4 (3.2%)				
Secondary malignancy	1 (1%)				
Mortality	4 (3.2%)				

TABLE 3 Comparison between Jordanian RB patients and Refuges with RB diagnosed and treated at King Hussein Cancer Center 2011-2020.

		Citizens		Refugees		P-value
		Number	%	Number	%	
Number of patients		124		30		
Number of eyes		175		46		
Median age at diagnosis (Bilateral, Unilateral)		6 & 28 months		10 & 32 months		
Gender	Male	69	56%	12	40%	0.133
	Female	55	44%	18	60%	
Laterality	Unilateral	73	59%	14	47%	0.159
	Bilateral	51	41%	16	53%	
Familial RB		18	15%	6	20%	
Presenting signs	Leukocoria	88	71%	15	50%	0.217
	Squint	25	20%	5	17%	
	Poor vision	5	4%	3	10%	
	Buphthalmous	1	1%	3	10%	
	By screening	5	4%	3	10%	
	Extraocular disease	0	0%	1	3%	
The median lag time between signs of the disease and starting treatment		1 month		3 months		
IIRC stage						

(Continued)

TABLE 3 Continued

	Citizens		Refugees		P-value
	Number	%	Number	%	
A, B, C	77	44%	13		0.046
D, E	98	56%	32		
Extraocular	0	0%	1		
Enucleation as primary treatment	44	25%	22	48%	0.003
Overall eye globe salvage rate	105	60%	15	32%	0.0014
Eye globe salvage rate for amended treatment	105	80%	15	62%	0.06
Metastasis	4	3.2%	2	7%	0.33
Mortality	4	3.2%	2	7%	0.33

1% of citizens) and 3% presented with an extraocular disease compared none the citizens (Table 3), In addition, only one single case was diagnosed by screening in Refugees versus 5 cases in citizens. The median lag time between signs of disease and starting treatment was 1 month for citizens and 3 months for refugees with Rb.

Refugees presented with a more advanced stage than citizens, as 70% of eyes in refugees with Rb were classified as group D or E eyes at diagnosis compared to 56% of the citizens (p= 0.046). Therefore, refugees mandated primary enucleation more than citizens did (p=0.003). Even though the overall eye salvage rate for citizens was higher than for refugees (60% compared to 32%, P =0.0014), the eye salvage rate for eyes that received conservative therapy was comparable (80% versus 62%, p= 0.06). Finally, there was no statistically significant difference in metastasis and overall survival rates (Table 3).

4 Discussion

Cancer care and care for rare diseases, for both adults and pediatrics, might not be a priority of refugees' health care in many host countries. Financial support is typically directed toward housing, food, and basic life needs. Ethical dilemmas ensue in such circumstances, especially when dealing with potentially curable cancers at a reasonable cost. Retinoblastoma is a rare life-threatening cancer in children that is curable if diagnosed early and treated adequately (4, 6, 10, 13). In this study we found, on average, a 2 months difference in lag time between groups in the diagnosis and initiation of treatment. This delay reduced the chance for eye globe salvage, without a significant impact on mortality.

The age-standardized rates (ASR) for age groups (0-14 and 0-19) for Rb were variable between different countries in the MENA region. The highest ASRs and the second highest worldwide were in Morocco with 9.2 and 7.1 cases per million person-years for the 0-14 and 0-19 age groups respectively. Followed by second place in Jordan with 7.1 and 5.1 cases per million person-years in both groups respectively. While the lowest ASRs recorded were in Qatar with 0.4 and 0.3 cases per million person-years years for the 0-14 and 0-19 age groups respectively. Tunisia recorded the same ASRs as Lebanon, with 3.6 and 2.8 cases per million person-years for the 0-14 and 0-19 age groups, respectively (27). Rb patients with delayed diagnosis and referral are expected to present with a more advanced tumor stage (25, 26, 28–30). In this study, 70% of the affected eyes in refugees had advanced intraocular stage (staged as group D or E), and 2% had an extraocular disease at diagnosis while only 56% of the affected eyes in Jordanian patients belonged to both groups, and none had an extraocular disease at diagnosis. This difference is expected because of the difference in the age at diagnosis directly related to the time lag between the first sign of the disease and the time of starting treatment. Our results showed that the median age at diagnosis for citizens with Rb was 4 months younger than the median age at diagnosis for refugees for both bilateral and unilateral patients. Furthermore, an extra 2-month lag time between signs of disease and starting treatment among refugees was noted in comparison to citizens.

The silent nature of Rb in the early intraocular stages, and the difficulties most refugee patients worldwide encounter in accessing medical care, may contribute to the late presentation seen among the patients in our study. Furthermore, the increased awareness of the disease, easy accessibility to health care, and the presence of the screening program for Rb in Jordan contributed to the difference in the promptness of diagnosis and starting treatment among Jordanian patients (29). For example, five Jordanian patients in this series were diagnosed by screening, compared to only a single refugee patient who had a parent and sister diagnosed with bilateral Rb. The signs and symptoms of Rb depend on its size and location. Leukocoria is the most frequent presenting sign of Rb, reported in approximately 50–60% of cases, followed by strabismus (25%) and inflammatory signs (6–10%) (30–33). In our study, 53% of refugees patients presented with leukocoria, followed by strabismus (20%) and buphthalmos

(10%), in comparison to 71% with leukocoria, 20% with a squint and 1% with buphthalmos among Jordanians.

Unfortunately, the impact of the delay in diagnosis was reflected in the treatment burden and management outcomes. Rb management guidelines recommend that the early diagnosed tumors (group A and a few of group B tumors) can be treated with focal therapy even without chemotherapy, while more advanced tumors need chemotherapy and sometimes radiation and/or enucleation, so the more advanced tumor at diagnosis the more treatment burden for the patient (34, 35). In this series, 25% of the affected eyes among Jordanian patients mandated primary enucleation, while 48% of the affected eyes among refugees mandated primary enucleation, as they presented with a more advanced stage. On the other hand, the chance for eye salvage was almost the same for the eyes that received conservative therapy (80% for Jordanian and 62% for refugees, p=0.06), probably a reflection of the unified treatment protocols in a specialized cancer center with the same team (13). The slight non-significant difference in the outcome might be a reflection of the difficulty of strict follow up for refugees living in camps where transportation and access to the central city for treatment is cumbersome. Eventually, the difference in the mortality rate for both Jordanians and refugees with Rb was not statistically significant (3% for Jordanian patients and 7% for refugees; p=0.33), a potential reflection of the centralization of care for all Rb patients in Jordan (13).

Policymakers should be aware that implementing cancer control programs across the continuum, from early detection to survivorship and palliative care programs, is cost-effective. For example, the 2019 World Health Organization report on cancer found that for every 1 USD invested in cancer, there is a direct productivity return of 2.30 USD and a total social return of 9.50 USD (23, 36). Although this might be less clear for rare diseases like Rb, Despite the clear unwarranted effect of delays in the diagnosis, thus the treatment for Rb patients in terms of decreased eye salvage rate and increased treatment burden, the mortality rates could be maintained at low levels once the patients are diagnosed and treated in specialized centers. An important issue with cancer care is the complicated management protocols, mandating a multidisciplinary-team approach that involves surgery, chemotherapy, radiation therapy, psychosocial support, supportive/palliative care, survivorship, and genetic counseling (13, 29), Therefore, policymakers should be advocates to manage refugees cancer patients in specialized tertiary cancer centers to achieve the best possible survival for this category of patients.

Our study shed light on the problem of the diagnosis and the management of Rb among refugees. We believe that highlighting these problems among refugee patients with rare tumors like Rb will help with developing solutions within healthcare systems that are directed toward refugees mainly in host countries with limited resources (like Jordan). We have shown that even with limited resources, having such rare diseases managed exclusively in specialized referral centers could offer the best outcome to those patients and could save lives. Our study has several limitations that need to be considered. This was a retrospective study with a limited number of patients from a single institution; thus, the findings might not be generalizable to the entire refugee population in Jordan or throughout the region. Nonetheless, the current study has several strengths; the data were obtained from the single referral cancer center (that exclusively treats all patients with Rb in the country) that has previously hosted and currently hosts a large number of refugees.

4.1 Strength and limitation

Our study was based on some strengths as all cases were under a strict follow-up program and they were treated in a single tertiary center at KHCC. This is due to that there is an unofficial agreement between Jordanian ophthalmologists that all Rb cases should be referred immediately to where all the cases are treated. On the other hand, It had some limitations as it can be improved by increasing the sample size which could have generated more accurate results, and integrating additional methods of data collection as a questionnaire could have increased the scope and depth of analysis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by King Hussein Cancer Center IRB. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

Conceptualization: YY, QA, MoM, IJ, MuM. Methodology: YY, HH, JK, MS, IS, MA-H, IA-N, MA. Software: RA, OA-H, KS. Validation: YY, IA-N, AM. Formal analysis: YY, QA, MoM, IJ, and MuM. Investigation: HH, JK, MS, IS, MA-H, IA-N, MA. Resources: RA, OA-H, KS. Data curation: IA-N, AM. Writing, original draft preparation: YY, QA,MoM, IJ, RA, OA-H,KS. Writing, review and editing: IA-N, AM, MuM, HH, JK, MS, IS, MA-H, IA-N, MA. Supervision: MA-H, IA-N, MM, AM. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Libyan cancer patients at King Hussein Cancer Center for more than a decade, the current situation, and a future vision

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Background: Since 2011, the Libyan civil war crisis had affected all dimensions of livelihood including cancer care. This has resulted in a steady incline in the number of Libyan patients with cancer seeking oncologic care and management in Tunisia, Egypt and Jordan, among others. King Hussein Cancer Center (KHCC) has been one of the main destinations for Libyan patients with cancer for more than a decade.

Aim: We are reporting on the characteristics of Libyan patients with cancer presenting to KHCC during the past fourteen years.

Methods: We performed a retrospective chart review of all Libyan patients with cancer presenting to KHCC between 2006 and 2019.

Results: A total of 3170 records were included in the final analysis. The overall sample was predominantly adults (71%) with a male-to-female ratio of 1:1.2. Overall, the most common referred cancers to KHCC were breast (21%), hematolymphoid (HL) (17%), and gastrointestinal tract (GIT) (16.2%) cancers. Breast cancer was the most common among adult females (41.7%), GIT among adult males (23.6%), and HL among pediatrics (38.5%). Around 37.8% of patients presented with distant metastasis at their first encounter at KHCC, among which 14.7% were candidates for palliative care.

Conclusion: The sustenance of treatment for Libyan patients with cancer requires extensive collaboration between governmental and private sectors. The Libyan oncological landscape could benefit from national screening and awareness programs, twining programs and telemedicine, introduction of multidisciplinary boards, and the formulation of a national cancer registry.

Adopting the successful models at KHCC can help to augment the oncology services within the Libyan healthcare sector.

KEYWORDS

Libyan cancer patients, King Hussein Cancer Center, breast, gastrointestinal tract, hematolymphoid, awareness, screening programs

1 Introduction

Disparity in cancer care exists on a fundamental economic level as patients with cancer in low or middle-income regions face significantly worse survival outcomes compared to those within the developed world (1). Being the 2nd most common cause of death after cardiovascular disease, the burden of cancer within low or middle-income countries is increasing (2). Such a burden is amplified by the presence of armed conflicts (e.g., wars, armed hostilities, etc.). These conflicts may increase cancer incidence, augment complications, and worsen survival outcomes as it disrupts care seeking and delivery in the short term among all aspects of oncological care (3, 4). Due to the changing political contexts and priorities during times of armed conflict, shifting of resources away from cancer care is expected. Other war-related determinants of cancer care continuity include forced migration, increased psychological burden, killing or fleeing of medical staff, and delivery of sub-optimal treatments (2). On the long term, war impacts cancer burden through intoxicating the environment or by encouraging unhealthy behaviors such as substance abuse (5, 6). The impact of armed conflict in war-torn areas is well documented within the literature. Prime examples of such an effect are Syria, Iraq, Afghanistan, and Gaza-Palestine (7–11). Patients from these areas often present with advanced stages and have high mortality rates owing to misdiagnosis, delays in diagnosis, lack of healthcare access, lack of essential treatment regimens, and interrupted treatment.

Over the past decade, Libya has witnessed two distinct civil wars which led to an ongoing conflict among rival factions seeking military and political control over the nation. Such conditions did not only subject Libyan patients with cancer to the aforementioned challenges of cancer care but also displaced them within the country and to neighboring, and sometimes distant, countries. Moreover, the true burden of cancer in Libya cannot be reliability determined. The lack of a national cancer registry, constantly shifting demographics, and incomplete records of patients with cancer leads to biased calculations of any cancer-related epidemiological parameter (12, 13); all of which were further amplified by the breakout of the Libyan civil leading to further cancer disparities (14). The most recent report on Libyan cancer statistics, based on the Misurata City Cancer Registry, describe a crude incidence rate of 71.1 per 100,000 with breast, colorectal, and lung cancer being the most prevalent cancers (12). A 2015 report, based on the Benghazi City Cancer Registry, documented a world age-standardized incidence of all site cancers were 135.4 and 107.1 per 100,000 for males and females, respectively (14). Moreover, lung and breast cancers were the most prevalent cancers among males and females, respectively. Nonetheless, epidemiological cancer statistics with regards to Libya lack generalizability due to the reasons mentioned above.

Jordan, an upper middle-income country with a GDP of 28.8 billion, provides cancer care to all of its citizens at no costs through public hospitals, university hospitals, and the King Hussein Cancer Center (KHCC) (15). Jordan's cancer care primarily targets the treatment element of the cancer care continuum as it does not have a national control policy or subsidized large scale prevention programs. Moreover, in terms of screening, Jordan's only active and institutionalized program is its breast screen program (16). Other programs pertaining to colorectal cancer and cervical cancer among others are extremely limited and have no associated databases. KHCC is Jordan's only specialized cancer care center and is a leading comprehensive center within the region (17). KHCC provides cancer care for patients from neighboring countries, especially those under difficult humanitarian conditions. Such countries include Iraq, Yemen, Syria, Sudan, Libya, Lebanon, and Palestine. The numbers of Libyan patients presenting to KHCC has significantly increased since the 2011 civil war. This was further boosted by an official agreement signed between KHCC and the Libyan Ministry of Health in 2017 by which the Libyan government aimed to treat its cancer patients within specialized centers by covering its costs at KHCC. However, such an agreement fell short in 2021 due to increasing and unpaid debts on the Ministry's behalf.

Due to the gap in the literature with regards to cancer epidemiology of displaced Libyan patients, we aimed to demonstrate the epidemiology of Libyan cancer patients who received treatment over more than a decade at KHCC, including the most common types of diagnoses, the stages at presentations at KHCC, and the treatment modalities received. Moreover, we aimed to provide concerned bodies with a number of relevant recommendations for potential use for future patient recruitment, treatment, and follow-up.

2 Methods

Relevant data on all Libyan patients with cancer previously presented to/treated at KHCC from 2006 to 2019 was extracted from the Center's Cancer Registry. The Registry was established in 2006 and is an electronic database that involves the demographic, clinical, and psychosocial data of any and all patients presenting to KHCC. Extracted variables included age at diagnosis, date of first contact with KHCC, definitive diagnosis, tumor details (e.g., site of tumor and histology), and treatment details. Stage at presentation was collected according to the American Joint Committee on Cancer (AJCC) TNM system and Surveillance, Epidemiology, and End Results (SEER) summary staging system. The 6th, 7th and 8th editions of the TNM systems were used, according to the time period at which the data were collected by the Registry. For the SEER summary staging system, cases before 2018 were stratified based on the 2000 edition, while the 2018 edition was effective on January 1st, 2018 onwards. For the purpose of comparison, data regarding SEER stage 7 for Jordanian cancer patients during the same time period, in terms of age, gender, anatomical site of disease, and pathological diagnosis were also collected. Categories of the 2000 and 2018 versions of the SEER summary stage are illustrated in Table 1 (18, 19). The aforementioned data was provided by the KHCC Cancer Registry manager, who was anonymized to the purposes of the study.

The resultant data was cleaned, re-organized, and re-categorized using Microsoft Excel. Data were later handled using SPSS version 23. Categorical variables were presented as frequencies [n(%)], while continuous variables were presented as means and their associated standard deviations. Data on cancer frequency and staging among patients were stratified by age (adults vs. pediatrics), biological sex (male vs. female), and nationality (Libyan vs. Jordanian). Any variable with more than 10% missing data was removed from the final analysis.

3 Results

3.1 Demographic details

A total of 3170 Libyan cancer patients were treated at KHCC between June 2006 and 2019. After the beginning of the political and military conflict in Libya in 2011, the number of Libyan patients increased significantly, with 2888 (91%) cases recorded between 2012 and 2019. In June 2017, an agreement was signed with the Libyan Ministry of Health to provide health care to Libyan cancer patients. This agreement was associated with a surge in the number of cases (n=1310, 41.3%). Since then, KHCC has treated 2100 patients, representing 66% of the total patients' number (Figure 1). For the whole group, there was an almost equal representation of males and females, with a ratio of 1:1.2 including 1445 male (45.6%) and 1725 female (54.4%) patients. The patients` age range was wide spanning newborns up to 93 years. The mean and median ages were 45 and 31.5 years, respectively. The patients were predominantly adults, with 71% (n=2251) ranging between 30 and 69 years. Only 355 patients (11%) fell into the pediatric age group. Age group distribution is illustrated in Figure 2.

3.2 Classification according to site of tumor origin

Tumors originating from the breast, hematolymphoid (HL) and gastrointestinal tract (GIT) were the most common,

TABLE 1 Description of different categories used in the 2000 and 2018 versions of the SEER summary stage.

Code	Definitions	
	2000 version	2018 version
0	In situ	In situ
1	Localized only	Localized only
2	Regional by direct extension only	Regional by direct extension only
3	Regional lymph nodes involved only	Regional lymph nodes only
4	Regional by both direct extension and lymph node involvement	Regional by both direct extension and lymph node involvement
5	Regional, NOS (Not Otherwise Specified)	*Can no longer be coded
7	Distant site(s)/node(s) involved	Distant site(s)/node(s) involved
8	Benign/borderline	Benign/borderline
9	Unknown if extension or metastasis (unstaged, unknown, or unspecified) Death certificate only case	Unknown if extension or metastasis (unstaged, unknown, or unspecified) Death certificate only case

*Code 5 (regional, NOS) in the 2000 version can no longer be used in the 2018 version.

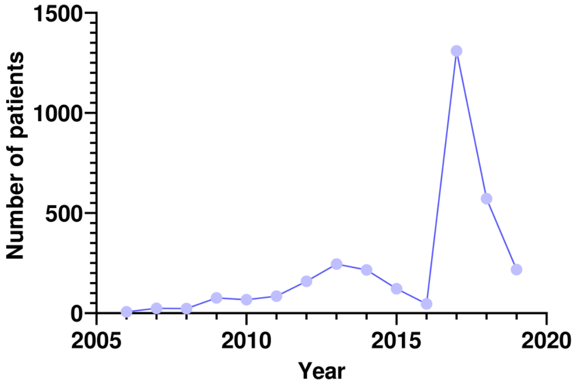


FIGURE 1
Trend of referral of Libyan patients with cancer between 2006 and 2019. Number of cases (n=3170) had significantly increased after the first the Libyan civil war in 2011. A surge of cases coincided with the Libyan Ministry of Health and KHCC treatment agreement signed in 2017.

constituting 54.2% (n=1719) of all cases collectively, including 21% (n=665), 17% (n=539) and 16.2% (n=515), of all cases respectively. Tumors in other locations constituted less than 10% each of the total number of cases. Table 2 lists the details of the location of tumors among Libyan cancer patients treated at KHCC.

3.3 Classification according to age and gender

3.3.1 Adult female cancer patients

In total, there were 1570 patients, with a mean and median age of 50.1 and 47 years, respectively. Breast tumors were the most common cancer in females (n=656, 41.7%), followed by GIT tumors (n=222, 14.1%), with a median age of 45 and 52 years, respectively. Tumors originating from the female genital tract accounted for 11.2% (n=177) of all tumors; almost half (n=84, 5.3%) of which affecting the endometrium in post-menopausal women (median age of 54 years). Interestingly, tumors of the endocrine system were more common in females (n=75, 4.7%), two-times the incidence of those in males (n=34, 2.7%). This was primarily a reflection of thyroid gland (n=48, 3%), and pituitary gland tumors (n=16, 1%). The median age for thyroid and pituitary gland tumors were 38 and 30 years, respectively, which was younger than the median age for all other types of malignancy.

3.3.2 Adult male cancer patients

In total, there were 1245 patients, with a mean and median age of 54.6 and 55 years, respectively. Gastrointestinal tract tumors were the most common among male patients (n=293, 23.6%), followed by HL malignancies (n=232, 18.7%). Lung carcinoma (n=127, 10.2%) and head and neck tumors (n=128, 10.3%) were the 3rd and 4th most common tumors among Libyan adult males. This prevalence is higher than what is

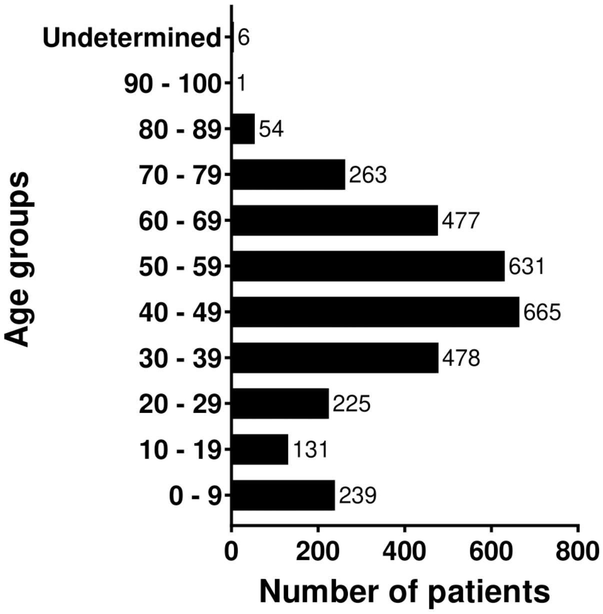


FIGURE 2
Libyan patients with cancer age distribution.

TABLE 2 Organ/system-based classification of all cases.

Organ/System	Number of cases (%)
Breast	665 (21%)
Hematolymphoid system	539 (17%)
Gastrointestinal tract	515 (16.2%)
Central nervous system	273 (8.6%)
Female genital tract	182 (5.7%)
Head and neck	166 (5.2%)
Lung	149 (4.7%)
Soft tissue	131 (4.1%)
Endocrine system	129 (4%)
Male genital tract	122 (3.8%)
Urinary system	95 (3%)
Pancreatobiliary system	76 (2.5%)
Bone	51 (1.7%)
Unknown primary	23 (0.7%)
Skin	23 (0.7%)
Liver	18 (0.6%)
Mediastinum	8 (0.3%)
Mesothelium	5 (0.2%)
Total	3170 (100%)

reported for adult Libyan females for lung carcinoma and head and neck tumors (n=21, 1.3%, and n=33, 2.1%, respectively). The median age for GIT, HL, Lung and head and neck tumors was 56, 43, 61, and 52 years, respectively. Tumors of the male genital tract ranked 5th (n=121, 9.7%) predominated by prostate cancer (n=108, 8.6%), mostly in elderly patients (median age of 66 years). Table 3 and Figure 3 depicts the distribution of cancer cases according to gender.

3.3.3 Pediatric cancer patients

In total, there were 355 cases, with a mean and median age of 6.8 and 5.0 years, respectively. Hematolymphoid tumors (n=137, 38.5%) were the most common among the pediatric age group. Acute leukemia represented around one quarter of cases (n=78, 22%), with a median age of 5 years. Central nervous system (CNS) tumors accounted for 19.5% of tumors among pediatric patients (n=69); a third of which (n=32, 9%) were infratentorial tumors mainly medulloblastoma (n=13, 3.6%) with a median age of 3 years. Also, 28 (7.8%) cases of eye tumors were predominated by retinoblastoma (n=26, 7.3%) with a mean age of 8 months and a median age of 1 year. Other tumors included bone tumors (n=30, 8.5%), and Wilms' tumor (n=12, 3.4%). Also, there were 20 (5.6%) cases of neuroendocrine tumors, with a predominance of neuroblastoma (n=16, 4.5%, median age 2 years). As a group, germ cell tumors were encountered in 6 cases (1.6% of the total malignant tumors in pediatrics), including 4 cases of ovarian tumors in females, and 2 cases of testicular and mediastinal germ cell tumors in male patients. Two cases of hepatoblastoma and malignant rhabdoid tumors, each were encountered. A single case of pleuropulmonary blastoma in a 2-year-old boy and a single case of cutaneous malignant melanoma were also diagnosed. A summary of pediatric tumors is presented in Table 4.

3.4 Classification according to stage of presentation at KHCC

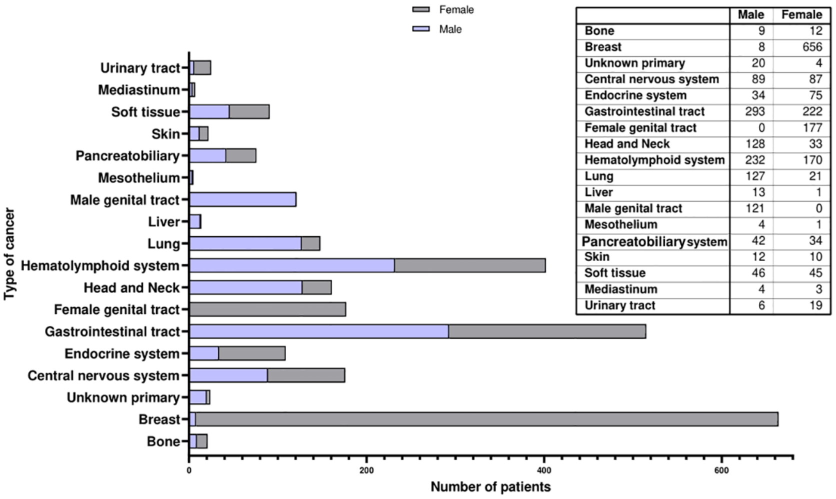
According to the 2018 version of SEER (Table 1) 37.8% (n=1201) of patients presented with distant metastasis (Stage 7; consistent with metastatic tumor), another 38% (n=1240) were distributed between stages 0–4. Based on the 6th, 7th and 8th editions of the AJCC TNM staging system, around half of cases presented with advanced stage at first encounter at KHCC; namely stage 4 (n=1199, 37.8%) and stage 3 (n=325, 10.2%). The exact TNM stage was not assigned for 873 patients (27.5%). Figure 4 displays further analysis. Among SEER stage 7 category, the most common age group affected was 40-59 years (n=475, 39.5%) and was equally distributed between male and female patients. Almost all (n=1189, 99%) were previously diagnosed prior to visiting KHCC, and around one-third (n=426, 35.4%) have already received different modalities of treatment/care, including palliative care (n=365, 30.4%). Lung represented the most common diagnosis (73%, n=109 out of a total of 194 cases) in this group of patients, followed by the GIT (41%, n=212 out of a total of 515 cases), female genital tract (25.8%, n=47 out of a total of 182 cases), and breast (25%, n=157 out of a total of 620 cases). In comparison, SEER stage 7 Jordanian cancer patients at the same period represented only 18.5% (n=5704) out of a total of 30709 cases. The overall distribution of cases is comparable between Libyan and Jordanian patients, with minor discrepancies. In Table 5, the proportion of SEER stage 7 among the two populations is significantly different. For example, in general, breast cancer cases constitute 21% (n=665) and 21.5% (n=6632) of Libyan and Jordanian patients, respectively. Unfortunately, 25% (n=157) of the Libyan breast cancer patients were seen for the first time at KHCC with metastatic disease, compared to 18.8% (n=1249) of their Jordanian counterparts. This applies also to female genital tract tumors, as Libyan patients were 2.5 times more likely to present as SEER stage 7 compared to Jordanian patients.

3.5 Classification according to treatment modalities received at KHCC

At first encounter at KHCC, almost all cases (n=3046, 96%) were previously diagnosed, and a third (n=1079, 34%) received

TABLE 3 Gender-based stratification of adult tumors.

System/Organ	Number	Male (%)	Female (%)
Bone	21	9 (0.7%)	12 (0.7%)
Breast	664	8 (0.6%)	656 (41.7%)
Unknown primary	24	20 (1.5%)	4 (0.2%)
Central nervous system	176	89 (7.1%)	87 (5.6%)
Endocrine system	109	34 (2.7%)	75 (4.7%)
Gastrointestinal tract	515	293 (23.6%)	222 (14.1%)
Female genital tract	177	–	177 (11.2%)
Head and neck	161	128 (10.3%)	33 (2.1%)
Hematolymphoid system	402	232 (18.7%)	170 (10.8%)
Lung	148	127 (10.2%)	21 (1.3%)
Liver	14	13 (1.0%)	1 (0.1%)
Male genital tract	121	121 (9.7%)	–
Mesothelium	5	4 (0.3%)	1 (0.1%)
Pancreatobiliary system	76	42 (3.5%)	34 (2.3%)
Skin	22	12 (1.0%)	10 (0.7%)
Soft tissue	91	46 (3.7%)	45 (2.9%)
Mediastinum	7	4 (0.3%)	3 (0.2%)
Urinary system	83	64 (5.1%)	19 (1.3%)
Total	2816	1246	1570



	Male	Female
Bone	9	12
Breast	8	656
Unknown primary	20	4
Central nervous system	89	87
Endocrine system	34	75
Gastrointestinal tract	293	222
Female genital tract	0	177
Head and Neck	128	33
Hematolymphoid system	232	170
Lung	127	21
Liver	13	1
Male genital tract	121	0
Mesothelium	4	1
Pancreatobiliary system	42	34
Skin	12	10
Soft tissue	46	45
Mediastinum	4	3
Urinary tract	6	19

FIGURE 3
Gender-based stratification of adult tumors.

TABLE 4 Frequency of site-specific tumors among pediatric Libyan patients treated at KHCC between 2006 and 2019.

System/Organ	Number of cases (%)
Hematolymphoid system	137 (38.5%)
Central nervous system	69 (19.5%)
Soft tissue	40 (11.3%)
Bone	30 (8.5%)
Eye	28 (7.8%)
Endocrine system	20 (5.6%)
Urinary tract	12 (3.4%)
Head and neck	5 (1.4%)
Female genital tract	5 (1.4%)
Liver	4 (1.1%)
Breast	1 (0.3%)
Lung	1 (0.3%)
Male genital tract	1 (0.3%)
Skin	1 (0.3%)
Mediastinum	1 (0.3%)
Total	355 (100%)

previous treatment, either at their home country “Libya” (n=1908, 60.1%) or in other neighboring countries including Jordan (outside KHCC), Tunisia, and Egypt among others. Only 3.7% (n=117) and 19% (n=600) cases were first diagnosed and treated at KHCC, respectively. King Hussein Cancer Center offered a wide range of treatment options according to the most recent national and international guidelines and based on multidisciplinary clinics’ decisions. Out of the 3170 cases, 15.7% (n=500) underwent different types of surgical interventions. Radiotherapy and chemotherapy were offered to 19% (n=608) and 28.8% (n=913) of all patients, respectively. A minority of patients received hormonal therapy (n= 229, 7.2%), immunotherapy (n=26, 0.8%), and bone marrow transplant (n=35, 1.1%). Unfortunately, 9.8% (n=312) patients were candidates for palliative care, and another 4.8% (n=155) have already been receiving palliative care at first presentation to KHCC, all of whom (n=467) were registered after the 2017 agreement. Treatment options are summarized in Figure 5.

3.6 The three most common types of malignant tumors in Libyan patients treated at KHCC

3.6.1 Breast

A total of 665 cases of breast tumors presented to KHCC with the vast majority being malignant (n=620, 93.3%), predominantly in females (n=612, 98.7%), with eight (1.2%) male patients. For malignant tumors, the age ranges between 24 and 82 years, with a mean and median of 47 and 45 years, respectively. Almost all cases (n=634, 95%) were diagnosed and 43.0% (n=287) treated prior to referral to KHCC. One-fourth of patients (n=157, 25%) had distant metastasis (SEER 7; AJCC TNM stage 4) at presentation to KHCC. Radiotherapy, hormonal therapy, and chemotherapy were given to 24.0% (n=150), 30% (n=187), and 31.5% (n=195) of all patients, respectively. Moreover, 79 patients (11.8%) received palliative care either before or after referral to KHCC.

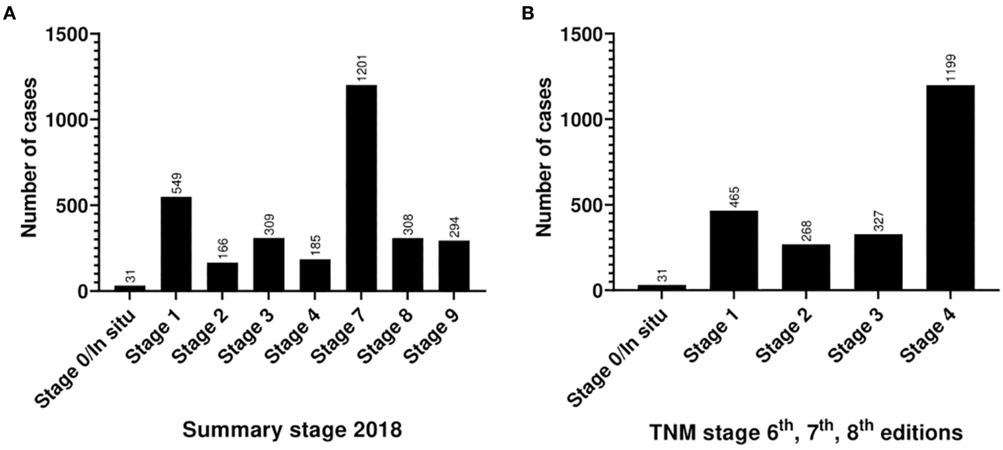


FIGURE 4
Stage-wise stratification of patients according to **(A)** the 2018 version of Summary Stage and **(B)** the 6th, 7th and 8th editions of the AJCC TNM staging system.

TABLE 5 Comparison of between Jordanian and Libyan patients with cancer in terms of cases presenting with SEER stage 7 advanced cancer.

System/ Organ	Libyan		Jordanian	
	All patients (n=3170)	SEER 7 patients (n=1201; 37.8%)	All patients (n=30709)	SEER 7 patients (n=5704; 18.5%)
Breast	665 (21%)	157 (25%)	6632 (21.5%)	1249 (18.8%)
Gastrointestinal tract	515 (16.2%)	212 (41%)	6810 (22.1%)	1098 (16.1%)
Lung	149 (4.7%)	109 (73%)	2430 (7.9%)	1078 (44.3%)
Female genital tract	182 (5.7%)	47 (25.8%)	6810 (7.3%)	211 (9.3%)

3.6.2 Hematolymphoid system

There were 539 patients with HL malignancy, with a mean and median age of 34 years with a male to female ratio of 2:1. Collectively, Non-Hodgkin lymphoma (NHL) (n=163, 30.3%) and acute leukemia (n=152, 28.2%) represented more than half of cases. The vast majority of patients (n=529, 98%) were previously diagnosed, and around one-third (n=163, 30%) received treatment before referral to KHCC. At KHCC, chemotherapy, radiotherapy, and bone marrow transplant were offered to 40.8%, (n=220), 10.2% (n=55), and 6.1% (n=33) of all patients, respectively. Seventy-eight patients (14.5%) received palliative care either before or after referral to KHCC.

3.6.3 Gastrointestinal tract

A total of 515 patients with GIT tumors presented to KHCC, including 82.0% (n=422) cases with malignant tumors, predominated by colon (n=412, 80%), followed by stomach (n=85, 16.5%). More than half of the cases affected males (n=294, 57%). The patients` age ranged between 20 and 87 years, with a median age of 54 years. The vast majority of cases were diagnosed (n=485, 94%) and many received treatment (n=192, 37%) before referral to KHCC. Forty-one percent (n=212) had distant metastasis (SEER7; AJCC TNM stage 4) at first presentation to KHCC. Twenty percent (n=104), 28.7% (n=148), and 9.5% (n=49) had surgery, received chemotherapy, and radiotherapy at KHCC. Palliative care was offered to 20.5% (n=104) of all patients with GIT tumors.

4 Discussion

Cancer is considered a leading cause of morbidity and mortality worldwide, regardless of the level of socioeconomic status (20). Under harsh humanitarian conditions, cancer diagnosis and management become more challenging. Cancer patients from areas of conflict; the Middle East as an example, often get diagnosed at late stages leading to poor outcome. This is probably due to the poor living conditions, lack of screening programs and awareness campaigns, limited access to care, and

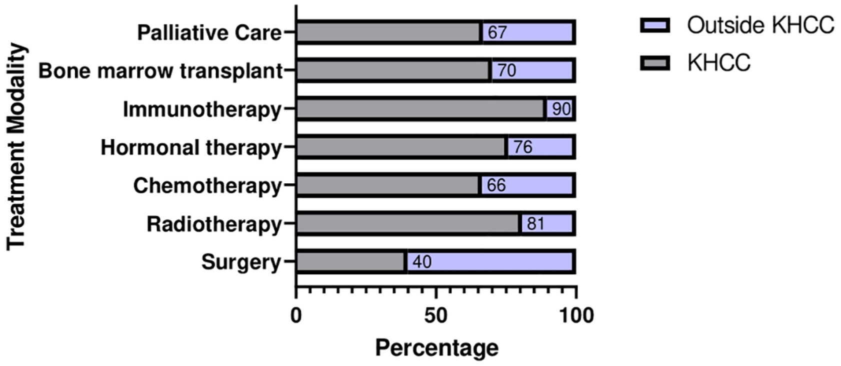


FIGURE 5
Comparison of treatment options offered to patients before and after referral to KHCC.

scarcity of the available resources. Even when they attempt to seek medical advice outside their home countries, they are unfamiliar with the newly encountered healthcare systems (21). By tracking the numbers of Libyan patients referred to KHCC over the last fourteen years, a steady increase is noted, especially after the Libyan political crisis in 2011, and the subsequent years of political turmoil. This has reflected negatively on all aspects of civil lives including insecurity and economic instability, in a manner that led to the flaccidity of the Libyan healthcare system.

According to GLOBOCAN's 2020 cancer statistics, the estimated world age-standardized incidence rate for all cancers in Libya is 185.4 per 100,000 people. The crude incidence rate of all cancers among Libyans is 209.8 per 100,000 people. Based on the report, the most common malignancies among the Libyan female population are breast cancer (47.3 per 100,000), colorectal cancer (15.6 per 100,000), cervical cancer (14.4 per 100,000), and lung cancer (13.7 per 100,000). In contrast, prostate cancer (30.6 per 100,000), lung cancer (30.0 per 100,000), colorectal cancer (22.4 per 100,000), and stomach cancer (15.0 per 100,000) are the most prevalent among Libyan males. These numbers are significantly higher to what was reported by the Benghazi Cancer Registry (14), which further accentuates the fact that single city registries underestimate the true burden of cancer. Particularly, the Benghazi Cancer Registry, which is the only source that provides comparable statistics to GLOBOCAN 2020, underestimates the incidence of prostate cancer (14.8 per 100,000) among males and lung (3.1 per 100,000) and cervical cancer (4.6 per 100,000) among females.

According to our data, breast remained the most common cancer referred to KHCC and the most common cancer in females, in alignment with the aforementioned statistics. Among adult Libyan males with cancer, lung cancer and prostate cancer ranked as the 3rd and 5th most common tumors referred to KHCC. Under-representation of prostate cancer in our cohort might be related to the general good outcome of treatment by hormonal therapies which might not demand referral abroad. Per the latest GLOBOCAN estimates of 2020, lung cancer is the 2nd most common diagnosed cancer among both sexes. It is the most common diagnosed cancer in males and the 3rd most common in females (22). Interestingly, referrals of lung cancer among our Libyan population are underwhelming as it ranks 7th among the whole group, 4th among males, and 10th among females. The poor representation of lung cancer among referred Libyan patients could be attributed to the complex paradigms affecting patient referral. Such factors include poor functional status, rapid deterioration of clinical status, patient-oriented factors, age, and lack of symptoms (23). Other factors influencing referral are the lack of awareness of primary physicians with systemic therapies for advanced lung cancer or the financial constrictions within which these cases fall. The latter is more relevant to our patients since many Libyan patients with cancer are dependent on governmental funding to be able to afford systemic therapy at KHCC.

While Libyan patients represent around 10% of treated Jordanian patients' volume, they are twice as likely to present with advanced stages. The nature of such presentations, in addition to the increasing volume of patients will most likely strain the oncology medical services provided within KHCC and across Jordan. Additionally, the costs of treatment will further overwhelm the healthcare infrastructure of a country with already limited resources. This was clearly demonstrated throughout the Syrian crisis as it costed King Hussein Cancer Foundation Goodwill Fund a total of around 11,400,000 million U.S. dollars to cover the treatment of only 356 Syrian patients with cancer (17). Using such data, it is estimated that the annual costs of treating Syrian patients with cancer is around 22,111,118 million U.S. dollars. Unfortunately, the financial strains of this ever-increasing volume of patients manifested as the cancellation of the governmental treatment agreement between the Libyan Ministry of Health and KHCC. Such was the case due to the rising amounts of debt held by the Libyan authorities which subjected their beneficiaries within Jordan to cancer care inaccessibility.

There are a few limitations encountered in the study. Such include the use of two different SEER summary staging systems for the classification of cases; 2000 and 2018 summary staging system. This has created some discrepancy as SEER stage 5 was used in the 2000 manual but is no longer used in the updated 2018 classification system (18, 19). Thus, it was not possible to reclassify patients registered in this group (n=137, 4.3%) using updated guidelines. Furthermore, a significant proportion of patients were diagnosed and treated before referral to KHCC; thus, documentation of their previous pathological diagnosis, laboratory tests, treatment plans, and follow-up visits was suboptimal and of which impact could not be reflected within the study. Also, outcome variables such as overall survival and recurrence free survival were not demonstrated for Libyan patients. Such is the limitation of the KHCC Cancer Registry as it only provides follow-up for international patients up until 6 months of their first contact with KHCC. Extracting such information, even within the sole context of this study, remains difficult as patients traveling back to Libya lose follow up due to a variety of reasons including travel and financial difficulties, and the volatile security and economic conditions.

4.1 Recommendations

Based on the presented data, we could draw on a number of recommendations. In absence of a well-established national Libyan cancer registry (12), the results of this study might lay the groundwork for the drafting and development of a cancer care strategy for the Libyan populace and their associated displaced populations. Both the literature and KHCC's data demonstrated that breast and GIT cancers were among the most prevalent cancers affecting this vulnerable population (22, 24). However, screening activities and their associated scale are extremely limited within Libya. This had predisposed patients to late diagnoses and presenting in advanced stages (25, 26). Therefore, the establishment of nationwide screening programs will aid in the early detection of cases which will reduce cancer burden and its costs for both affected individuals and the concerned authorities. Such programs should complement the already successful programs within big Libyan cities such as Tripoli and Benghazi. Moreover, the initiation of efforts within larger, more populated cities would cut off the costs of raising new capital through the pre-existing programs and facilities.

Screening programs should be complemented by simple cost-effective measures as to increase their effectiveness and reach within the population. Awareness campaigns for cervical cancer were already launched in many Libyan cities as of 2020 and adopted a digital format as of 2021 (24). Such campaigns must be sustained and extended to other prevalent cancers. It is documented that patients, especially those within conservative communities, may refrain from pursuing cancer care or diagnosis due to social stigma (e.g., cancer diagnosis may lead to divorce among families) (9). KHCC's experience in leading the "Jordanian Breast Cancer Program" can be emulated as a proof-of-concept model.

It appears that patients referred to KHCC for palliative care demand better triaging of advanced cases. While the palliative care track does exist within the Libyan healthcare system, it faces a significant shortage across the entire country. Libya's National Cancer Control Program is trying to address such an issue (24). Therefore, it is important to devise a referral strategy for palliative care patients that takes into account the emotional, psychological, and financial burdens associated with this vulnerable group.

Taking advantage of the overlapping culture, language, demographics and risk factors of the Libyan and Jordanian populations, the success and resilience of the KHCC model can be adopted within Libya through a satellite center (27–29). This can help to establish an optimum solution to the challenges facing cancer management in Libya, through augmentation of the Libyan oncology healthcare service to provide a more convenient atmosphere for patients, as they will be treated among their families, leading to a better psychosocial support, and subsequently reserve outside referral only for those who need complex and major interventions.

The implementation of twining programs (30) and telemedicine oncology services (28, 31) as means to discuss cases has revolutionized the management of rare and difficult cases at KHCC. A "twining program" refers to the extended and long-term collaboration and sharing of skills and experience between an experienced cancer center in an upper-income country with a cancer program in a low- or middle-income country (32). While most twinning programs involve personnel exchanges between different centers, others utilize telemedicine as a medium of facilitating such interactions in the aim of evolving patient care (27). KHCC's twinning program with Canada's Hospital for Sick Children was established in 2003 and has proved effective in augmenting the multidisciplinary care of pediatric neuro-oncology cases (30). Twining, through videoconferencing, is a cost-effective tool that is able to provide input on treatment, improve case approach, educate personnel, and introduce novel concepts of cancer care. Similarly, the twinning program between KHCC and Saint Jude's Children's Hospital, which was established in 2003, proved the effectiveness of such endeavor as outcomes of patients with retinoblastoma equaled that of developed nations (31).

Twining programs can be supported with the establishment of multidisciplinary clinics in which cancer experts from all fields of the cancer care continuum meet to discuss the most optimal approach for complex cases. In addition to their ease of implementation, these programs have proved their efficacy in improving patient outcomes, particularly mortality rate (33). Multidisciplinary programs were shown to be cost effective within an oncological context. The implementation of such boards for breast cancer in Mozambique and for lung cancer at the Kingston Health Sciences Center improved both outcomes and reduced costs (34, 35). Such reduction is attributed to decreased patients' visits, better planning and administration of treatment, improved clinical course, and more efficient resource utilization. If cemented across Libya and its neighboring countries, these efforts could also enable the accurate monitoring of patients' follow-up data and survival status.

That being said, any and all policies that may be discussed among Libyan concerned bodies and cancer care authorities must base its priorities on a strong ground of epidemiological data. Therefore, the creation, maintenance, and constant expansion of a national comprehensive cancer registry is vital in the understanding of the burden of cancer among the Libyan populace. The lack of such reliable data can be sensed within the literature as only a handful of studies attempted to deconstruct their respective population-based/center-based registers, of which results had shown significant underestimation compared to international figures. With regards to such a case, the Jordanian experience might be a suitable model as its cancer registry, Jordan Cancer Registry, is considered a well-established database of high international standards.

4.2 Conclusion

Treatment of Libyan patients with cancer requires high quality services necessitating collaboration of the various governmental and private sectors. The cooperation between KHCC and the Libyan Ministry of Health facilitated the proper treatment of Libyan patients with cancer. However, war and ongoing conflicts still emanate a direct negative impact on the survival outcomes of Libyan cancer patients. Therefore, the drafting and implementation of large, long-term policies in collaboration with experts and concerned bodies, which target the facilitation of cancer care to such vulnerable populations, are essential to the improvement of their outcomes and overall wellbeing.

Data availability statement

All data/data sets associated with this project will be made available by the corresponding author upon reasonable request.

Ethics statement

The research was approved by the Institutional Review Board (IRB) at King Hussein Cancer Center under number 20KHCC66. The request for Waiver of Informed Consent was granted by KHCC- IRB, since the study, involves collection of existing data from the electronic medical records and the Center's Cancer Registry, with no direct interaction with participants.

Author contributions

Conceptualization: MA-H and AM; Methodology: ME; Formal analysis: ME and AA; Writing – Original Draft: MA-H, AM, and ME; Writing – Review & Editing: MA-H and AA; Supervision: MA-H and AM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Investigating the impact of COVID-19 on patients with cancer from areas of conflict within the MENA region treated at King Hussein Cancer Center

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Background: There is a paucity of evidence regarding the impact of COVID-19 on cancer care among refugees or patients from areas of conflict. Cancer care for these populations remains fragmented due to resource scarcity and limited infrastructure.

Aims: To explore the effect of COVID-19 on cancer care among patients from areas of conflict treated at King Hussein Cancer Center (KHCC).

Methodology: We performed a retrospective chart review of all patients from areas of conflict, treated at KHCC from 2018 to 2021. Patients' demographics and clinical characteristics are presented in the form of descriptive statistics. Interrupted Time Series (ITS) analysis was utilized to investigate the impact of COVID-19 on the number of admissions throughout the study's period.

Results: A total of 3317 patients from areas of conflict were included in the study. Among these, 1546 were males (46.6%) while 1771 (53.4%) were female. Libyans (34.6%), Palestinians (24.8%), Iraqis (24.5%), Syrians (15.3%), and Sudanese patients (0.9%) constituted our study sample. ITS analysis demonstrated that the start of the COVID-19 lockdown significantly decreased admissions by 44.0% ($p = 0.020$), while the end of the COVID-19 restriction significantly improved admissions by 43.0% ($p = 0.023$). Among those with available SEER stages, more than a quarter of patients had distant metastasis ($n = 935$, 28.2%) irrespective of age and biological sex. Advanced presentations during 2020 had approximately a 16% and 6% increase compared to 2018 and 2019, respectively. Breast cancer (21.4%), hematolymphoid cancers (18.1%), and cancers of the digestive system (16.5%) were the most common cancers among our cohort.

Conclusion: Restrictions associated with COVID-19 had a significant effect on the number of admissions of patients from areas of conflict. In the long term, this effect may impact the survival outcomes of affected patients.

KEYWORDS

Areas of conflict, cancer care, COVID-19, Middle East, time series analysis

1 Introduction

The United Nations High Commissioner for Refugees (UNHCR) estimates that around 89.3 million people are forcibly displaced worldwide including 27.1 million refugees (1). In the Middle East, millions of Palestinian, Iraqi, Yemini, Libyan, Sudanese, and Syrian populations were displaced due to the invasions, prosecutions, and armed conflicts in the region (2). These conflicts across the region uprooted both the healthy and the ill alike. Populations from areas of conflict face significant and complicated healthcare challenges. In addition to war-related deaths and injuries, such vulnerable populations may already have diseases or develop new ones, necessitating interventions from healthcare systems, including those of their host countries. Previously, displacement crises mainly occurred in low-income and less developed countries leading to the spread of infectious diseases and malnutrition among refugees. However, in the 21st century, this scenario has become more diverse and considerably long-lasting and occurs in camp and non-camp settings, as well as low and middle-income settings alike. Similar to that trend, reported data from refugee camps in Jordan showed that the main reasons for mortality among refugees were not due to infectious causes, but rather non-communicable diseases (NCDs) (3, 4). This category of diseases has been given very little attention despite their increasing burden (5).

Of all NCD diseases, cancer is among the most important in this category as it is common, leads to substantial mortality and morbidity, and has significant economic burdens on patients and healthcare systems (6). Cancer and other NCDs are critically overlooked aspects of health in areas of conflict. Although actions in those regards have the potential to prevent thousands of deaths in these populations, reasons for such neglect stem from misconceptions of cancer as being too complex and expensive to treat, lack of agreement on cost-effective measures, and the inability of host healthcare systems to adopt new cancer services with the constant underfunded humanitarian responses (7). People from areas of conflict are susceptible to developing cancer due to many hardships including low-income. In addition, they are more likely to present with advanced stages and suffer more complications because of poor hygiene and living conditions, as well as limited access to care and resources available (8). For refugees, host countries encounter serious challenges in health provision to cancer patients considering the economic pressures they face and the lack of infrastructure, all of which lead to suboptimal care delivery to this subset of patients (9, 10). Furthermore, the course of treating many types of cancer requires a robust healthcare system with the ability to provide effective screening programs, diagnostic services, and treatment modalities (e.g., surgery, radiotherapy, or chemotherapy) (11).

Furthermore, the impact of COVID-19 on the accessibility and quality of cancer care was heavily noted within literature (12). COVID-19 has affected the entire spectrum of cancer care as it was responsible for delaying diagnosis, halting clinical trials, decreasing the capacity for cancer-related surgery, pushing towards the usage of more convenient treatment regimens versus optimal regimens, and leading to a general reprioritization of resources which may have impacted disease follow up. Moreover, cancer screening and treatment delivery has been subjected to significant delays (13). The net effect was a significant increase in cancer-related mortality (14); delays of as little as 4 weeks for surgical, systemic, or radiotherapeutic regimens were associated with increased mortality among patients with cancer. Interestingly, there exists no literature denoting such effects or their magnitude on immigrants, populations residing in areas of conflict, and refugees.

Cancer is the second most common cause of death in Jordan and still represents a significant challenge to the burdened healthcare systems in the Middle East (15, 16). King Hussein Cancer Center (KHCC) is a comprehensive cancer care facility in the region and is the only hospital solely dedicated to cancer management in Jordan, providing treatment for more than 4,000 new patients and 110,000 patients every year (17). On average, KHCC treated patients with cancer from areas of conflict, which represented 25% to 30% of all new cases diagnosed and managed each year (Center's Cancer Registry). Cancer care for refugees in Jordan remains substandard and heavily fragmented because of the finite financial support and limited access. In addition, there is a lack of information about cancer in areas of conflict populations in low-income and middle-income countries with very little data on cancer surveillance, registries, patterns, and outcomes in populations at risk (18, 19). Epidemiological studies on this topic are also scarce and were not undertaken in many conflict-affected countries before their crises. Cancer inequalities persists within areas of conflict due to the rapid rates of growth of population in these areas, pre-mature war-related deaths, and financial hardships (7).

In light of the above, the study aims to investigate the impact of COVID-19 on cancer care among patients from areas of conflict, seeking treatment at KHCC for 2018-2021.

2 Materials and methods

We performed a retrospective chart review of all non-Jordanian cancer patients visiting KHCC between January 2018 to December

2021. The patients were defined as those being treated at KHCC due to cancer care inaccessibility in their home country due to conflict. Areas of conflict (e.g., wars, political unrest) included Iraq, Libya, Palestine, Sudan, and Syria. From KHCC's Cancer Registry, which was established in 2006, the following was extracted for all potential patients: date at first contact, age at diagnosis, biological sex, cancer site, cancer histopathology, treatment type and duration, and SEER summary stage.

The data was analyzed using SPSS version 23. Categorical data were presented as frequencies [n (%)], while continuous data were reported as means ± standard deviations. Demographic and clinical data were described for the entire cohort and then stratified according to age group (adults vs. pediatrics, cut-off is 18 years of age), biological sex (male vs. female), year of first contact (i.e., 2018, 2019, 2020, 2021), and area of conflict (i.e., Iraq, Libya, Palestine, Sudan, Syria). For each stratum, the following was reported: frequency of cancer sites, SEER stage, treatment modalities, and mean age at diagnosis. Mean differences between certain subgroups in terms of continuous variables were examined using t-test and ANOVA.

The impact of COVID-19 on the number of admitted patients during the timeframe between 2018 and 2021 was modeled using Interrupted Time Series (ITS) analysis. The ITS model incorporated 3 distinct time frames which are a result of (1) the start of the national COVID-19 lockdown and (2) the end of all COVID-19 restrictions. Those time frames include: pre-COVID-19 era (January 2018 – February 2020), COVID-19 lockdown era (March 2020 – August 2021), and post-COVID-19 era (September 2021 – December 2021). Pre-COVID-19 data was collected as early as 2018 as to provide the model with a large enough number of observations for trend assessment. The Autoregressive Integrated Moving Average (ARIMA) model was used to evaluate the impact of COVID-19 lockdown on patients with cancer from areas of conflict. The SPSS Expert Modeler produced a best-fitting ARIMA model of (0,1,0). The fitness of the model and autocorrelations were assessed by the Ljung-Box Q test ($p = 0.582$). The model stationary R-squared and R-squared values were 0.759 and 0.754, respectively. All statistical tests were conducted with a 95% confidence interval and a 5% error margin. A p-value of less than 0.05 was considered statistically significant.

3 Results

3.1 Demographic characteristics

We included a total of 3317 patients from areas of conflict with cancer treated at KHCC from 2018 to 2021. A total of 1086 (32.7%), 1119 (33.7%), 489 (14.7%), and 623 (18.8%) patients presented in 2018, 2019, 2020, and 2021, respectively. Among these, 1546 were males (46.6%) while 1771 (53.4%) were females. A total of 2833 patients were adults (i.e., 18 years of age and older) and 484 (14.6%) were children and adolescents (i.e., younger than 18 years of age). In terms of nationality, 812 (24.5%) were Iraqi, 1149 (34.6%) were Libyan, 821 (24.8%) were Palestinian, 29 (0.9%) were Sudanese, and 506 (15.3%) were Syrians.

3.2 Time trends

Throughout 2018, a median of 75.5 [62.2 – 114.5] admissions was recorded ranging from a peak of 174.0 during April to a trough of 53.0 during September. Similarly, across 2019, a median of 82.0 [74.7 – 119.5] admissions were recorded ranging from 130.0 in October to 58 in January of the same year. In 2020 (start of the COVID-19 pandemic), median admissions were reduced to a median of 34.0 [22.7 – 41.5] ranging from 16.0 in May to 104.0 in January (before the actual COVID-19 spread in Jordan). Between February of 2020 and March of 2020 (COVID-19 lockdown started), admissions dropped from 87.0 to 43.0. A trend of sub-50 admissions continued throughout the year, until August of 2021 (End of COVID-19 restrictions) when admissions reached 80.0 signifying an upward trend. ITS analysis demonstrated that the start of the COVID-19 lockdown significantly decreased admissions by 44.0%, while the end of the COVID-19 restriction significantly improved admissions by 43.0% (Figure 1). From 2018 to 2021, a total of 15,619 Jordanian patients were admitted to KHCC. With the start of the COVID-19 lockdown, the number of Jordanian patients dropped from 310 in February to 205 in March. These numbers reached their deepest trough in April (n = 132). Figure 2 demonstrates the time trends between Jordanian and patients from areas of conflict. The number of

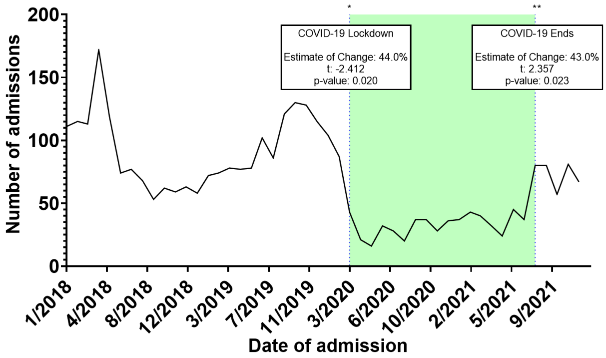

FIGURE 1
Interrupted time series (ITS) analysis of different COVID-19 related events on the admissions trends of patients from areas of conflict.

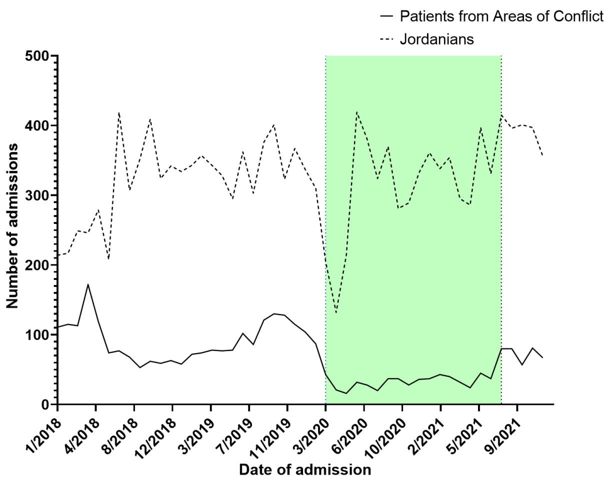

FIGURE 2
A parallel comparison between admission trends between Jordanian patients with cancer and patients from areas of conflict from 2018 to 2021.

admissions from 2018 to 2021 stratified by nationality is demonstrated in Figure 3.

3.3 Clinical characteristics

Across our cohort, the mean age at diagnosis was 45.1 ± 20.6 years. Participants presenting in 2019 had the highest mean age at diagnosis (46.6 ± 19.8), while those presenting in 2020 had the lowest (42.0 ± 22.5). Sudanese and Iraqi patients had the highest mean age at diagnosis with 51.3 ± 16.3 and 49.7 ± 19.5 years, respectively. On the other hand, Syrian refugee patients had the lowest mean age at diagnosis at 37.6 ± 21.7 years. Statistical differences between sexes in terms of age at diagnosis were statistically insignificant (44.9 ± 22.4 (Males) vs. 45.2 ± 19.0 (Females); $p = 0.558$). Of the reviewed patients, 1597 (48.1%) underwent surgery, 929 (28.0%) received radiation therapy, and 1947 (58.7%) received chemotherapy. A total of 287 (8.7%) experienced tumor recurrence. Tables 1, 2 describe the site-specific frequencies of cancer among patients stratified by nationality and year of contact.

For a total of 924 patients (27.9%), the SEER summary stage was unknown or could not be retrieved. Among those with available SEER stages, 935 (28.2%) had distant metastasis, 669 (20.2%) had localized disease, and 757 (22.8%) had regionally extending disease by direct extension or lymph nodes metastasis or both. Table 3 and Figure 4 describe the available SEER summary stage frequencies of all cases among patients stratified by nationality and year of contact. Clinical characteristics for both site-specific cancer frequencies and SEER summary stages stratified by biological sex and age can be found within Supplementary Tables 1, 2.

4 Discussion

In this observational study, we reviewed clinical records of 3317 patients from countries with conflict who received cancer care at

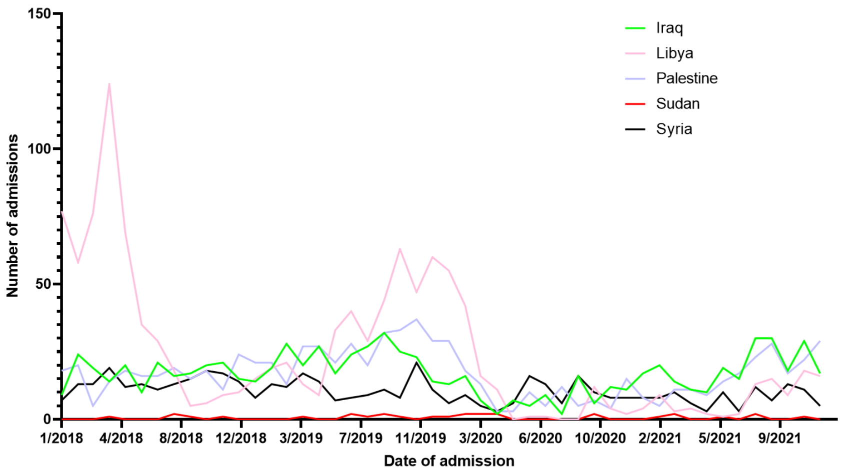

FIGURE 3
Admissions trends of patients from areas of conflict stratified by nationality from 2018 to 2021.

TABLE 1 Site-specific frequencies of cancers in patients from areas of conflict who presented to the King Hussein Cancer Center between 2018 and 2021 stratified by nationality.

Site	Total (n = 3317) *n* (%)	Iraq (n = 812) *n* (%)	Libya (n = 1149) *n* (%)	Palestine (n = 821) *n* (%)	Sudan (n = 29) *n* (%)	Syria (n = 506) *n* (%)
Breast	710 (21.4)	227 (28.0)	206 (17.9)	169 (20.6)	5 (17.2)	103 (20.4)
Hemolymphoid	599 (18.1)	86 (10.6)	233 (20.3)	162 (19.7)	5 (17.2)	113 (22.3)
Digestive System	547 (16.5)	143 (17.6)	212 (18.5)	128 (15.6)	5 (17.2)	59 (11.7)
Lung and Pleura	196 (5.9)	50 (6.2)	70 (6.1)	46 (5.6)	4 (13.8)	26 (5.1)
Female Genital System	182 (5.5)	53 (6.5)	67 (5.8)	32 (3.9)	3 (10.3)	27 (5.3)
Endocrine System	180 (5.4)	45 (5.5)	43 (3.7)	62 (7.6)	2 (6.9)	28 (5.5)
Urinary system	168 (5.1)	29 (3.6)	57 (5.0)	49 (6.0)	1 (3.4)	32 (6.3)
Male Genital System	163 (4.9)	40 (4.9)	66 (5.7)	36 (4.4)	1 (3.4)	20 (4.0)
Brain	141 (4.3)	23 (2.8)	61 (5.3)	36 (4.4)	0 (0.0)	21 (4.2)
Bone and Soft Tissue	140 (4.2)	37 (4.6)	44 (3.8)	28 (3.4)	2 (6.9)	29 (5.7)
Head and Neck	108 (3.3)	22 (2.7)	45 (3.9)	28 (3.4)	1 (3.4)	12 (2.4)
Eye	63 (1.9)	21 (2.6)	16 (1.4)	10 (1.2)	0 (0.0)	16 (3.2)
Larynx	50 (1.5)	15 (1.8)	15 (1.3)	11 (1.3)	0 (0.0)	9 (1.8)
Skin	36 (1.1)	11 (1.4)	6 (0.5)	14 (1.7)	0 (0.0)	5 (1.0)
Unknown	17 (0.5)	7 (0.9)	4 (0.3)	5 (0.6)	0 (0.0)	1 (0.2)
Nose and Ear	17 (0.5)	3 (0.4)	4 (0.3)	5 (0.6)	0 (0.0)	5 (1.0)

TABLE 2 Site-specific frequencies of cancers in patients from areas of conflict who presented to the King Hussein Cancer Center between 2018 and 2021 stratified by year of first contact.

Site	Total (n = 3317) *n* (%)	2018 (n = 1086) *n* (%)	2019 (n = 1119) *n* (%)	2020 (n = 489) *n* (%)	2021 (n = 623) *n* (%)
Breast	710 (21.4)	224 (20.6)	257 (23.0)	111 (22.7)	118 (18.9)
Hemolymphoid	599 (18.1)	196 (18.0)	198 (17.7)	90 (18.4)	115 (18.5)
Digestive System	547 (16.5)	198 (18.2)	177 (15.8)	69 (14.1)	103 (16.5)
Lung and Pleura	196 (5.9)	54 (5.0)	75 (6.7)	28 (5.7)	39 (6.3)
Female Genital System	182 (5.5)	72 (6.6)	57 (5.1)	24 (4.9)	29 (4.7)
Endocrine System	180 (5.4)	56 (5.2)	52 (4.6)	30 (6.1)	42 (6.7)
Urinary system	168 (5.1)	53 (4.9)	50 (4.5)	25 (5.1)	40 (6.4)
Male Genital System	163 (4.9)	55 (5.1)	59 (5.3)	23 (4.7)	26 (4.2)
Brain	141 (4.3)	46 (4.2)	45 (4.0)	26 (5.3)	24 (3.9)
Bone and Soft Tissue	140 (4.2)	44 (4.1)	44 (3.9)	24 (4.9)	28 (4.5)
Head and Neck	108 (3.3)	34 (3.1)	40 (3.6)	16 (3.3)	18 (2.9)
Eye	63 (1.9)	15 (1.4)	22 (2.0)	8 (1.6)	18 (2.9)
Larynx	50 (1.5)	14 (1.3)	15 (1.3)	7 (1.4)	14 (2.20)
Skin	36 (1.1)	15 (1.4)	14 (1.3)	5 (1.0)	2 (0.3)
Unknown	17 (0.5)	4 (0.4)	8 (0.7)	2 (0.4)	3 (0.5)
Nose and Ear	17 (0.5)	6 (0.6)	6 (0.5)	1 (0.2)	4 (0.6)

TABLE 3 The SEER summary stage at presentation of patients from areas of conflict who presented to the King Hussein Cancer Center between 2018 and 2021 stratified by nationality.

Site	Total (n = 3317) *n* (%)	Iraq (n = 812) *n* (%)	Libya (n = 1149) *n* (%)	Palestine (n = 821) *n* (%)	Sudan (n = 29) *n* (%)	Syria (n = 506) *n* (%)
In situ	32 (1.0)	5 (0.6)	6 (0.5)	15 (1.8)	0 (0.0)	6 (1.2)
Localized	669 (20.2)	219 (27.0)	167 (14.5)	178 (21.7)	4 (13.8)	101 (20.0)
Regional by direct extension	230 (6.9)	54 (6.7)	77 (6.7)	49 (6.0)	2 (6.9)	48 (9.5)
Regional to lymph nodes	331 (10.0)	102 (12.6)	68 (5.9)	99 (12.1)	2 (6.9)	60 (11.9)
Regional by direct extension and lymph nodes	196 (5.9)	49 (6.0)	60 (5.2)	54 (6.6)	5 (17.2)	28 (5.5)
Distant	935 (28.2)	195 (24.0)	320 (27.9)	237 (28.9)	13 (44.8)	170 (33.6)
Unknown	205 (6.2)	68 (8.4)	37 (3.2)	66 (8.0)	2 (6.9)	32 (6.3)
None	719 (21.7)	120 (14.8)	414 (36.0)	123 (15.0)	1 (3.4)	61 (12.1)

KHCC during the years 2018 – 2021. Our study is the first to report changes on the trends of these cancer cases in light of the COVID-19 pandemic. The data herein showcases that breast cancer was the most common in the female cohort across all nationalities while hemolymphoid malignancies were most common among their male counterparts except for Iraqi and Sudanese male patients. Cancers of the digestive system ranked first among male Iraqi and Sudanese patients and second among Palestinian, Syrian, and Libyan male, and Libyan female patients. Hematolymphoid cancers were the second most common among Palestinian and Syrian female patients. Moreover, we have demonstrated that a significant number of these patients presented with distant metastasis irrespective of gender, age, or nationality. Overall, the frequency of presentation with advanced stage cancer (i.e., distant metastasis) increased amidst the COVID-19 lockdown.

We have observed a significant decline of 44% of cancer cases after the onset of the COVID-19 lockdown around March 2020. These effects were counterbalanced by the lifting of COVID-19 social and travel restrictions on August 2021 as it was associated with a 43.0% increase in cancer cases. Our results are echoed within the literature as an investigation of cancer patients hospitalized at the Massachusetts General Hospital demonstrated a reduction of admissions reaching as high as 45.4%, particularly during April 2020 (20). The study also shows that the inpatient census increased following the ease of the COVID-19 surge within the Boston region. Overall, the effect of COVID-19 on cancer diagnosis, screening, and treatment is well documented throughout literature (21–25). Our results further add to the growing body of literature by demonstrating the overall impact of these changes within the context of cancer patients from areas of conflict.

Interestingly, when comparing our target population to Jordanian patients with cancer treated at KHCC, both populations experienced a significant decrease in admissions around March 2020. However, for patients from areas of conflict, it took around 18 months for their numbers to recover to pre-COVID-19 rates. This was in contrast with Jordanians, whose numbers stabilized back to their pre-COVID-19 thresholds in a matter of few months. This observation is expected as Jordanian patients with cancer did not experience the travel restrictions and delays associated with COVID-19 control policies.

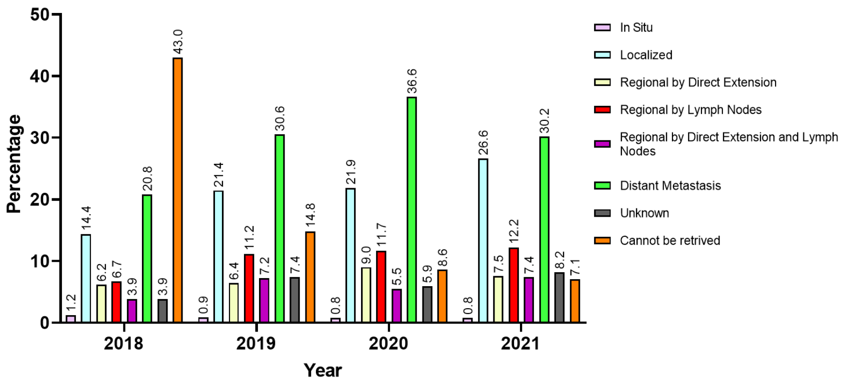

FIGURE 4
The SEER summary stage at presentation of patients from areas of conflict who presented to the King Hussein Cancer Center between 2018 and 2021 stratified by year of first contact.

The COVID-19 pandemic has been a particularly challenging time for patients with cancer. On one hand, those patients are often vulnerable because of their immunocompromised state, while increasing evidence showed that patients with cancer are at a higher risk of COVID-19 infection (26). This dilemma may have predisposed patients to be more reluctant to consult their primary physician with regard to their disease or scheduled follow-ups (27–29). As for cancer care delivery, emergency planning strategies and policies during the onset of the pandemic were focused on relocating all healthcare resources to the containment of the virus, including those dedicated to cancer services (30). Data from 356 centers across 54 countries showed the devastating impact of COVID-19 on cancer healthcare as it reported interruption of cancer-specific care ranging from 36.5% to 80.0%. These manifested as treatment delays, missing treatment, and entire obstruction of cancer care delivery due to lack of capacity (31).

Not only did the COVID-19 pandemic affect the activity of general and specialized practice, but it also disrupted the coordination between different practices and hospitals which led to decreased referrals for possible cases of cancer to specialized centers (32, 33). This is especially important when considering that KHCC is Jordan's only specialized tertiary center where the cornerstone multi-modal interventions are available (17). Studying the impact of COVID-19 on cancer care outlines the inflection at which new cases are presented to healthcare systems after the alleviation of restrictions. This also poses questions about whether the pandemic has affected diagnostic patterns and stages at diagnosis, therefore, outcomes. A national, population-based study in the United Kingdom demonstrated that the delays in diagnosis of four tumors associated with the COVID-19 lockdown (breast, colorectal, lung, and esophageal), led to over 3,000 avoidable deaths and more than 59,000 years of life lost (34). It should be noted that the impact of these delays on patient outcomes is not entirely known. These challenges are especially important in the context of underserved cancer patients in areas of conflict seeking treatment at our center, further preventing them from accessing appropriate cancer care. The noted interruptions in cancer care delivery across the healthcare systems could have deleterious effects on patients' outcomes on aspects such as increased tumor size, higher chances of node invasion at diagnosis, along with increased rates of mortality on both short and long term periods (35–37). These patterns, which align with our results, come as no surprise, as policies during the early months of the pandemic were primarily executed to address the complications of the early aggressive COVID-19 strain on the vulnerable public while ensuring the safety of healthcare providers.

Being a leading cause of mortality, cancer exerts a colossal burden on global healthcare. Also, it is associated with an ever-rising interest from international communities to provide more effective and efficient methods of treatment, diagnosis, screening, and prevention; however, cancer care is still widely inequitable around the world. This is especially evident when observing underprivileged populations such as those residing in politically unstable regions (38). Such populations often encounter many hardships that delay diagnosis, impede care delivery, and render screening almost impossible. The detrimental effects of such challenges are reflected upon patients as they often present with advanced stages which generally lead to poorer survival and quality of life outcomes (39–41). Our results delineate that more than a quarter of patients had already presented with distant metastasis during the pandemic; a trend which only increased in frequency after the implementation of the COVID-19 lockdown in 2020, as more than a third of patients presented with distant metastasis.

Studies exclusively studying the Syrian populations in Turkey reported that the majority of Syrian refugees present with breast cancer and advanced stages. On the other hand, Jordanian reports showed a dominance of localized breast cancer cases among Syrian refugees (10, 42, 43). The UNHCR demonstrated that, in general, refugees in formal camps have very poor survival outcomes even when diagnosed early with cancer. This is mainly due to the inadequacy of their received treatment plans as well as the overall poor health infrastructure of their camps which are primarily tailored to treating communicable diseases. Furthermore, the clinical and surgical services in those camps are geared towards 'classical' refugee health, mainly dealing with trauma and benign diseases (18, 44).

Here, we note the importance of National Cancer Control Plans (NCCPs) in designing policies that aim to reduce the burden of cancer in Jordan among Jordanians in general and among refugee populations in specific. In addition to investing in cost-effective cancer screening measures, evidence shows that primary cancer prevention through controlling cancer risk factors, such as smoking, diet (e.g., obesity), and environmental pollution are critical in reducing cancer incidence and cancer-related healthcare costs (45, 46). According to expert stakeholders, designing holistic cancer control plans, which include the entire cancer journey spectrum from early detection to survival and palliation, is ultimately cost-effective in the long run as it decreases treatment costs for advanced and highly sophisticated cases (47). The World Health Organization laid out in its 2019 cancer report that for every 1 USD invested in those programs, there is a 2.30 USD of direct productivity return and 9.50 USD of social productivity return (48).

Estimating the true burden of cancer in refugees is imperative to the design of cost-effective cancer control strategies. However, such a process is hindered by a variety of factors. Firstly, cancer is not one disease entity but rather a spectrum of related diseases, each with a unique set of risk factors and clinical behaviors. Secondly, the availability of data poses an important challenge as patients coming from areas of conflict including refugees often come from lower income settings where registries are inadequate or absent (49). These limitations are augmented by many folds when considering the significant rates of attrition of these patients due to poor economic standards. This loss of data makes a reliable calculation of survival rates extremely burdensome, let alone controlling it for possible confounders. Thirdly, factors affecting cancer care among this particular group of patients are dynamic and multileveled ranging from differences in risk exposure, and access to healthcare, to behavioral/psychosocial changes (50). The literature highlights the paucity of epidemiological data on cancer patients in low-to-middle-income countries and their associated changes in risk factors, presentation delays, and access to care (50). In addition, the aforementioned literature is often methodologically weak and at times contradictory.

Our paper falls prey to a number of limitations. Firstly, the study's retrospective design may have limited the range of extracted variables. Secondly, due to the participants' temporary residence within Jordan, maintenance of follow-up is often hindered and may have restricted our ability to reliably calculate and compare outcome measures (e.g., overall survival). Finally, staging data per the 2018 SEER guidelines were not available for all patients.

5 Conclusion

We have demonstrated that the restrictions associated with COVID-19 had significantly affected the number of admissions of patients from areas of conflict within the MENA region. This effect, manifesting as missed treatments or treatment delays, may be projected as worse survival outcomes for a population that is already vulnerable, both clinically, and socially. Therefore, concerned bodies are encouraged to form policies that aim to sustain the well-being of those patients during times of extreme hazard.

Data availability statement

All data/data sets associated with this project can be requested from the corresponding author at a reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the KHCC (Amman, Jordan), protocol number 22KHCC171. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MA-H and AM. Methodology: MA-H and AA-A. Formal analysis: AA-A and LA-H. Writing – Original Draft: All authors. Writing – Review & Editing: All authors. Supervision: MA-H and AM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1088000/full#supplementary-material

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Save lives and relieve suffering: The twin imperatives of humanitarian response and the role of palliative care

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Introduction

Humanitarian emergencies and crises (HECs) are large-scale events that often cause injuries, illness or death on a massive scale, social breakdown, forced displacement, and all types of physical, psychological, social, and spiritual suffering. They rarely are caused by a single factor and are usually the result of mixed climatic/geologic, human-made, environmental, political and economic causes and vulnerabilities (1, 2). The principles of humanitarianism explicitly require efforts both to save lives and to prevent and alleviate human suffering, and these two imperatives rarely are in conflict (1, 3–5). Yet throughout the world, humanitarian medical response focuses primarily on saving lives and lacks adequate attention to preventing and relieving suffering (6–9). This moral failing appears to have several causes including lack of adequate palliative care content in humanitarian response guides and training; legal or logistical barriers to opioid access in fragile, conflict-affected, and vulnerable settings; and negative attitudes toward palliative care (10).

Palliative care in humanitarian emergencies and crises

Palliative care entails prevention and relief of serious physical, psychological, social or spiritual suffering of patients, chronic or acute, and psychological, social and spiritual suffering of their family members (1). The World Health Organization (WHO) recognizes that the specific types, scale, and severity of suffering often varies by geopolitical location, by economic situation, by culture, and, in the setting of HECs, by the type of emergency or crisis (1). But basic palliative care training and supplies are adequate to alleviate most types of suffering in any situation. In HECS, services to prevent and relieve suffering should be made accessible for anyone suffering physically, psychologically, socially, or spiritually and not only for those with life-threatening conditions. There is a particular ethical imperative, based on the medical and ethical principles of beneficence and non-abandonment, to providing palliative care and symptom control for patients whose death is deemed unavoidable under prevailing circumstances. Failure to benefit these highly vulnerable patients by treating aggressively and immediately any physical and psychological suffering constitutes abandonment and is thus ethically unacceptable. Yet it is crucial to avoid equating palliative care with end-of-life care and instead to recognize that palliative care should be provided in response to any moderate or severe suffering in an HEC, regardless of the patient's prognosis (1, 11).

Palliative cancer care in humanitarian emergencies and crises

As Caglevic et al. powerfully state, "war breeds cancer—delaying diagnosis, preventing treatment, and increasing risk (12)." Hospitals often redirect care to trauma victims, leaving fewer resources available to manage medically fragile patients with cancer or other serious illness (13). HECs, especially armed conflict, disrupt and prevent cancer treatment, divert resources from oncologic care, expose vulnerable patients with cancer to additional risks such as infection, and lead to delays in diagnosis (12). Delaying surgery for breast cancer by 12 weeks leads to a 26% increase in mortality, with similar findings reported for bladder, colon, head and neck, and non–small-cell lung cancers (14). All of these factors lead to an increased need for palliative care in patients with cancer in HECs.

Palliative care is never an acceptable alternative to cancer prevention, diagnosis, and treatment. Efforts always should be made to assure access to comprehensive cancer care including prevention, early diagnosis, and treatment. But while access to cancer chemotherapy or radiotherapy may be lost in an HEC, access to palliative care always can and should be maintained. Using the essential package of palliative care for humanitarian emergencies and crises (EPPCHECs) recommended by WHO, palliative care is relatively simple to provide in areas where more comprehensive cancer care may not be immediately available, such as areas of conflict (1).

While it is never ethically permissible to regard palliative care as a substitute for comprehensive cancer care, the reverse is also true; it is not ethically permissible to focus on cancer prevention and treatment while ignoring the responsibility to palliate the suffering of patients and families (15). It has been shown that palliative care can prolong the lives of some cancer patients (16). Additionally, chemotherapy, radiation, and surgery are all aspects of comprehensive palliative care for patients whose cancer is incurable and can be a valuable means of addressing suffering. Thus, there is a not a dichotomy between cancer treatment and palliative care.

Lastly, as palliative care emphasizes attention to social and family histories, personal values, and whole-person care, the inclusion of palliative care in response to humanitarian crises can also promote cultural sensitivity and adaptation to local culture. It is vital that any humanitarian response be attuned to local culture and include local people. A key principle of palliative care integration in HECs is recognition of local colleagues' expertise, with a focus on assisting local colleagues to do the work needed and to build or rebuild healthcare infrastructure. Part of this role would be providing training in palliative care and assistance in developing culturally-adapted, sustainable palliative care services (and other cancer services).

Discussion

To make palliative care accessible to all in need in HECs, it should be thoroughly integrated into international and national humanitarian response protocols and organizations. This will require significant but feasible and affordable changes in humanitarian response policy, clinical guidance, triage, training, essential supplies, and indicators. The leading humanitarian response organizations, including the United Nations High Commission on Refugees (UNHCR), the International Committee of the Red Cross (ICRC), the International Federation of Red Cross and Red Crescent Societies (IFRC), the Doctors Without Borders organizations (MSF), the Save The Children organizations, Catholic Relief Services (CRS), and others, should make clear in their policy statements and field guides that prevention and relief of physical, psychological, social, and spiritual suffering with palliative care is "an ethical responsibility" (17). We applaud the editors of the 2018 revision of The Sphere Handbook, the world's leading handbook of humanitarian response, for inviting one of us (ELK) to contribute a section on palliative care as one of the "minimum standards in humanitarian response" (4). However, the final edited version propagates the misconception that palliative care is only for dying patients. Future guidance documents should emphasize the twin imperatives of saving lives and relieving suffering and make clear that palliative care is not only for the dying.

In developing policies and clinical guides, it is crucial that conflict over nomenclature or "turf" be avoided between experts in related fields such as anesthesia, mental health, social support, and palliative care. Excellent guidance on mental health and psychosocial support in emergency situations already exists, and social supports already are a standard part of most humanitarian response (18–20). Whether psychological first aid, for example, is called mental health care or palliative care, and whether relief of acute pain from traumatic injury is called anesthesia or palliative care, is unimportant. What matters is that humanitarian responders be trained to provide all needed services and that guidance on saving lives, on preventing and relieving physical, psychological, social, and spiritual suffering, and on strengthening local health care systems be easily accessible in one place and in many languages. Humanitarian responders cannot be expected to access multiple manuals on all relevant topics.

Palliative care should be an integral part of triage protocols. Allocation of "expectant" patients, those whose survival is not possible with available resources, to the color black at the bottom of triage protocols suggests that they be abandoned and is unethical. We support the WHO proposal of a revised triage protocol that includes palliative care at all levels and makes clear that expectant patients require care (Table 1).

TABLE 1 WHO recommended triage categories in humanitarian emergencies and crises (1).

Category	Colour code	Description
1a. Immediate	Red	Survival possible with immediate treatment
		Palliative care should be integrated with life-sustaining treatment as much as possible.
2a. Expectant	Blue	Survival not possible given the care that is available
		Palliative care is require
	Yellow	Not in immediate danger of death, but treatment needed soon.
		Palliative care and/or symptom relief may nevertheless be needed immediately.
3. Minimal	Green	Will need medical care at some point, after patients with more critical conditions have been treated.
		Symptom relief may be needed.

The colors are adapted by the World Health Organization from colors of standard triage categorization in humanitarian emergencies and crises.

The WHO essential package of palliative care for humanitarian emergencies and crises (EPPCHECs) should be a standard part of the equipment of all international and national humanitarian response organizations. The EPPCHECs includes a set of safe, effective, inexpensive, off-patent and widely available medicines, simple and inexpensive equipment, basic social supports, and the trained human resources needed to apply them appropriately, effectively, and safely (1). Morphine, in oral fast-acting and injectable preparations, is the most clinically important of the essential palliative care medicines and should be accessible in all HECS to treat moderate or severe pain and refractory terminal dyspnea (21). Although WHO has guidelines designed to enable emergency import of controlled medicines for HECs (22), humanitarian responders often report that morphine and other controlled medicines are not available or that efforts to import them for humanitarian response often prove futile (23, 24). The need for access to basic palliative care medications, especially pain medications, is especially great in cancer patients whose care is likely to be disrupted in HECs. Thus, the mechanism for emergency importation of controlled medicines requires revision based on global consensus. Maximizing accessibility of controlled medicines for medical uses must be balanced by reasonable precautions to prevent diversion and non-medical use. Model guidelines for this purpose are available (25).

Additionally, training is an integral component of implementing palliative care in HECs, especially for patients with cancer. Humanitarian responders should be trained in palliative care (basic or intermediate training—not just for cancer patients, but for many patients for whom palliative care skills are needed).

Finally, a standard instrument for data collection on humanitarian response is needed to assess not only patients' diagnoses and mortality rates but adequacy of palliative care such as those developed by WHO and The Sphere Handbook (4, 26, 27).

Conclusion

People with cancer and other serious illnesses are at particular risk of suffering in the settings of HECs. Access to palliative care is crucial to realization of the human right to the highest attainable standard of health and well-being, and it is an essential component of comprehensive care for people with these illnesses. Under normal circumstances, it should be integrated with prevention, diagnosis, and treatment of such illnesses and should never be considered an acceptable alternative to them. But when such services are disrupted or unavailable due to conflict or other crises, both the need for palliative care and the moral imperative to provide it increase dramatically. Provision of the WHO essential package of palliative care remains feasible even when other services such as chemotherapy, radiation therapy, and surgery are not. To ensure access to palliative care for people affected by humanitarian crises, humanitarian response policies and guidance documents should include palliative care, all humanitarian responders should be trained and equipped to provide palliative care, and research on humanitarian crises should include indicators of palliative care need, provision, and quality.

Author contributions

All authors contributed to the writing and editing of this article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cancer care in times of conflict: Treatment of patients from Afghanistan, in Pakistan

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Introduction: Afghanistan has been in a near-continuous armed conflict, which has degraded the country's health infrastructure. Due to this, Afghans have opted to seek cancer treatment in Pakistan. This manuscript aims to understand the complex cancer journey of patients from Afghanistan seeking care in the largest tertiary care cancer institutions in Pakistan.

Methods: This retrospective study explores the demographics, epidemiology and outcomes of Afghan cancer patients treated at the Shaukat Khanum Memorial Cancer Hospital and Research Centres (SKMCH&RC) in Lahore and Peshawar, Pakistan, over the period from 1995 to June 2022.

Results: A total of 6,370 patients from Afghanistan have undergone cancer care since 1995. The mean age at presentation was 40.7 years, 57% were male, and 87% were adults >19 years. Close to 30% of these patients came from Kabul and Nangarhar districts. 56% of all patients presented with stage III or IV disease. 34% of adult patients achieved a complete response to treatment, but more than half of all patients have since been lost to follow-up. Children generally had better outcomes, with 43% showing a complete response to treatment.

Discussion: The cancer journey for these patients remains long and difficult and the inability to ensure follow-up in so many remains frustrating for both patients and providers. The lack of a cancer infrastructure in Afghanistan after decades of conflict, means that policymakers need to develop and support alternative systems and structures to provide post-conflict domestic and cross-border cancer care.

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Introduction

Worldwide, 89.3 million people are currently forcibly displaced as a result of persecution, conflict, and other events disturbing public order. Low- and middle-income countries host 83% of these individuals. By the end of 2021, approximately 2.7 million Afghans were displaced across borders, and an estimated 3.5 million were displaced internally. These figures have risen for each of the preceding fifteen years (1). Armed conflicts have short and long-term socio-economic, geopolitical, and health consequences and the international community has repeatedly responded to refugee crises, mostly through United Nations (UN) agencies and non-governmental organisations (NGOs) (2). These efforts, however, have focused primarily on providing acute medical care, or on controlling public health issues such as malnutrition and outbreaks of infectious disease (3). Non-communicable diseases, especially cancer, in refugee and migrant populations have received much less international attention. Refugee and migrant populations often present with advanced disease, are unfamiliar with health systems in host countries and are not usually enrolled in formal care programmes, all of which make it more likely that they will have poor health outcomes (3–5).

Pakistan shares a long border with Afghanistan. Following the invasion of Afghanistan by the former Union of Soviet Socialist Republics (USSR) in 1979, millions of people from Afghanistan crossed the border to seek refuge in Pakistan. At its peak, the refugee population within Pakistan numbered over 3.3 million people (1, 3).

The Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC) was set up in Lahore, Pakistan in 1994. The intake mechanism for cancer patients is based on a diagnosis of cancer, without regard to financial status, ethnicity, or nationality. Nearly 30% of all patients seen in the hospital in Lahore have been from the north-western province of Pakistan, bordering Afghanistan, called Khyber Pakhtunkhwa (KP), or from Afghanistan. Recognising the need for a specialised tertiary care cancer hospital in KP, a second SKMCH&RC was established in Peshawar, the provincial capital, in 2015.

We have previously published data regarding the clinical, geo- and socio-demographic features of refugees from Afghanistan who sought care at SKMCH&RC (3). However, since then, the geopolitical landscape of Afghanistan has changed, and SKMCH&RC has opened another hospital near the Afghanistan border in Peshawar, which has increased the number of patients receiving care. Hence, we present an updated retrospective analysis to help understand the complex cancer journey of patients from Afghanistan seeking care in the largest tertiary care cancer institutions in Pakistan.

Materials and methods

A retrospective review of patients identified as Afghan nationals, or patients who provided an address in Afghanistan at the time of initial registration at Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH&RC), between the 1st of December 1995 and the 30th of June 2022 was performed. From this cohort, all male and female patients who received treatment for cancer were evaluated further. Patients with benign aetiology or those who did not complete diagnostic work-up were excluded from further analysis.

One of the core principles of SKMCH&RC, enshrined in its mission statement, is to provide the best possible cancer treatment to all our patients, irrespective of their ability to pay. SKMCH&RC has Walk-In clinics across the country, where patients with an established cancer diagnosis, as well as those with a suspicion of cancer, may come to be assessed for acceptance into the system. It is estimated that there are close to 180,000 new cancer diagnoses each year in Pakistan alone and of these, close to 45,000 patients come to one of SKMCH&RC Walk-In clinics, seeking treatment, each year.

At SKMCH&RC, most chemotherapy and all radiation treatments are day-case or outpatient procedures. Almost all patients need a place to stay near one of our two hospitals for the duration of their treatment and while some may stay in small hotels which have sprung up nearby, most cannot afford even this Spartan accommodation. To cater to the needs of such individuals, supporters of the Hospital have provided access to nearby hostel facilities, or Musafirkhanas, for three hundred patients, where free accommodation and meals are provided to these patients as well as to one carer each. A significant proportion of the patients who access these facilities are Afghans or Pakistani Pashtun patients from KP, and this has led to the development of an environment where Pashtu and Farsi (Persian) are spoken, and where an informal support system has grown organically, helping to ameliorate the difficulties these patients experience at a difficult time and in a somewhat alien environment.

Since we cannot treat all the cancer patients who come to us, we accept patients based on diagnosis and cancer stage, the intention being to accept those most likely to be curable. Nonetheless, once patients are accepted for treatment, they are eligible for all treatments available, even when their cancers progress, regardless of their ability to pay and irrespective of their nationality or ethnicity.

SKMCH&RC uses a custom-built electronic medical record system consisting of patient registration, clinical information, order entry, and results viewing modules. The system was commissioned in 2000, before which the medical record was paper based. Older, paper-based records have since been scanned, archived, and integrated into the electronic system.

The data for all participants was de-identified, and patient records were reviewed to gather data on patient demographics, including address within Afghanistan, gender, cancer diagnosis, stage, treatment provided and follow-up details. The descriptive analysis was conducted on Microsoft Excel.

Results

A total of 113,384 patients were registered for cancer care between December 1995 and June 2022 at SKMCH&RC. Among these, 7,468 (6.6%) patients were identified as Afghan nationals. The records of 1,098 (14.7%) patients were excluded, as they did not receive treatment at SKMCH&RC due to benign aetiology, because they did not return after an initial visit or because they failed to complete staging investigations.

Of the 6,370 patients included in this study, 57% were male. The mean age at presentation was 40.7 years and 87% of the participants were adults (Figure 1A). There was a dramatic increase in Afghan migrants registering for care from 2012 onwards, peaking in 2018, despite relative peace and stability, at least in some parts of Afghanistan, during this period (Figure 1B). Most patients were born in Afghanistan (92%), and a slightly lower percentage had an active Afghanistan address (83%). The largest number of patients came from Kabul (19%) followed by Nangarhar (11%), Herat (6%), Balkh (5%) and Ghazni (4%). Each of the other provinces accounted for less than 5% of the patients seen. The province of origin for 16% of patients was unknown.

Over 56% of all patients (56% of adults and 41% of children) presented with advanced disease (Stage III and IV), while cancer stage was not documented in 16%. Details of cancer stages of the participants are given in Table 1. 54% of patients were lost to follow-up, 23% of patients were being actively followed-up at the time of data extraction, and 8% were known to have died. These results are stratified in Table 2.

Upper gastrointestinal malignancies including oesophageal (20%) and gastric cancer (10%) were the most common cancers among adult patients, followed by breast (10.1%) and colorectal cancer (7%). Haematological malignancies including Hodgkin lymphoma (21%), acute lymphoblastic leukaemia (17%) and non-Hodgkin lymphoma (14%), were the most common cancers in paediatric cases (Figure 2).

The most common cancers among males were oesophageal (17.2%), gastric (13.7%), and colorectal. In females, by contrast, the commonest cancers seen were of the oesophagus (24.2%) and breast (20.6%) (Table 3).

Patients received a range of treatments, in keeping with the heterogeneity of cancer diagnoses. Nearly three-quarters of patients were treated with chemotherapy (CTX) or a combination of chemotherapy and external beam radiation (XRT), with or without surgery. Other treatments provided included surgery, alone or in combination with other treatment modalities, in 44%, hormone therapy (HTX) and immunotherapy (Figure 3). Amongst adult patients, 34% achieved a complete response, 10% had a partial response, 8% had stable disease and 29% relapsed or had progressive disease. We were unable to assess disease outcome in 19% of patients. 43% of paediatric patients achieved a complete response to therapy, 12% had a partial response, 3% had stable disease and 16% relapsed or had progressive disease. We were unable to assess disease outcome in 26% of paediatric patients. More than two-thirds of paediatric patients were treated with CTX alone, in keeping with the types of cancer diagnoses (Table 4).

Discussion

Most patients who presented to SKMCH&RC hospitals from Afghanistan were treatment-naïve, but the majority had had some initial work-up, including a biopsy to establish a cancer diagnosis, in their own country. While a small number had had an attempt at

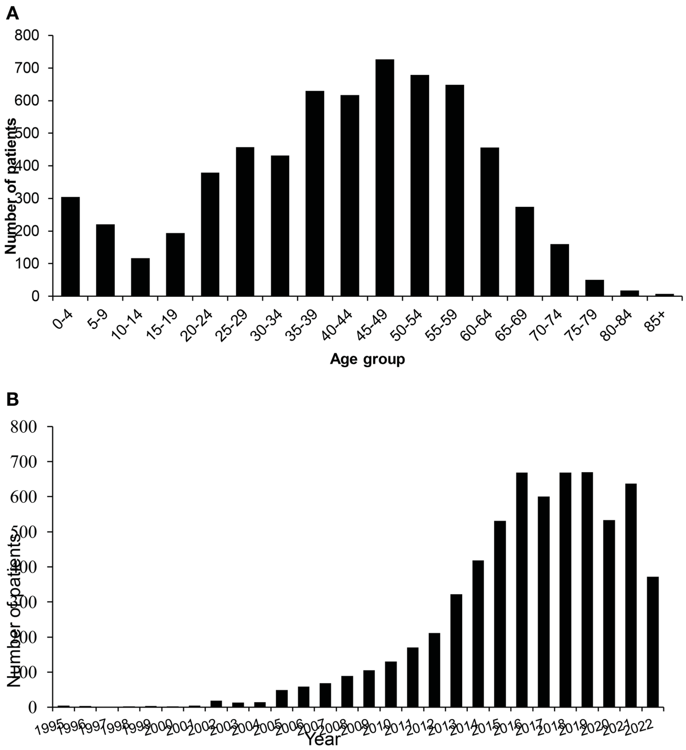

FIGURE 1
Afghan migrants treated at SKMCH&RC (n = 6,370) from 1995 to 30th June 2022. **(A)** Age distribution. **(B)** Frequency of Afghan patients by year.

TABLE 1 Stage distribution among paediatric, adult, and total patients.

	No. (%)		
	Paediatrics (n = 836)	Adult (n = 5,534)	Total (n = 6,370)
Stage 0	0 (0.0)	24 (0.4)	24 (0.4)
Stage I	122 (14.6)	525 (9.5)	647 (10.2)
Stage II	96 (11.5)	1,101 (19.9)	1,197 (18.8)
Stage III	199 (23.8)	2,047 (37.0)	2,246 (35.3)
Stage IV	151 (18.1)	1061 (19.2)	1212 (19.0)
Unknown/Not applicable	268 (32.1)	776 (14.0)	1044 (16.4)

curative surgery, very few had received chemotherapy, and none had radiation therapy, since there are currently no radiation-treatment facilities in Afghanistan.

More than half of the patients we saw from Afghanistan presented with advanced-stage disease. We postulate that there may be many reasons for this, including the taboo associated with cancer, poor health quotient, the lack of local health care facilities, low socioeconomic status, hesitancy to seek care, or because of traveling difficulties involved in seeking care overseas (6, 7). While many patients presented from parts of Afghanistan close to, or contiguous with Pakistan, others travelled up to 2,000 km or for up to 26 hours, in order to seek cancer treatment at our hospitals (3). The poor travel infrastructure, compounded by the perilous security situation, make these journeys extremely arduous (8). Half of all patients were lost to follow-up following initial definitive treatment, undoubtedly due, at least in part, to travel and visa obstacles. All Afghan patients coming to Pakistan do so on a visa. Typically, visas are issued for periods of 2 to 4 weeks at a time, and patients undergoing prolonged cancer treatment need to go back and forth in order to renew their visas. As a result, many miss important appointments for investigations or treatment, and the difficulties involved in this process undoubtedly dampen enthusiasm to return for follow up appointments, once treatment has been completed.

The most common malignancy among adults in the present study cohort were upper gastrointestinal malignancies, including oesophageal and gastric cancers, followed by breast and colorectal cancer. Oesophageal and gastric cancers were the most common cancers among males, and oesophageal and breast tumours had the highest incidence among females. Similar results among Afghans have been reported by others (9, 10). Interestingly, these numbers are comparable to the cancer statistics among Pakistanis and Iranians (10–12). A recent study of Afghan oesophageal cancer patients has suggested that living in a rural area, illiteracy, consuming oral snuff, drinking hot tea, lack of physical exercise, modest consumption of fruit, and positive family history of cancer were significantly associated with the development of oesophageal cancer (13).

Similarly, among the paediatric population, haematological malignancies, including Hodgkin lymphoma, acute lymphoblastic leukaemia, and non-Hodgkin lymphoma, were common. The literature on the incidence of malignancies among the paediatric population in Afghanistan is relatively scarce and ambiguous (10, 13–15). Nonetheless, prior investigations have shown that lymphoma and acute lymphoblastic leukaemia are the most common haematological malignancies seen in the Afghan paediatric population (14, 15).

In the present study, patients received a wide array of oncological therapies in different combinations. The complete response rate was less than 50%, with a lower response rate in adults than in the paediatric population, with all rates being lower than those reported in high-income countries. Though the causal relation of this disparity is beyond the scope of this manuscript, prior studies suggest late presentation and initiation of cancer treatment, barriers to access adequate care, lack of public awareness, limited healthcare facilities, and exposure to common cancer modifiable risk factors as possible reasons for these differences (10, 16).

As previously discussed, many Afghan patients come from provinces that are on the other side of the country, much closer to Iran than to Pakistan. The fact that SKMCH&RC provides free cancer treatment to those who cannot afford to pay, coupled with the fact that it allows unrestricted access to patients from

TABLE 2 Distribution of select outcomes among paediatric, adult, and total patients.

Select outcomes	No. (%)		
	Paediatrics (n = 836)	Adult (n = 5,534)	Total (n = 6,370)
Dead	126 (15.1)	398 (7.2)	524 (8.2)
Discharged	56 (6.7)	227 (4.1)	283 (4.4)
Lost to follow-up	325 (38.9)	3,142 (56.8)	3,467 (54.4)
On follow-up	215 (25.7)	1,244 (22.5)	1,459 (22.9)
On treatment	114 (13.6)	523 (9.5)	637 (10.0)

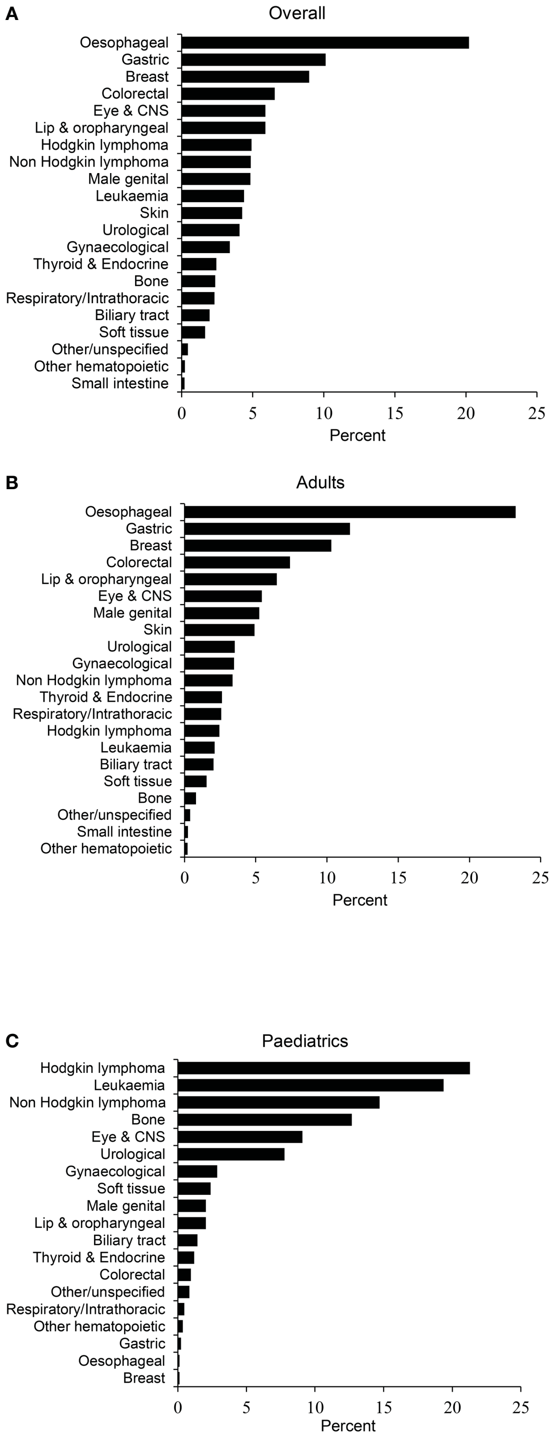

FIGURE 2

Distribution by site. **(A)** Overall, **(B)** Adult, and **(C)** Childhood cancers. ALL, Acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; CNS, Central Nervous System; NHL, non-Hodgkin lymphoma; AML, Acute myeloid leukaemia.

Afghanistan, may explain why patients choose to come to Pakistan. Anecdotally, many patients state that visas for Iran are much harder to obtain than those for Pakistan and, of course, it is very likely that the large number of Afghan patients receiving treatment and attending follow-up appointments at our hospitals have disseminated information about our facilities, and the model on which they operate, within Afghanistan.

We have attempted to highlight here some of the issues faced by patients in Afghanistan in cancer diagnosis and treatment, as well as data related to incidence, tumour types, age at presentation and regional distribution of cancers. Obviously, not all patients suffering from cancer in Afghanistan are able to come to SKMCH&RC for treatment, and there is no accurate estimate of incidence and prevalence of cancer in that country. In this paper, we have tried

TABLE 3 Most frequent primary cancers by gender (n= 6,370).

S. No	Primary Site	Female (n = 2,742)		Male (n = 3,628)		Total (n = 6,370)	
		Cases	%	Cases	%	Cases	%
1	Esophagus	663	24.2%	625	17.2%	1288	20.2%
2	Stomach	148	5.4%	497	13.7%	645	10.1%
3	Breast	566	20.6%	5	0.1%	571	9.0%
4	Colorectal	131	4.8%	287	7.9%	418	6.6%
5	Hodgkin lymphoma	84	3.1%	229	6.3%	313	4.9%
6	Non-Hodgkin lymphoma	92	3.4%	218	6.0%	310	4.9%
7	Leukemia	94	3.4%	185	5.1%	279	4.4%
8	Skin	83	3.0%	190	5.2%	273	4.3%
9	Brain and spinal cord	94	3.4%	172	4.7%	266	4.1%
10	Testis	0	0.0%	182	5.0%	182	2.9%
11	Kidney	71	2.6%	105	2.9%	176	2.8%
12	Lip and oral cavity	66	2.4%	110	3.0%	176	2.8%
13	Bone	48	1.8%	102	2.8%	150	2.4%
14	Nasopharynx	37	1.3%	98	2.7%	135	2.1%
15	Thyroid	88	3.2%	42	1.2%	130	2.0%
16	Prostate	0	0.0%	125	3.4%	125	2.0%
17	Cervix uteri	112	4.1%	0	0.0%	112	1.8%
18	Soft tissues	46	1.7%	59	1.6%	105	1.6%
19	Urinary bladder	20	0.7%	63	1.7%	83	1.3%
20	Gallbladder & extrahepatic bile ducts	32	1.2%	36	1.0%	68	1.1%
21	Ovary and uterine adnexa	61	2.2%	0	0.0%	61	1.0%
22	Trachea, bronchus & lung	18	0.7%	38	1.0%	56	0.9%
23	Eye and adnexa	23	0.8%	31	0.9%	54	0.8%
24	Hypopharynx	20	0.7%	32	0.9%	52	0.8%
25	Larynx	2	0.1%	41	1.1%	43	0.7%
26	Nasal cavity and accessory sinuses	14	0.5%	22	0.6%	36	0.6%
27	Corpus uteri and uterus, NOS	35	1.3%	0	0.0%	35	0.5%
28	Pancreas	14	0.5%	21	0.6%	35	0.5%
29	Liver and intrahepatic bile ducts	10	0.4%	12	0.3%	22	0.3%
30	Other miscellaneous sites	70	2.6%	101	2.8%	171	2.7%

to draw attention to the difficulties such patients face - as well as the opportunities for treatment that are made available to them – when they choose to seek treatment in Pakistan, as a result of the very limited healthcare resources available within their own country. Their journey is difficult and often dangerous because of ongoing conflict. Cancer care is hard enough at the best of times, but cancer care during times of conflict presents a unique set of challenges. Patients often travel with several relatives, adding to the overall cost as well as causing significant disruption to family life, and to livelihoods.

One reason why cancer care in refugee and migrant populations is under-funded may be the simplistic view that all types of cancer have a uniformly poor prognosis and it is perhaps time to start thinking of the costs of cancer treatment as an investment in the future, rather than simply as a drain on resources.

Educational campaigns to raise public awareness about cancer and cancer prevention, including information on when and where to seek help, should be developed to help detect and treat early-stage cancer which would be less expensive to treat and would also have better outcomes.

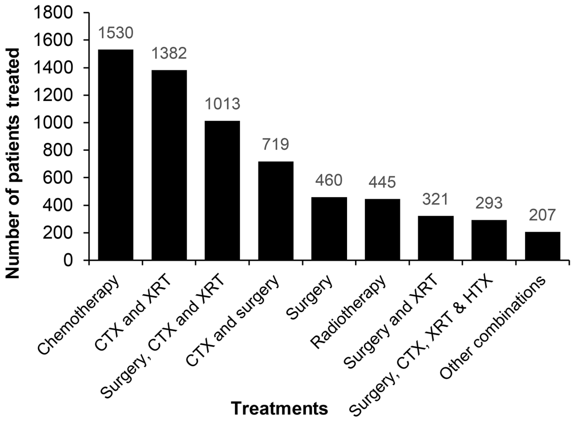

FIGURE 3
Treatment outcomes for adult male and female patients.

TABLE 4 Distribution of treatment responses among paediatric, adult, and total patients.

Select outcomes	No. (%)		
	Paediatrics (n = 836)	Adult (n = 5,534)	Total (n = 6,370)
Complete response	355 (42.5)	1,906 (34.4)	2,261 (35.5)
Partial response	103 (12.3)	541 (9.8)	644 (10.1)
Stable disease	27 (3.2)	423 (7.6)	450 (7.1)
Progression/relapse	136 (16.3)	1593 (28.8)	1,729 (27.1)
Unknown	215 (25.7)	1071 (19.4)	1,286 (20.2)

We feel our data is important in drawing attention to the possible scale of the problem. Such information ought to be helpful for national health policy planners, as well as for international funding agencies, such as the UNHCR. The nascent efforts to establish cancer services in Afghanistan, which we hope to help with, will hopefully form the nucleus around which such services can develop in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon request.

Ethics statement

All studies involving human participants are reviewed and approved by Shaukat Khanum Memorial Cancer Hospital and Research Centre, Institutional Review Board (IRB). The IRB reviewed this study and awarded it exempt-status, meaning that individual patient consents did not need to be sought, since this is a retrospective review and no patient-identifiable data are discussed.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comprehensive analysis of microbiota signature across 32 cancer types

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Microbial communities significantly inhabit the human body. Evidence shows the interaction between the human microbiome and host cells plays a central role in multiple physiological processes and organ microenvironments. However, the majority of related studies focus on gut microbiota or specific tissues/organs, and the component signature of intratumor microbiota across various cancer types remains unclear. Here, we systematically analyzed the correlation between intratumor microbial signature with survival outcomes, genomic features, and immune profiles across 32 cancer types based on the public databases of Bacteria in Cancer (BIC) and The Cancer Genome Atlas (TCGA). Results showed the relative abundance of microbial taxa in tumors compared to normal tissues was observed as particularly noticeable. Survival analysis found that specific candidate microbial taxa were correlated with prognosis across various cancers. Then, a microbial-based scoring system (MS), which was composed of 64 candidate prognostic microbes, was established. Further analyses showed significant differences in survival status, genomic function, and immune profiles among the distinct MS subgroups. Taken together, this study reveals the diversity and complexity of microbiomes in tumors. Classifying cancer into different subtypes based on intratumor microbial signatures might reasonably reflect genomic characteristics, immune features, and survival status.

KEYWORDS

microbiota signature, survival outcomes, genomic features, immune profiles, bacteria in cancer, the Cancer Genome Atlas

Introduction

Various and complex microorganisms inhabit the human body, composing what is called the human microbiota (1, 2). Evidence shows the interaction between the human microbiome and host cells plays a central role in multiple physiological processes and organ microenvironments (3, 4). For instance, the gut microbiota regulates host metabolism and the immune system through putative-specific microbes, metabolites, and toxins (5–7). Certain bacterial components of the human microbiota can drive tumorigenesis and development in various cancers. Numerous evidence found that the bacterium Helicobacter pylori contributes to atrophic gastritis, peptic ulcers, gastric cancers *via* Wnt/b-catenin pathway, and chronic inflammatory response (8–10). Fusobacterium nucleatum has been found highly abundant in colorectal cancer (CRC) tumors and metastasis tissues than in matched normal tissues, which was associated with poorer prognosis for CRC patients (11–13).

Microbial dysbiosis contributes to tumor susceptibility through complex mechanisms, including inducing tumorigenesis and progression through inflammation, remodeling immune and stromal cells in the tumor microenvironment, and interfering with anticancer drug pharmacodynamics (14–17). An analysis of 16 rRNAs found in stool discovered that the structure and function of gut microbiota in patients with lung cancer were unbalanced, and the imbalance between firmicutes and Bacteroides contributed to tumorigenesis and progression of lung cancer (18, 19). Moreover, the diversity of gut microbiome has been found to positively correlate with the efficacy of immunotherapy in various cancer types (20, 21). Fusobacterium nucleatum is an oral anaerobe that has been found to be prevalent in colorectal cancer and breast cancer, which promoted tumor growth and metastatic progression by attaching tumor-displayed Gal-GalNAc *via* Fap2 (13, 22, 23).

Although the majority of related studies focus on gut microbiota (24–26), several studies have recently characterized the existence, metabolic activity, and functional importance of intra-tumoral microbiota in various cancers (23, 27–30). Exploring the alteration in the microbial community derived from human tissues and organs will help us better understand the occurrence, progression, and therapeutic approaches for tumors. Bacteria in Cancer (BIC, http://bic.jhlab.tw/) reveals a collection of curated, decontaminated tissue-resident microbiota of 32 cancer types based on samples from the TCGA program (31). The microbial signatures of tumor and normal samples from 32 cancer types can be estimated from BIC at different taxonomic levels, which provides an excellent and powerful resource for studying the abundance and alternation of microbial components in various cancers.

The objective of the current study was to investigate the microbiota profile across 32 cancer types. First, we identified the relative abundance of microbiota in tumor tissues compared to normal tissues at various taxonomic levels. Next, we estimated the prognostic value of various microbial compositions. Then, three microbiome-based clusters were determined by NMF clustering analysis based on candidate prognostic microbiota. A microbial-based scoring system (MS) was established by applying the least absolute shrinkage and selection operator (LASSO) regression algorithm, a machine learning-based approach that selected features that were predictive of survival outcomes. Furthermore, the correlation between MS and patients' survival outcomes, genomic features, and immune profiles was further investigated by combining the BIC microbial profile with the genomic and clinical data from the TCGA cohort.

Materials and methods

Data acquisition from BIC and TCGA

In this study, the microbiota profiles of samples from 10,362 cases (including 9,687 tumor tissues and 675 adjacent normal tissues across 32 cancer types) at the phylum, class, order, family, and genus levels were obtained from the BIC database (http://bic.jhlab.tw/); the corresponding genomic and clinical data for patients were obtained from the TCGA dataset (https://portal.gdc.cancer.gov/repository). Figure 1 displays an overview of the study design, and the information on included tumor types is summarized in Table S1.

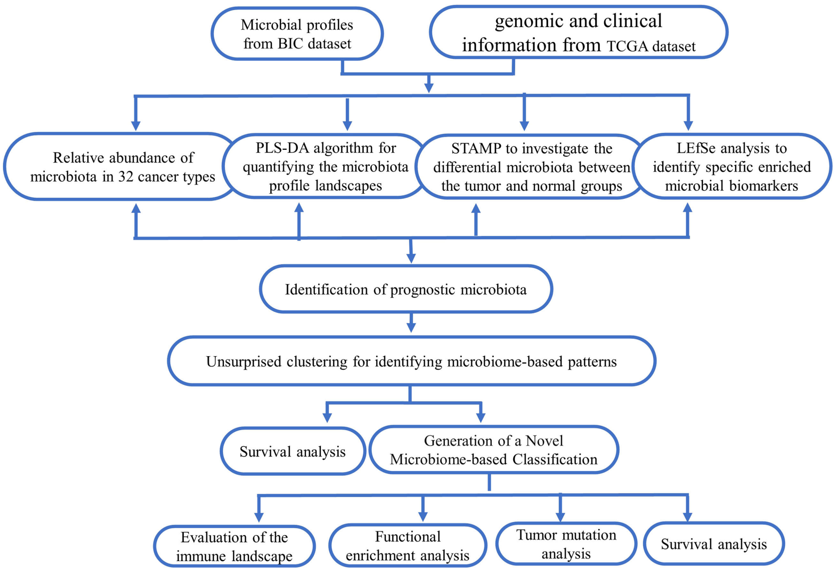

FIGURE 1
Schematic overview of the study design and workflow.

Microbiota abundance analysis of tumor and normal tissues

First, we calculated the relative abundance of microbiota between the tumor and normal groups at the phylum, class, order, family, and genus taxonomic levels. Then, we applied Partial least squares discrimination analysis (PLS-DA) to visualize the microbiota profile landscapes between tumor and normal samples by using the package "mixOmics". Next, we performed a statistical analysis of metagenomic profiles (STAMP) to investigate the overall differences in microbiota profiles between the tumor and normal groups. Moreover, Linear discriminant analysis effect size (LEfSe) analysis was used to identify specific enriched microbial biomarkers for each group. Linear discriminant analysis (LDA) was further applied to evaluate the microbial effects for different groups.

Analysis of global microbiota profiles among 31 cancer types

We first identified the cross-tumor abundant microbiota taxa at the phylum, class, order, family, and genus levels, respectively. Then, we calculated the relative abundance of microbiota across 31 tumor types (except for GBM, which only had normal tissues in the BIC program) at the phylum, class, order, family, and genus taxonomic levels.

Non-negative matrix factorization clustering analysis

Patients with survival data and follow time ≥ 30 days were chosen for survival analyses. First, we investigated the prognostic significance of microbiota by performing a univariate Cox proportional hazards model. Then, NMF was applied to identify distinct microbiome-based clusters based on the abundance of candidate prognostic microbes. The optimal number of clusters and their stability were determined by the consensus clustering algorithm. The R package "NMF" was used to perform the consensus clustering (32).

Generation of a novel microbiome-based classification

To quantify the microbiome features of individual patients, we explored a novel microbial-based scoring system (MS) to investigate the microbiota features of the individual patients. Specifically, candidate prognostic microbiomes were chosen from the Lasso regression algorithm to construct the microbial scoring system. The MS was calculated by the corresponding coefficients of selected microbiota signatures:

$MS = \Sigma i$ Coefficient (microbiota)* Abundance (microbiota)

Where i represents the selected microbial signatures.

Gene set variation analysis and gene set enrichment analysis

GSVA enrichment analysis was performed to investigate the variation in biological processes between different MS subgroups by using "GSVA" R packages (33). The gene sets of "c2.all.v2022.1.Hs.symbols" and "h.all.v2022.1.Hs.symbols" were downloaded from the MSigDB database. Adjusted P value <0.05 was considered statistically significant. GSEA was used to explore the signaling enrichment between different MS subgroups by applying the "Clusterprofile" R package (34). The FDR $q < 0.25$ and $P < 0.05$ were considered statistically significant.

Estimation of TME cell infiltration

The ssGSEA algorithm was used to quantify the relative abundance of 29 immune cell types in the TME (35, 36). The relative abundance of each immune cell type in each sample was represented by the enrichment scores that were calculated by the ssGSEA analysis. The CIBERSORT algorithm was applied to analyze the compositions of 22 types of tumor-infiltrating immune cells among different MS subgroups (37).

Significantly mutated genes and tumor mutation burden in different MS subgroups

Using the R package maftools (38), the overall mutation landscape was summarized in patients with high and low MS subgroups in the TCGA cohort. Then, TMB scores based on the TGCA somatic mutation data were calculated to evaluate the mutation status between different MS subgroups.

Statistical analysis

Student's t-tests were applied to analyze normally distributed variables and the Wilcoxon rank-sum test was performed to evaluate non-normally distributed variables. One-way ANOVA and Kruskal-Wallis tests were used to conduct difference comparisons of more than two groups. Kaplan-Meier survival analysis and Cox proportional hazards model were chosen to investigate the prognostic significance of microbiota and microbiota-based subtypes by applying the survival and survminer packages. All statistical P values were two sided, with $p < 0.05$ being statistically significant. All data processing was done in R 4.0.5 software.

Results

Differential microbiota signatures in tumor and normal tissues

Overall, we collected and integrated the microbiota profile and clinical characteristics of 10,362 samples from 32 cancer types. A total of 47, 56, 127, 303, and 1,607 microbial taxa were obtained for each sample at the phylum, class, order, family, and genus levels, respectively. First, the average relative abundance of differential microbiota between tumor and normal tissues was calculated (Figures 2A–E), which shows the phylum, class, order, family, and genus levels, respectively. Then, the PLS-DA plot exhibited the microbiota profile landscapes between the tumor and normal samples (Figure 2F). We next explored the differential microbial compositions for each group. Overall, 8, 10, 17, 25, and 66 differential microbial components were found between tumor and normal tissues at the phylum, class, order, family, and genus levels, respectively (Figures 2G).

At the phylum level, Chordata, Firmicutes, Fusobacteria, Bacteroidetes, and Planctomycetes were the main bacteria groups in tumor samples, while Proteobacteria and Actinobacteria were the main groups in normal tissues. At the class level, the microbial composition of Actinobacteria, Alphaproteobacteria, and Betaproteobacteria were significantly abundant in normal tissues, whereas Fusobacteriia, Clostridia, Bacilli, and Bacteroidia were increased in tumor samples. Other differential microbial composition signatures between tumor and normal tissues are shown in Figure 2G and Table S2. The top 30 differential microbial taxa between tumor and normal tissues are shown in Figure 2H.

LEfSe analysis helps to identify tumor- and normal-enriched microbiota

The LDA score of specific microbial taxa in the tumor and normal groups showed the compositional abundances of p_Bacteroidetes, c_Bacteroidetes, o_Nostocalles, f_Prevotellaceae, and g_Ruminococcuss were higher in tumor tissues, while the compositional abundances of p_Actinobacteria, c_Actinobacteria, o_Actinomycetales, f_Moraxellaceae, and g_Acinetobacter were enriched in normal tissues (Figure 3A and Table S3). Cladogram further showed the distinct tumor- and normal-enriched microbiota (Figure 3B). Next, we analyzed the cross-tissue abundant microbiome in 32 cancer types at the phylum, class, order, family, and genus levels, respectively. The average relative abundance of microbiota among 31 cancer types (except for GBM, which only had normal tissues in the BIC program) was further explored, which shown in Figures 3C–G. Moreover, the top 10 most differential microbial taxa across 31 cancer types were shown in Figures 3H–L at the phylum, class, order, family, and genus levels, respectively.

Exploring prognostic microbiota and different clusters mediated by microbiota

We first investigated specific candidate microbial taxa that correlated with survival outcomes by integrating the microbial

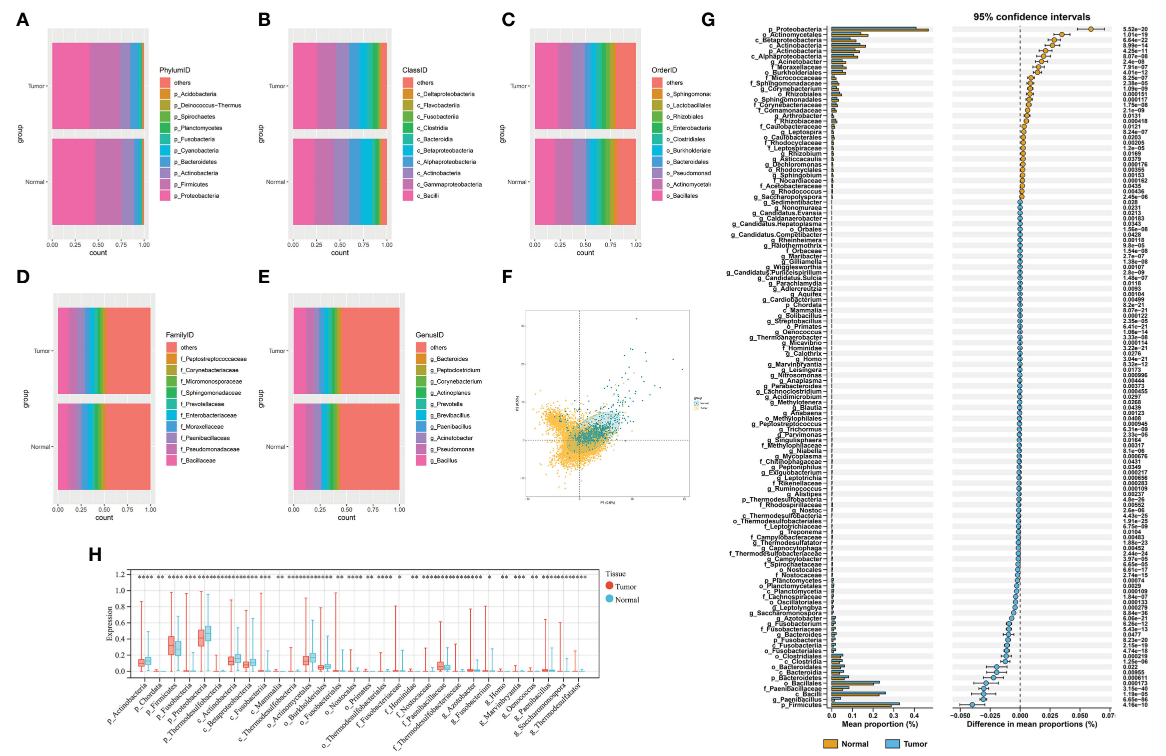

FIGURE 2
(A–E) The differential composition of microbiota in tumor and paired normal tissues at the phylum, class, order, family, and genus levels, respectively. **(F)** PLS-DA plot of microbe signature in tumors and adjacent normal tissues. **(G)** STAMP plot of the differential microbiota composition signatures between tumors and adjacent normal tissues. **(H)** The top 30 differential microbial taxa in tumor and paired normal tissues. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$.

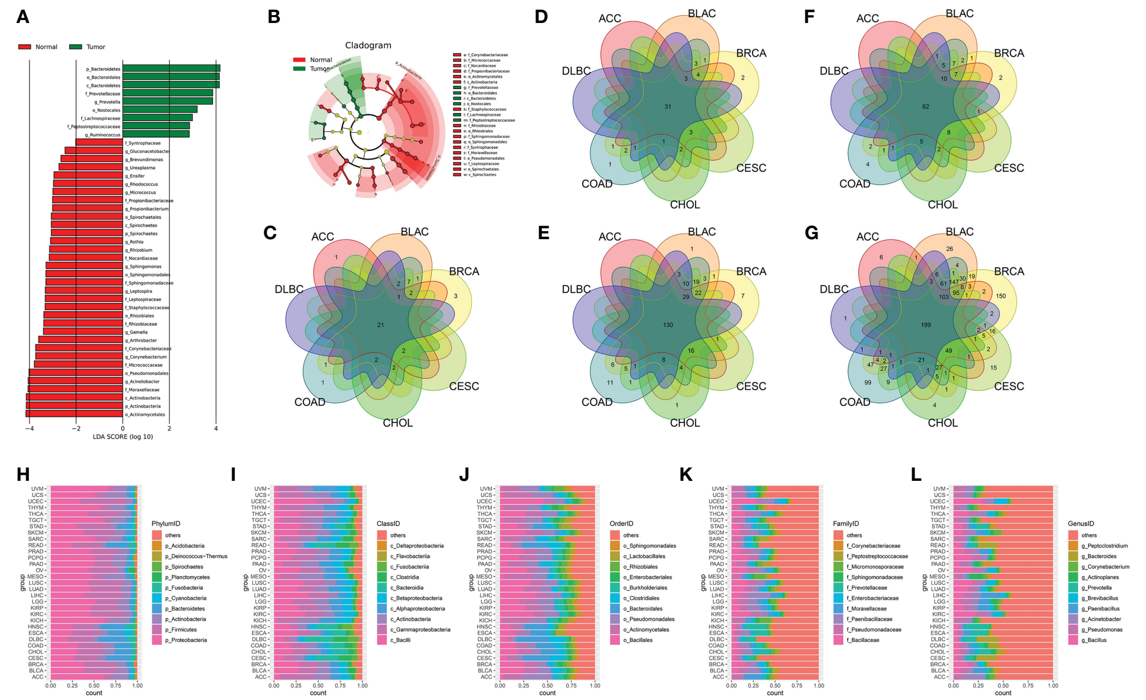

FIGURE 3
(A) The LDA score of specific microbial taxa in the tumor and normal group. **(B)** Cladogram showing tumor- and normal-enriched microbial taxa. **(C–G)** Venn diagram of the cross-tumor abundant microbiota taxa at the phylum, class, order, family, and genus levels, respectively. **(H–L)** The top 10 most differential microbial taxa across 31 cancer types at the phylum, class, order, family, and genus levels, respectively.

abundance profile from BIC and survival information from TCGA. The results showed that a total of 182 microbiota were significantly associated with overall survival (OS) (Table S4) and 112 microbiomes were significantly associated with disease-specific survival (DSS) (Table S7). Then, Consensus Clustering analysis of the NMF algorithm was applied to classify patients with qualitatively different clusters based on the abundance of 182 prognostic microbiota (Figure 4A). Three distinct microbiome-based clusters were eventually identified, including 4,592 cases in cluster 1, 1,223 cases in cluster 2, and 3,460 cases in cluster 3. A tSNE plot further showed the performance of microbiome-based clusters to distinguish tumor samples in the TCGA cohort (Figure 4B). A Kaplan-Meier plot revealed a particularly prominent survival advantage in cluster 2, whereas the worst prognosis was found in cluster 3 (Figures 4C, D). The proportion of distinct clusters in 31 tumor types are shown in Figure 4J.

Construction of microbial signature and microbiome-based scoring system

The Lasso regression algorithm based on the 182 prognostic microbiota was performed to find candidate microbial signatures (Figures 4E–G). A total of 64 selected microbial taxa were identified from the Lasso regression algorithm (Table S5). Then, a novel microbiome-based scoring system was constructed to quantify the microbial profiles of individual patients, which we termed as microbial score (MS). Consistent with the NMF clustering analysis, two distinct MS subgroups were found and we named these two subgroups MS-low and -high. Further survival analysis indicated significant prognostic differences between the low- and high-MS subgroups (Figures 4H, I). The performance of 64 selected microbial signatures to classify different MS groups was further analyzed by using PLS-LA (Figure 4K). To better illustrate the association between the established MS with prognosis, an alluvial diagram was applied to visualize the attribute changes of individual patients (Figure 5A). LEfSe analysis was further performed to identify specific enriched microbial biomarkers for high- and low-MS groups (Figures 5B, C, and Table S6).

TME cell infiltration characteristics in distinct MS subgroups

The CIBERSORT algorithm was used to show the differences in the compositions of tumor microenvironment (TME) immune cell types between distinct MS subgroups. As shown in Figure 5D, remarkable differences in immune cell infiltration were observed between the high and low-MS groups, which suggested that intratumor microbiota plays an inevitable role in tumor microenvironment immune profiles. Furthermore, the GSVA algorithm showed significant differences in KEGG pathways, cancer hallmarks, and immune profiles among the distinct MS subgroups (Figures 5E–G). The GSEA algorithm showed nucleotide excision repair, cell cycle, DNA replication, homologous

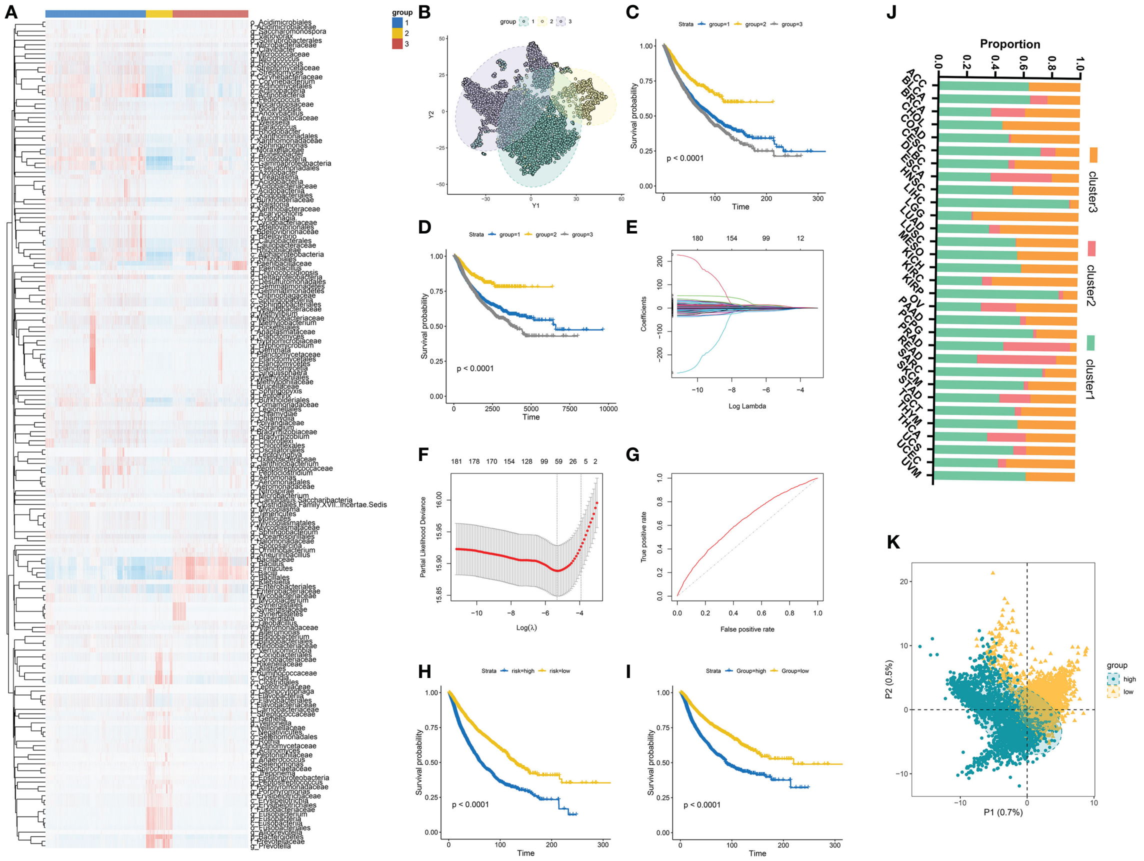

FIGURE 4
(A) Three distinct clusters were established based on the abundance of prognostic microbial taxa. **(B)** tSNE plot showed the performance of microbiome-based clusters to distinguish tumor samples. **(C, D)** Kaplan-Meier plots of OS and DFS among different clusters in the TCGA cohort. **(E, F)** 64 prognostic microbial taxa were further selected by the Lasso regression algorithm. **(G)** Receiver-operating characteristic curves of the microbial signature predicted performance to predict OS. **(H, I)** Survival analyses for OS **(D)** and DFS **(E)** among different MS groups in the TCGA cohort. **(J)** The distribution of different clusters across 31 cancer types in the TCGA cohort. **(K)** PLS-DA plot of microbial signature in high and low-MS groups.

recombination, cytosolic DNA sensing pathway, pyrimidine metabolism, proteasome, spliceosome, and P53 signaling pathway were significantly enriched in the MS-high subgroup (Figures 6A–I).

Landscape of genomic variation and expression of different MS subgroups

We further analyzed the distribution differences of somatic mutation and TMB between low- and high-MS subgroups in the TCGA cohort. The top 20 genes of mutation frequency of the low- and high-MS subtypes are shown in Figure 7A, B, respectively. The top differential mutated genes between the low- and high-MS subtypes are shown Figure 7C. Moreover, a remarkable diversity of tumor mutation burden (TMB) was found between the distinct subgroups (Figure 7D). The abovementioned results indicated the potentially complex interaction between genomic variation and microbial components in cancers, which might be novel regulators for tumorigenesis and progression.

Discussion

Increasing evidence suggests microbiome plays an important role in carcinogenesis and progression of various cancer types (24, 39, 40). However, the pan-cancer microbial heterogeneity and their functions are least understood. Here, we conducted a comprehensive analysis of the intratumor microbiota across 32 cancer types, which could provide a better understanding of microbiota dysbiosis and establish a new foundation for studying host-microbiota interactions in tumorigenesis and malignancy in cancer.

We first characterized the global microbial composition at the phylum, class, order, family, and genus levels of tumor and adjacent normal tissues across 32 cancer types. Consistent with previous studies, the relative abundance of Firmicutes and Fusobacteria significantly enriched tumor tissues, whereas that of Proteobacteria, Actinobacteria, Alphaproteobacteria, and Betaproteobacteria were remarkably predominant in adjacent normal tissues (41–47). The LEfSe analysis further supported that microbial taxa, including p_Firmicutes/c_Clostridia, p_Bacteroidetes/c_Bacteroidetes, and p_Fusobacteria/

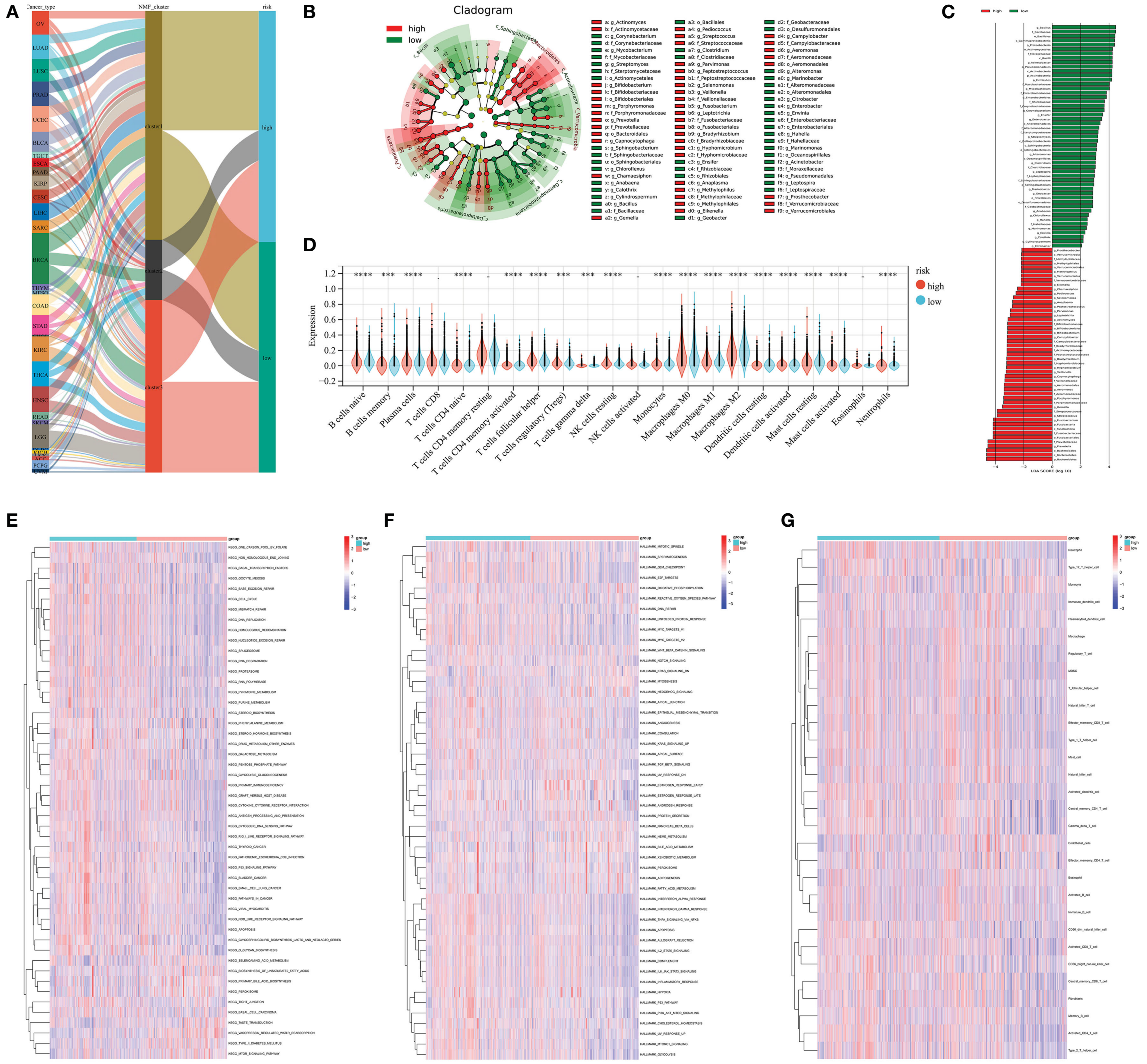

FIGURE 5
(A) Alluvial diagram showing the changes in cancer types, clusters, and MS subtypes. **(B, C)** LEfSe analysis identifying differential microbiota profiles between low- and high-MS groups. **(D)** Cibersort reveals the abundance of each TME infiltrating cell between the low- and high-MS groups. **(E)** Differences in KEGG pathways **(E)** and cancer hallmarks **(F)** between the low- and high FS groups. **(G)** Associations between microbial signature and the ssGSEA scores of tumor microenvironment cell infiltration. *** P < 0.001 and **** P < 0.0001.

c_Fusobacteria/o_Fusobacteriales, were tumor-enriched microbes, while p_Actinobacteria/c_Actinobacteria, p_Spirochaetes/c_Spirochaetes, and p_Proteobacteria/c_Alphaproteobacteria were normal-enriched microbes, suggesting that distinct microbial component in tumor and normal samples, and specific microbes might play an essential role in tumorigenesis and development of cancer.

Previous studies reported that certain intratumor microbiota of human tumors could also be a potential biomarker for survival outcomes and chemotherapy/immunotherapy (4, 23, 30, 46, 48, 49). Here, we identified specific microbial components that were associated with prognosis in patients from the TCGA cohort. Consistent with other studies, the relative abundance of Actinobacteria, Firmicutes, Fusobacteria, and Proteobacteria were found to be associated with prognosis in cancer. We further established a scoring system (MS) based on candidate microbial signatures that was somehow predictive of survival outcomes, molecular alternation, and immune profiles.

GSVA showed differential genomic function between the high- and low-MS groups. The high-MS group was remarkedly enriched in cell cycle and mismatch repair signaling pathways, while selenoamino acid metabolism and primary bile acid biosynthesis signaling pathways were found significantly enriched in the low-MS group. It is well established that cell cycle and mismatch repair are involved in cancer cell proliferation, sphere-forming capacity, metastasis, and chemotherapeutic/immunotherapeutic sensitiveness (50–54). The interaction between bile acid and microbiota was found to play an essential role in gastrointestinal inflammation and carcinogenesis (55). Considering that, specific microbiomes and their relative biological functions may be involved in the development and malignancy of tumors.

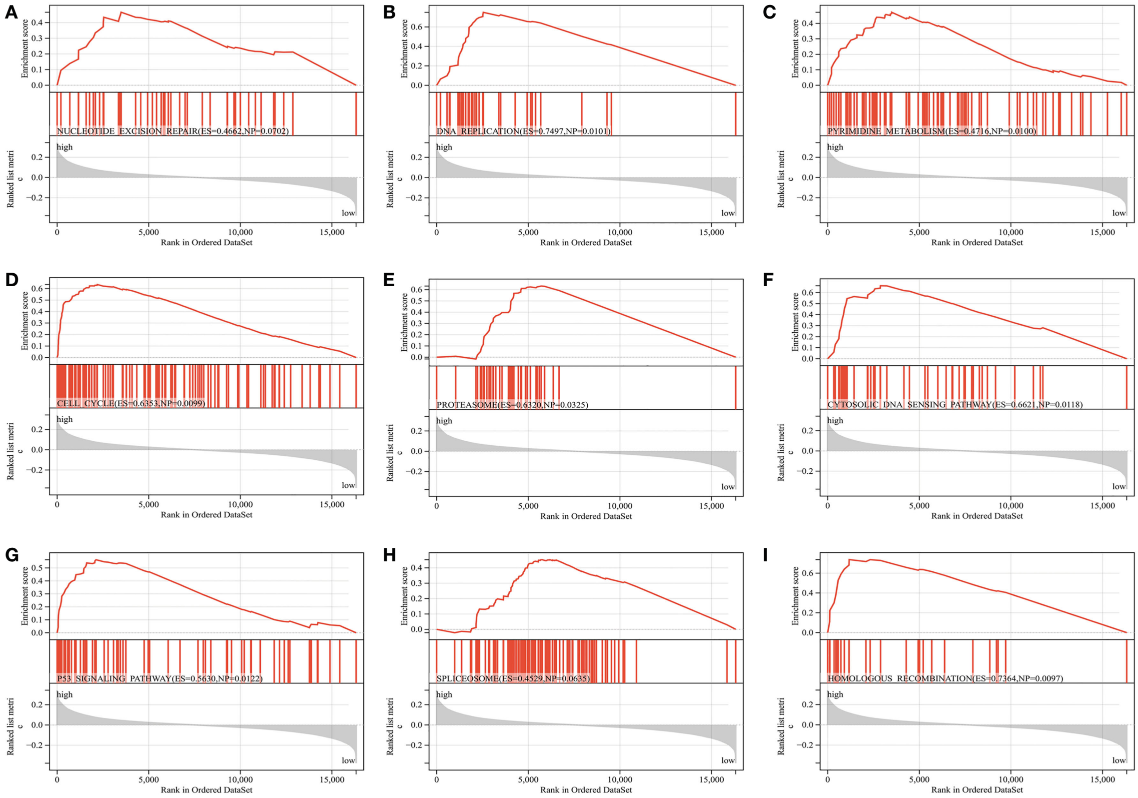

FIGURE 6
GSEA reveals the key differential signaling pathway between the MS-low and MS-zero subgroups **(A–I)**.

It has been well known that microbiota mediates the host immune system by a complicit mechanism (56, 57). In accordance with previous studies, we demonstrated that microbiota displayed an important role in tumor immune profiles. Furthermore, our study showed that the TMB encounters significant changes between the distinct MS groups. Furthermore, significant gene mutation diversity was observed between the high- and low-MS groups, which indicated the intratumor microbial component might also exert an effect on the immune profile and genomic heterogeneity of tumors.

Compared with recent studies on microbiota alternation in tumors, our research performed a more comprehensive investigation of microbial characteristics in 32 cancer types. However, several limitations need to be clarified in this study. First, the study was analyzed based on the TCGA dataset, so external verification should be

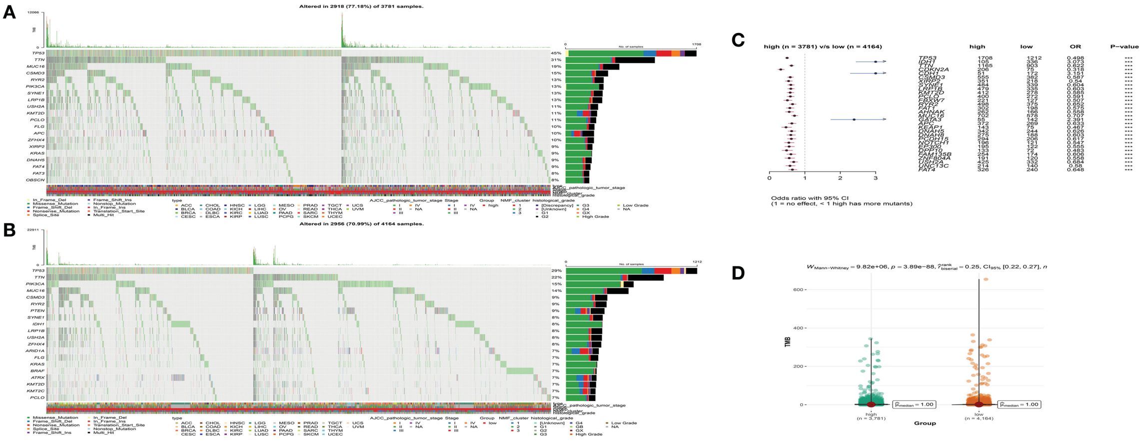

FIGURE 7
The waterfall plot of tumor somatic mutation of the low- **(A)** and high-MS subgroups **(B)**. **(C)** The differential somatic mutation profile between the low- and high-MS subgroups. **(D)** The TMB status between the low- and high-MS subgroups.

performed based on clinical samples to eliminate the false correlation drawing from bioinformatics data in the future. Second, the current study is more of a observational research paper that focuses on the pan-cancer level. The alteration in the microbial community in specific cancer subtypes should be further investigated. Besides, the biological functions and underlying mechanisms of selected microbiota in this study are warranted for further experimental validation.

Conclusion

In this study, we conducted a comprehensive analysis of the intratumor microbiota in 32 cancer types. Significant differences in the microbial components were found between the tumor and adjacent normal tissues. Several candidate microbial biomarkers were further identified and correlated with tumor prognosis. The potential functions of these microbes in tumors merit further study. Furthermore, we established a microbial-based scoring system, which was significantly related to genomic characteristics, immune features, and survival status of patients in the TCGA cohort. We expect that our research will facilitate a better understanding of the intratumor microbiome and provide a new perspective on the role of the microbiome in tumors.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The study was approved by the Ethics Institutional Review Board of Sir Run Run Shaw hospital Hospital of Zhejiang University, School of Medicine.

Author contributions

XY designed, performed the study, and wrote the manuscript. GF, YH, and HA contributed to data and statistical analysis. XY and ZJ supervised the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1127225/full#supplementary-material

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Concerns and priority outcomes for children with advanced cancer and their families in the Middle East: A cross-national qualitative study

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Introduction: Palliative care access is limited in the Middle-East, with few specialist centers and forcibly displaced migrants facing additional struggles to access care. Little is known about the specificities of providing palliative care to children and young people (CYP) with cancer. They are rarely asked directly their concerns and needs, which limits the provision of quality patient-centered care. Our study aims to identify the concerns and needs of CYP with advanced cancer and their families, in Jordan and Turkey.

Method: A qualitative cross-national study in Jordan and Turkey with framework analysis was conducted two pediatric cancer centers in Jordan and Turkey. In each country, 25 CYP, 15 caregivers and 12 healthcare professionals participated (N=104). Most caregivers (70%) and healthcare professionals (75%) were women.

Results: We identified five areas of concern: (1) Physical pain and other symptoms (e.g. mobility, fatigue); (2) Psychological concerns and needs (e.g. anger, psychological changes); (3) Spirituality, uncertainty over the future and use of "Tawakkul" (e.g. use of religion as a coping mechanism); (4) Negative impact on social life (e.g. social isolation, loss of support); (5) Burden on caregiver and their families (e.g. financial issues, siblings left behind). Psychological concerns were a priority for both CYPs and caregivers (particularly for refugee and displaced families) but often overlooked during routine care. CYP were able to share their own concerns and care priorities.

Conclusions: Advanced cancer care must ensure assessment and management of concerns across the concerns identified. Developing child- and family-centered outcomes would ensure monitoring the quality of care. Spirituality had a more important role compared to similar investigation in other regions.

KEYWORDS

palliative care, children, cancer, Middle East, Jordan, Turkey, conflict, pediatrics

1 Introduction

The majority of children with palliative care needs (97%) live in low- and middle-income countries (LMIC) (1, 2). Cancer is the most common cause of serious health-related suffering at the end of life (3), and the Middle-East is predicted to have the highest increase of such suffering by 2060. Palliative care is an essential Universal Health Coverage service but relatively new in the region, with no countries reporting fully integrated palliative care within its health system (4, 5).

Data on symptoms and concerns of children and young people (CYP) with advanced illness are scarce. Methodological and ethical challenges of conducting primary research with this potentially vulnerable group have led to a lack of outcomes-focused research (6). A systematic review found that self-report primary data from CYP with advanced illness was rare (6, 7), and a subsequent study in Africa found it was feasible to conduct primary data collection with this population (7).

Little is known about the cultural specificities of pediatric palliative care in the Middle-East region. Further, the region has large-scale migration flux and hosts many refugees with advanced cancer facing additional challenges of compounded trauma and fragmented social support systems (8–10). A systematic review found that patients at the end of life and their families in Muslim-majority countries feel "selflessness" in their duties to family and caregivers, ambivalence towards being hopeful and hopeless, and strongly believe in an afterlife (11).

The lack of primary data collected with CYP in the Middle East is a key reason for the limited development of pediatric palliative care in the region (5). In 2018, Jordan had 11 million inhabitants, of whom 45% are aged under 18 (12), and Turkey had 82.3 million inhabitants and 28% of the population is under 18 (13).

It is crucial that evidence from adults is not used to drive quality care for children (7). The COVID epidemic has highlighted the pre-existing lack of investment in palliative care capacity, and challenges in ensuring culturally-appropriate decisions around treatment withdrawal (14).

Our study aimed to identify the palliative care symptoms and concerns of CYP with advanced cancer, and their families, in Jordan and Turkey.

2 Methods

2.1 Study design

This qualitative cross-sectional study adhered to COREQ reporting guidelines. It was framed within pragmatic epistemology to inform clinical practice (15). The local research teams SY, MS, GA, WA, SA (psychologist involved in care provision (n=1), researcher (n=1), and researchers and palliative care nurses not connected to the interviewees (n=3); male (n=1) and female (n=4) conducted in-depth semi-structured interviews.

2.2 Setting

The sites (one in each of Turkey and Jordan) provide multidisciplinary paediatric palliative care within relatively large and diverse populations including refugees and displaced people (16).

2.3 Sampling and recruitment

2.3.1 Inclusion and exclusion criteria

We sampled three stakeholder populations. First, CYP aged 5 to 17 living with advanced cancer (stage III or IV), and seen by the palliative care team for at least one consultation at either study site. Second, an adult parent or caregiver (17) responsible for the care needs of a child below 18 who met the inclusion criteria above. Third, palliative care staff (medicine, nursing, social work, psychology or allied health professional) who had been providing paediatric palliative care for at least 6 months.

The following exclusion criteria were used:

- CYP unable to communicate their views or wishes via self-report during an in-depth interview or with the support of their caregiver, or via "draw & talk" and play methods; those speaking a language not supported by the study sites (Arabic, Turkish and English); currently enrolled in another study; deemed unable to give assent by their treating clinician.
- Caregivers deemed clinically unable to give consent by their child's treating clinician.

- Staff with less than 6 months experience of clinical paediatric palliative care.

2.3.2 Sampling

The estimated sample size per study site to achieve maximum variation and reach data saturation was: CYP n=25; parents or caregivers (hereafter referred to as "caregivers") n=15; palliative care staff n=12. We purposively sampled on the following CYP characteristics: primary malignancy, gender, age and communication difficulty, and country of birth. For the caregivers, we purposively sampled by age, gender and relationship to patient, and country of birth, and for the HCP by age, gender, years of experience and profession.

2.3.3 Recruitment

Clinicians identified eligible participants during weekly multidisciplinary team meetings, then discussed the study with the family at their subsequent clinical appointment. Those who expressed an interest were directed to the research team who shared the child age-specific and the caregiver information sheets, and addressed any further questions. In Jordan, all the eligible participants approached by the research team accepted to participate. In Turkey, 103 patients were identified eligible, and 53 agreed to participate.

2.4 Data collection

Interviews were conducted face-to-face at a quiet convenient place (e.g. empty clinic, meeting room) and audio recorded by researchers (SY, GA, WA, SA and MS), from 21 March 2019 to 08 January 2020 in Turkey and 23 April 2019 to 29 July 2020 in Jordan. Study-specific training sessions were delivered with ongoing support (PG and RH, e.g. qualitative research methods, interview skills with children). Due to introduction of COVID-19 restrictions, five interviews in Jordan were conducted by telephone.

Topic guides were developed for each stakeholder group, and for each child age grouping using appropriate language. Standard verbal probing, "draw and write" and the use of toys to express feelings were used. For children with communication difficulties, caregivers supported the child to express themselves. Children aged 16-17 with sufficient capacity could choose to be interviewed alone.

2.5 Data management and analysis

Audio recordings were transcribed verbatim, translated into English, reviewed by the researchers for quality check then imported into NVivo 12 Pro for analysis.

Collaborative analysis was conducted across the partner sites (UK, Jordan and Turkey) using framework analysis. (18) Five researchers (SB, SY, GA, FA and WA), including the three main interviewers, with different expertise (palliative care nursing, psychology, global public health, epidemiology) collaborated to optimise data analysis and interpretation. Firstly, they each familiarised themselves with the data and developed preliminary codes using three to five interviews randomly selected (at least one per stakeholder group). The lead analyst (SB) integrated the preliminary codes and identified similar emergent themes, and presented a preliminary joint framework to the cross-national analysis team. Regular online meetings were conducted to discuss and refine the framework, which was subsequently applied by the whole analysis team to five further transcripts each adding any new emergent codes. Ongoing team discussions refined the framework. The framework was then agreed and presented to the senior team (TK, OS, RH) for review and refinement, before being applied to the remaining dataset. The key themes were charted into a single framework matrix, with cross-national discussions to interpret findings.

2.6 Ethics

Informed assent was obtained from all child participants, with informed parental consent. Caregivers and healthcare professionals (HCP) gave informed consent. Ethical approval was obtained from King's College London (ref: HR-18/19-8838); Hacettepe University (ref: 16969557-25 or GO 19/40) and KHCC (proposal No. 18 KHCC 162).

3 Results

3.1 Participants

We recruited 105 participants (52 in Jordan, 53 in Turkey). One interview could not be completed due to the interviewed patient's distress. Therefore, a total of 104 interviews were analyzed. Tables 1, 2 report the sample's characteristics (N=104). The

TABLE 1 Participants' age (N=104).

	Overall (N=104)			Jordan (N=52)			Turkey (N=52)		
	median	IQR	N	median	*IQR*	N	median	*IQR*	N
CYP	13	9-16	50	15.4	10-17	25	11.5	9-14	25
Caregiver	35	29-36	30	35	26-41	15	36	32-38	15
HCP	32	31-39	24	32	27-35	12	32	31-41	12

CYP, Children and Young People; HCP, Healthcare Professional.

TABLE 2 Participants' characteristics (N=104).

	CYP (N=50)		Caregiver (N=30)		HCP (N=24)	
	n	%	n	%	n	%
Gender:						
Female	27	*54*	21	*70*	18	*75*
Male	23	*46*	9	*30*	6	*25*
Country of birth:						
Azerbaijan	1	*2*	1	*3*	–	-
Jordan	21	*42*	10	*33*	–	-
Libya	1	*2*	2	*7*	–	-
Palestine	1	*2*	2	*7*	–	-
Syria	2	*4*	1	*3*	–	-
Turkey	24	*48*	14	*47*	–	-
Child's diagnosis classification*						
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	6	*12*	5	*17*	–	-
II. Lymphomas and reticuloendothelial neoplasms	13	*26*	5	*17*	–	-
III. CNS and miscellaneous intracranial and intraspinal neoplasms	2	*4*	4	*13*	–	-
IV. Neuroblastoma and other peripheral nervous cell tumors	–	-	10	*33*	–	-
IX. Soft tissue and other extraosseous sarcomas	5	*10*	1	*3*	–	-
VI. Renal tumors	2	*4*	2	*7*	–	-
VII. Hepatic tumors	–	-	1	*3*	–	-
VIII. Malignant bone tumors	19	*38*	2	*7*	–	-
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	2	*4*	–	-	–	-
XI. Other malignant epithelial neoplasms and malignant melanomas	1	*2*	–	-	–	-
Relationship to child:						
Mother	–	-	20	*67*	–	-
Father	–	-	9	*30*	–	-
Grandmother	–	-	1	*3*	–	-
Healthcare profession:						
Medical (nurse, oncologist)	–	-	–	-	16	*67*
Non-medical**	–	-	–	-	8	*33*

*Classification using the International Classification of Childhood Cancer (ICCC) 3rd edition. Main Classification Table from the ICCC-3 based on ICD-O-3. Available at: https://seer.cancer.gov/iccc/iccc3.html.
**Non-medical professions include: for Jordan: Child Life specialist (n=3); Psychosocial Consultant (n=1); Social Worker (n=1); for Turkey: Nutritionist (n=2); Ergotherapist (n=1).
CYP, Children and Young People; HCP, Healthcare Professional.

median age of the 50 CYPs was 13 (IQR: 9.0-16.0). Caregivers (70%) and palliative care staff were mostly female (75%) (See Supplementary Files for the sample's characteristics by country).

3.2 Overview of key concerns and needs

The analysis revealed five key domains of concerns and priorities: (1) Physical pain and symptoms; (2) Psychological concerns and needs; (3) Spirituality, uncertainty over the future and use of "Tawakkul"; (4) Negative impact on social life; and (5) Burden on caregiver and their families (see Table 3).

3.2.1 Physical pain and symptoms

Pain was by far the most important concern reported by participants, including procedural pain (e.g. fear of needles and invasive procedures) but also disease-related pain that had profound effects.

TABLE 3 Key concerns and priorities for children and young people with advanced cancer, their families and palliative care providers in Jordan and Turkey.

Key themes	Sub-themes
1. Physical pain and symptoms	Symptoms or concerns related to physical health.
	i. Pain
	ii. Other physical signs and symptoms (e.g. mobility, fatigue)
2. Psychological concerns and needs	Psychological wellbeing.
	i. Psychological signs and symptoms:
	- *Anger and emotional distress*
	- *Changes in mood*
	ii. Psychological concerns and needs:
	- *CYP and caregivers need to talk, and their issues to be heard and addressed*
	- *Need reassurance*
	- *Need for professional psychological support*
	iii. Importance of sharing and gathering experience throughout the illness journey:
	- *Own experience: Importance for CYP and caregivers to build their own experience of, for example, hospitalization and symptoms*
	- *Other people's experience: Importance for CYP and caregivers to hear about other people's experience to normalize their own experience*
3. Spirituality, uncertainty over the future and use of "Tawakkul"	Spiritual concerns, sources of uncertainty over the future faced by CYP and caregivers and use of religious coping.
	i. "Tawakkul", faith and reliance on God ii. Hopeful/Hopelessness
	iii. Uncertainties over the future related to child's disease, child's immediate and longer-term future can cause anxiety and existential concerns.
4. Negative impact on social life	Detrimental effect on social life of patients and their families, such as activities, relationship, and interactions with the broader society.
	i. Social isolation
	ii. Need to social support from extended family and beyond
	iii. Importance for the child to play and go to school
5. Burden on caregivers and their families	Burden on families' personal life and social function, including siblings
	i. Caregivers' life and work are shattered
	ii. Caring for and addressing other sibling's needs
	iii. Financial burden (direct and indirect economic costs affecting families, and the mechanisms that are needed to access appropriate care in practice)

> *"The most prominent thing was the pain and my appearance, like I was always in pain, always, always in pain. My appearance changed. I didn't recognize myself" - Jordanian male CYP aged [11-16]*

Painful treatments gave children negative associations with HCPs and hospital, and children particularly feared needles

> *"When you enter the hospital you're not in pain, but when they give you chemotherapy the exhaustion starts and the nausea and the vomiting and more than one things […] I'll never do what the doctors say again. It always hurts" Turkish male CYP aged [05-07]*
>
> *"She was scared of the nurses, anyone dressed in blue made her shake. At first, she would start shaking whenever she saw a nurse, she was scared of needles." Jordanian mother aged [31-35]*

Pain was described as a major barrier to children performing their daily and leisure activities

> *"M: I also can't eat most things. I have a stomach ache when I eat." Turkish male CYP aged [08-10]*

A child explained that the pain made her think about the end of life

> *"Patient: After the operation, I never expected the operation like this. I had a lot of pain, and I could never move my foot. I said, it's over now, that's it. Mean it is fate. This fate.*
> *Interviewer: What was it fate?*
> *Patient: I don't know [laughs], I guess that moment…. I mean something like the end of life, at that moment it was really hard for me […] My world is almost finished. [laughs]" Turkish female CYP aged [11-16]*

HCPs related this back to the importance of pain relief to enable the child to mobilize and undertake independent function.

> *"But the most important point is controlling the pain and for the child to have the ability to move or to reach the bathroom, to move. This is one of the most uncomfortable things for the child and his parents" Medical HCP female in Jordan aged [46-50]*

Additionally, common reported physical symptoms were fatigue, weakness/numbness, nausea, vomiting, constipation, fever, swelling of a body part, sleep issues, headache, loss of appetite, and a few reported breathing difficulties. Changes in physical appearance (e.g. deformity, hair loss, yellow in the eyes, weight change) had a serious impact on mental health.

Mental health issues may also have a physical impact on the child

> *"Some people have diarrhea or constipation, but constipation and diarrhea are not just protocols of treatment, some people get them from fear, some people get numbness in their ends and headaches as well from overthinking not just from chemotherapy and radiation therapy." Non-medical HCP female in Jordan aged [26-30]*

Conversely, HCPs also reported a psychological impact of the child's physical problems

> *"There was a patient that I will never forget, it was really sad, she had met all over her body, she had rhabdomyosarcoma but it was very dysmorphic, her face, her hands, everything was different, there were masses all over, I have never seen such a thing. She first came three years ago and I had just recently started working here, and this girl, [T], I will never forget her, she went through a lot, she was so tough to look at, even her siblings couldn't come and see her." Medical HCP male in Jordan aged [31-35]*

3.2.2 Psychological concerns and needs

The majority of CYPs and caregivers identified psychological concerns and needs as their major concern.

> *"Psychology is 50% of the treatment" Jordanian male CYP aged [11-16]*

These needs were often seen as not addressed by HCP, who concurred that physical care was their priority despite recognizing psychological needs' importance. Anger and irritability were common emotions reported by caregivers and especially in CYPs, who were also concerned about boredom. Changes in CYP's behaviors seemed to be indicators helping to monitor their physical and mental health. HCPs also described anger and aggression reactions.

> *"So kids who are less than 3 years for example, they feel pain but it's mostly severe exhaustion that they experience and they can't move and some of them become angry in a way and they can't handle anyone, and from 3 to 5 years old, they also become very angry as well. They hit their siblings and some of them might use a lot of profanity in their speech" Medical HCP female in Jordan aged [46-50]*

This was compounded for migrant children

> *"We stayed at the border for three days, we slept in the middle of the desert. I thought he was scared of the police or the shootings, and he was stuck to me the entire time. When I got off to open the suitcase at the checkpoint, he would scream his head off, I thought he was scared. He has been normal his entire life, he never complained." Palestinian mother receiving care in Jordan aged [31-35]*

Both caregivers and CYPs' interviews highlighted the need to talk through their experiences and to receive professional psychological support. Almost as importantly, caregivers and CYPs expressed the need for their issues *to be heard* and addressed by HCP. CYPs, and in particular caregivers, needed reassurance from the HCP.

Further, most of the CYP, especially the oldest, wanted to be informed about their diagnosis but were often excluded from discussions about their health. A few shared that they were glad their parents concealed negative information.

3.2.3 Spirituality, uncertainty over the future and use of "Tawakkul"

Faith and reliance on God were a predominant concept identified as "tawakkul" (10). Religious belief enabled coping with uncertainty and keeping hope for the future. Most interviews referred to expressions such as "Thank God" or to putting their fate "in God's hands".

> *"Hope Allah cures everybody and us too. If only God heals our child, as long as the child is with me, I can accept to be beggar*

> *from door to door [which means she accepts to be poor]." Turkish grandmother aged [51-55]*

Caregivers reported performing religious rituals with the child when s/he had uncontrolled pain, and several reported that they increased their religious practice after the diagnosis.

> *"We don't say anything but just when it's the right moment, we tell him that the same thing all the time, because we are the believers. This is a test world, we will pass this test. I mean the God made us that, examined us, we will pass it, we will get out of here with God willing" Turkish father aged [36-40]*

A CYP highlighted that she stopped praying due to the illness although her spirituality was very important

> *"Sometimes people are too sick to wash up for prayer, or in so much pain, or too upset to pray" Jordanian female CYP aged [11-16]*

Religion also shaped the understanding of diagnosis

> *"I am confused, some people say I am possessed, some people come and read the Quran for me. They say I am envied[1] and bring over Sheikhs." Jordanian female CYP aged [08-10]*

A sense of acceptance of the disease as part of life also supported coping

> *"I don't worry so much anymore. Because all rivers fall into the sea. No matter how much I am worried, whatever will be, will be. There is no more than that. Because, when we are worried, this place becomes more unbearable." Syrian girl patient receiving care in Jordan aged [17-18]*

A CYP advised peers to find peace by accepting the situation and socializing in the hospital:

> *"In this process, iiiii[2] when I first came here, I had a hard time. So, I had a lot of difficulties before I had surgery. I can even give some advice, I was never with peace here [laughs]. I was hating this hospital. I tried to get used to a bit after the surgery. I made friends. So it's easier. I can advise to be at peace with here. [laughs]" Turkish female CYP aged [11-16]*

The ability to keep or lose hope was an important feature of participants' spirituality and shaped their emotional journey and ability to cope

> *"Let me tell you clearly that, I have no hope. Because we've been here for 5 months, 10 children we've stayed with have passed away. This disease, the doctors … I mean they're doing more than they can, but there's nothing they can do.[…] I can't get rid of the pain inside of me. Because there's nothing to do." Turkish father aged [41-45]*

Despite a reliance on prayer for a positive outcome, it was also difficult to remain hopeful over time:

> *"I say, we'll pray, we'll get better, she says, "Mommy, we've been here for two years, I'm not getting better now." I said such a thing cannot happen, you don't know the future, and you just act as if she will recover. I said if you want to heal, you will struggle to get better. I always try to give her support, because we, as a family, my husband, my children, my mother, father, sister, the whole family, the road gets longer, the less our patience and the heavier our burden, we fall into pessimism. We say everything is in vain." Turkish mother aged [36-40]*

HCP reported hesitance in discussing spirituality and end of life with CYP

> *"It's hard to discuss spiritual topics with children because it's a sensitive topic and it may emotionally provoke them. […] The problem is that for some time, we wouldn't frankly talk about death in our sittings, especially if the kids were present; we wouldn't bring up spiritual topics much like what will happen after they die. Maybe we'd talk to the parents more about it when their child isn't present. We'd tell them that if their child passes away, God will replace their losses or that God will choose the best fate. It's hard to discuss spiritual topics with children because it's a sensitive topic and it may emotionally provoke them." Medical HCP female in Jordan aged [31-35]*

Uncertainty over the future was one of the major concerns of CYPs and led to existential questioning and hopelessness. Most CYP, and some caregivers, were worried about treatment duration and outcomes like their ability to walk, go back to school or play, i.e. to go back to normal.

> *"I feel sad. Then, when it is over, I wonder how I will keep up with things? The other operation forced me a lot. Now, because of the outpatient treatment, my walking distress, though it has decreased but there is a little bit. I can't walk like every other person, I'm getting tired anyway. Uh, it pushed me hard a little bit, how do things will be going when I start school. I wonder how I will keep up with a…. fast-paced life, the tempo, when*

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[1] in this context, this refers to harmful envy [hasad] and sending him the 'evil eye' [al 'ayn]

[2] Turkish equivalent for "mmmmm"

> *the school starts, home work, exams etc. I am a little scared anyway, I have some worries" Turkish female CYP aged [11-16]*

Some, especially teenagers, were particularly worried about their future education

> *"I am going to waste my future, the semester is almost over." Jordanian female CYP [17-18]*

Few CYP worried about cancer stigma preventing employment and marriage prospects

> *"I had a patient that told me that he won't ever be able to work or get married because he'll always be labelled as a cancer patient even if he gets better. This patient didn't have a curative prognosis, but he still thought that even if he was ever cancer-free, he'd still be labelled as someone with cancer. He said that families would reject his marriage proposals just because he had cancer." Non-medical HCP female in Jordan aged [26-30]*

For HCPs, CYP and caregivers described fear of death. They felt that younger children may not grasp the concept of death, but that realization may grow

> *"There were 6 cycles, but the treatment is not finished. When we say let's give 3 more, let's give 5 more, that kid understood that this is not going straight. No matter what medicine you give. Then the child understands and fears death without saying that things are not going well." Medical HCP female in Turkey aged [36-40]*

Some HCPs acknowledged that there was a lack of support for grieving and bereavement for caregivers after their children's death. This may cause distress for caregivers, and HCP who may feel they abandon them in difficult times

> *"someone once said to me "my wife and I are mentally destroyed" he even changed the room he was in, we even forget the families, we forget the families after being DNR, after the patient dying, our relationship with them gets cut off. " Medical male HCP aged [31-35] in Jordan*

3.2.4 Negative impact on social life

Social isolation was one of the biggest concerns expressed by CYPs and caregivers. Accessing cancer treatment often meant being far from the rest of family and social support. Infection control also caused physical separation. For caregivers (mostly mothers) additional duties such as physical care work (e.g. carrying or bathing the child), emotional labor (e.g. addressing children's need for attention) and the fear of infection were the most reported reasons for social isolation.

Caregivers' needs ranged from practical support to caring for siblings, to social interaction without mentioning the disease, and professional psychological support. Social isolation was particularly concerning for immigrants, refugees or those who had travelled far for treatment.

> *"We just come out and walk around. We're not seeing anyone. In fact, this is the most important, we are going through an unsocial process." Turkish mother aged [36-40]*
> *"In Gaza I am with my family, but here I am not." Palestinian female CYP receiving care in Jordan aged [08-10]*

It was a key concern that children could not play with or see friends or go to school because of pain, symptoms, or fear of infection. They missed "hanging out" with friends and family outdoors although they used technology to remain connected with loved ones or to fight boredom.

Finally, participants reported concerns about the lack of awareness about cancer in the society that could lead to stigma and gossip

> *"people outside look at me pityingly, look at your child pityingly. They should not look like that. No one should look at anyone pityingly […] people should not say, do not come close to this child otherwise you will get it too, saying ahh, saying aww saying thhuu … Or they shouldn't say why you don't have hair. Or they shouldn't say why you are wearing a mask." Turkish mother aged [18-25]*

3.2.5 Burden on caregivers and their families

Caregivers were distressed by not being able to be with all their children, who were often taken care of by other women of the family like an aunt or grandmother. Mothers, in particular, reported concerns about leaving other children behind.

> *"My mother and father [took care of them]. My daughter was in kindergarten, she would go to her aunt's, her aunt has kids around her age, and my son would stay with my mother. I went through very tough times, the last year was very tough." Jordanian mother aged [31-35]*

Most of interviews with caregivers and HCP described caregivers' emotional distress

> *"As we see the suffering of children, we are ruined. […] I do not think that any mother can survive with this feeling. [Sighed]" Turkish mother aged [26-30]*

A major concern in caregivers' interviews and corroborated in HCP's were the indirect costs and logistical challenges in accessing care far from home.

> *"Their father works in the city council, he is a cleaner, and I spend most of my time in the hospital. We have a hard time with transportation, we call a bus to drive us around. The bus costs me 30 JD. Yesterday she had an appointment with Dr. [name], he said she is not to be admitted, and told us to go back home and come back the next day. I told him I couldn't afford it, I can't pay 30 JD twice in two days, my husband only gets paid 228 JD, he works on a daily-basis payment and he's not fixed. I told them I would stay in the ER till the next day, and once a room is available I'll transfer to it." Jordanian mother aged [46-50]*

Several caregivers reported they had to take unpaid days off work to accompany the child to hospital, and worried about losing income or getting fired. Some mothers had to stop working **care for the child.**

> *"I'd go to work with my heart on fire. I wait and count the hours and wonder when I'm going home, when I can retire. If they don't deduct from our salaries, I would leave work and sit at home with them. I have no relationships, I don't even see my neighbor. I just go to my Caregivers' house and come back. So honestly, I have dedicated all of my time to the children" Jordanian mother aged [41-45]*

The interviews revealed that refugees and foreign patients had additional financial barriers related to currency difference and transport.

> *"Like I spent 3 Dinars on a taxi, that's 15 Libyan Dinars. You understand? It's like the 3000 Jordanian Dinars I exchanged over 3 or 4 days, 17000 Libyan Dinar. Three or four days I'm not talking about a treatment trip, you understand? Like I went and bought 10 Dinars worth of fruit or I don't know what a meal, multiply that by 5." Libyan father in Jordan aged [41-45]*

Additional direct costs for refugees and foreign patients included hospital and treatment fees, met from various sources including family or co-workers.

4 Discussion

4.1 Main findings and comparison with existing literature

Our data reveal five dominant domains of concern among CYP with advanced cancer and their families in Jordan and Turkey. These substantive findings add new insight to the small self-report evidence base for this population. Our findings highlight the importance of pain management for CYP, and the urgent need to improve access to psychosocial support for patients and families, with particular attention to refugee and foreign patients. Pain management, therefore, need to embrace the "total pain" concept (19) to improve palliative care provision.

Concurring with other research on cancer experiences in the region, we identified faith and reliance on God (tawakkul) as an important coping mechanism for families and patients that helps overcoming fear of death and end-of-life (8, 10, 20). Tawakkul is an important concept for Muslim patients. 97% of the population in Jordan and 99% in Turkey are Muslim (21, 22). However, there is no consensus yet on what spiritual needs are and little is known about whether or how religion could have a positive or negative impact on mental health (23). The prior systematic review of symptoms and concerns among CYP with advanced illness reported a dearth of evidence in the spiritual domain (24). Within our study, CYPs did not discuss their fear of dying directly or fear of going to sleep. Fear of death was mostly reported by HCPs and rarely by caregivers, which may be related to the cultural context and a need to hold on to 'tawakkul'.

Our data suggests that CYP tend to be excluded from discussions about their own health despite willingness to be informed. While family-based models encourage shared decision-making, it is not widely spread in pediatric care (25) and in the Middle East (26). Further, the limited evidence about shared decision-making models' effectiveness on patient outcomes and its focus on Western countries (27–29) calls for further investigation on existing shared-decision models in the region.

4.2 Implications for practice

Our findings support a family-centered care approach for pediatric palliative care in Jordan and Turkey. It is in line with other studies describing the central place of extended families in care, and its importance culturally as suggested in other research in Muslim-majority countries and in life-threatening illness among adults in the region (8, 11, 30). The isolation of the children and their caregivers, far from people providing them with social support, was an important source of distress, which was amplified for migrant and refugee patients (9).

Our findings demonstrate the urgent need to address the financial and psychosocial burden faced by caregivers, especially for foreign and refugee patients and those with limited resources. A 2021 systematic review of the burden of out-of-pocket expenditures faced by patients diagnosed with cancer and their caregivers in LMIC showed the significant out-of-pocket costs related to treatment "most of which is spent on cancer medications, followed by caregiver expenses, and transport and travel expenses" (31). However, no study was identified from the Middle-East region.

4.3 Strengths and limitations

Our study has successfully recruited and interviewed CYP with advanced cancer, which has been an omission in studies in this population generally, and has not been conducted previously in this region (24). It provides multistakeholder perspectives on the themes, and included experiences of refugees. Our innovative collaborative approach to data analysis strengthened culturally and contextually relevant identification and interpretation of findings. The analysis was, however, time-intensive and demanding.

Our research also presents some limitations. Given the limited availability of palliative care research and practice in the region and the difficulty of conducting such research, we only focused on cancer and included one site per country, which are regional leaders of palliative care. The needs identified may be therefore underestimated and may not be generalizable to the whole region. The care offered in both centers and countries were overall similar but had some variation for non-medical services. This led researchers to sometimes emphasize issues that may be locally relevant. Finally, collecting data among children, especially on a sensitive topic, and with caregivers was challenging in terms of both communication with the interviewees, and emotional impact on the research team.

4.4 Conclusion

Our study described what matters for children and young people with advanced cancer and their families in the Middle East. Outcome measures can improve pediatric palliative care by ensuring that the care addresses the needs of patients and their families (27). This study provides the primary data to develop child- and family-centered assessment and outcome measurement that reflect what matters (1). Pain needs to be considered holistically by palliative care professionals so as to address CYP and their caregivers' significant psychosocial support needs. The additional high emotional, social and financial burden faced by caregivers, recognized by their HCPs, calls for a sustainable investment in palliative care in line with Universal Health Coverage to better support patients and families.

Data availability statement

The datasets presented in this article are not readily available because the data are qualitative and we cannot share the transcripts. Requests to access the datasets should be directed to SB, sabah.boufkhed@manchester.ac.uk.

Ethics statement

Ethical approval was obtained from King's College London (ref: HR-18/19-8838); Hacettepe University (ref: 16969557-25 or GO 19/40) and KHCC (proposal No. 18 KHCC 162). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

PG, RH, OS, and TK contributed to conception and design of the study. SY, GA, WA, FA, SA and MS collected the data. SB organized and managed the data, and led and coordinated the cross national. SB, SY, GA, FA, and WA analyzed and interpreted the data. SB wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1120990/full#supplementary-material

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Access to advanced cancer care services in the West Bank-occupied Palestinian territory

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Introduction: Universal Health Coverage (UHC) identifies the provision of palliative care for people with advanced disease as an essential health service. Palliative care is also stipulated as a human right under existing covenants. Oncology services provided by the Palestinian Authority under Israeli military occupation are limited to surgery and chemotherapy treatment. Our study aimed to describe the experiences of patients with advanced-stage cancer in the West Bank in accessing oncology services and meeting their health care needs.

Methodology: We conducted a qualitative study among adult patients diagnosed with advanced lung, colon, or breast cancer in three Palestinian governmental hospitals, and with oncologists. Thematic analysis was conducted on the verbatim interview transcripts.

Results: The sample consisted of 22 Palestinian patients (10 men and 12 women) and 3 practicing oncologists. The findings reveal that cancer care is fragmented, with limited access to the services needed. Patients face referral delays in accessing treatment which worsen their health condition in some cases. Some patients reported difficulties in getting Israeli permits to access radiotherapy treatment in East-Jerusalem, and others experienced interruptions of their chemotherapy treatment sessions due to the unavailability of chemotherapy medications caused by Israeli-side delays. Other reported problems were related to the Palestinian health system and service delivery and quality, including fragmentation of services, infrastructure issues, and unavailability of medications. Advanced diagnostic services and palliative care are almost absent at Palestinian governmental hospitals, and patients need to seek these services in the private sector.

Conclusion: The data demonstrate specific access restrictions to cancer care in the West Bank due to Israeli military occupation of Palestinian land. This affects all stages of the care pathway, from restricted diagnosis services, to limited treatment and then poor availability of palliative care. Cancer patients will continue to suffer if the root causes of these structural constraints are not addressed.

KEYWORDS

occupied Palestinian territory (oPt), access, cancer, care, services, Israeli military occupation; conflict, challenges

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Introduction

Cancer is a leading cause of death in low-and middle-income countries (LMIC), where higher rates of cancer mortality exist compared to high-income countries (1–3). This can partially be explained by a higher proportion of cancer patients diagnosed at late stages and lack of access to the needed health services (2, 4). Additionally, it is expected that by year 2035, the incidence rate of cancer will rise in LMIC, with a projection that two-thirds of cancer cases will be present in developing countries, including countries in the Middle East and North Africa (MENA) (2, 5).

Developing countries face many challenges in providing cancer care (1–5), with health systems incapable and unprepared to provide comprehensive cancer care. Cancer control, including prevention, screening and early diagnosis, is hardly available and is inaccessible for many people (3). Moreover, cancer treatment is constrained by a lack of advanced diagnostic services, a dearth of oncology health providers, shortage of radiation therapy services, and the fragmentation of cancer services (2, 3). In areas affected by armed conflict, as in some MENA countries, cancer care is much more difficult to obtain (5, 6). Physicians' departure "brain drain", is an additional challenge (7, 8). By 2060, serious health-related suffering will be experienced by 16.3 million people dying with cancer each year (compared to 7.8 million in 2016). The increase will be greatest in low- and middle-income countries (9–11).

In the Israeli-occupied Palestinian territory (oPt), the focus of this study, cancer was the second leading cause of death in 2017 and 2019 (12, 13). Similar to other conflict-affected areas, access to cancer care in the oPt is hampered by numerous impediments. In this paper, we aim to understand experiences of patients with advanced cancer in accessing care and their care needs in the West Bank, including Palestinian East-Jerusalem, which is illegally annexed by Israel and not accessible to Palestinians from the West Bank without permits (which are difficult to obtain).

The oPt consists of the West Bank, Gaza Strip and Palestinian East Jerusalem (14). East Jerusalem has been controlled by Israel since its annexation in 1967 and is isolated from the rest of the West Bank by the Israeli Separation Wall (15). Moreover, the West Bank is severely fragmented due to the building of illegal Israeli settlements, the Separation Wall, and the Israeli permanent and flying military checkpoints. Movement of people and goods is restricted, with ongoing direct and indirect violence against Palestinians (14), detentions, demolition of homes and attacks on Palestinian land (15). This complexity creates significant barriers to accessing health care (16–18).

Cancer treatment in the West Bank is mainly provided in small oncology units in three Palestinian governmental hospitals in addition to newly established oncology units in two private hospitals that are contracted by the Palestinian Ministry of Health (MoH) (12, 13). The governmental oncology units lack specialized pathology laboratories, and advanced diagnostic and imaging facilities. They mainly offer chemotherapy treatment and some surgical care. Moreover, there is no radiation therapy in any of the West Bank hospitals (these are not permitted by Israeli authorities) and patients who need radiotherapy are usually referred to East Jerusalem or hospitals in Israel (12, 13, 19). Referrals for cancer patients to East Jerusalem, Israel and neighboring countries are also provided for advanced diagnostic services such as nuclear medicine scanning and advanced treatment (12, 19, 20).

To access cancer services that are not available in hospitals within Palestinian Authority areas in the West Bank and Gaza Strip, cancer patients from West Bank and Gaza Strip need special Israeli permits to access these services at an East-Jerusalem Palestinian-led hospital with comprehensive oncology services (12, 13, 20). The process for obtaining Israeli permits is lengthy, confusing, and entails a lot of uncertainty (17, 20, 21). Of all permit applications from the Gaza Strip to attend hospital appointment in September 2021, 69% were accepted and 30% had no response by the appointment date. In the West Bank for the same period, 84% were approved, 12% were denied and 4% were waiting for a reply (22). Cancer patients with permit applications initially denied or delayed are less likely to survive (20).

Companions for patients attending clinical appointments/admissions are crucial to provide social support (especially for children and older people) and to provide informal care due to staff resource limitations. However, only 39% of the permit requests for companions from the Gaza Strip in September 2022 were approved, while 59% received no response. In the West Bank, 78% of companion applications were approved, 17% were refused, and 5% received no response (22).

Given the urgent need to meet the palliative care goals of UHC, evidence is needed to understand the pathway to advanced cancer care that can inform health system improvement. Our study aims to describe the experiences of patients with advanced-stage cancer in the West Bank in accessing oncology services and meeting their health care needs.

Materials and methods

This study utilizes a qualitative methodology with in-depth interviews conducted between September-November 2021.

Setting

The study was conducted in three Palestinian governmental hospitals located in the north, center and south of the West Bank.

Ethics

Ethical approval was granted by the Research Ethics Committee at the Institute of Community and Public Health, Birzeit University (ref number 2020(3 – 1) and at Kings College London (ref number HR-20/21-18199).

Recruitment and data collection

Inclusion criteria for potential participants (identified by medical oncologists working in the three participating hospitals) were as follows: adults with advanced-stage cancer (stage 3 or 4, as determined by their treating oncologist) of the lung, colon, or breast. These primary cancers were selected as they had the highest mortality rates in the West Bank in 2019 (13). We purposively sampled patients based on locality, gender, age and type of cancer care they receive. We informed the medical oncologists working in the three hospitals of our inclusion criteria. They selected participants from the hospitals' registered patients based on the criteria who were present on the day of our visit to the hospital for us to approach. We made sure to have variety in the selected participants with attention to cancer type and gender. Exclusion criteria were: patients having any other type of cancer or cancer stage 1 or 2 (as determined by their treating oncologist), or patients who were unaware of their cancer diagnosis. Selected patients were approached and briefed by the study researchers on the purpose and goals of the study, and provided with information sheets. Informed consent was obtained orally from participants, including consent to record the interviews. Based on our research experience and understanding of the local context, we have found that people become uneasy when asked to sign consent and generally prefer oral consent. Interviews lasted between 30 and 90 minutes and were conducted by researchers from the Institute of Community and Public Health (Birzeit University).

The semi-structured topic guide included diagnosis, treatment plan, knowledge about disease and treatment, coping strategies, effects on the patient's life, the role of the family, pain management, challenges in accessing cancer treatment, communication with health providers, support accessed, and patients' recommendations to improve cancer care.

Additionally, we interviewed oncologists working in the hospitals where we recruited the patients, to better understand the treatment protocols, referral system, and cancer services provided at these hospitals. The primary aim of the interviews with oncologists were to understand the context of care. The interviews with the oncologists were conducted before the patients' interviews and were not meant to explain identified themes resulting from patients' interviews. They were selected for the interviews because they are the main oncologists in the participating hospitals, and they have extensive knowledge of the cancer services in the West Bank. The appointments for the interviews with the oncologists were arranged through preliminary visits or phone calls. The oncologists provided oral consent to conduct the interview but did not consent to being recorded. Consequently, the researcher(s) took written notes during the interview. The notes were saved on a password-protected computer. All interviews with patients were audio recorded, transcribed verbatim, and files saved on a password-protected computer.

Data analysis

We analyzed the data using a thematic analysis approach (23). We first coded the interview transcriptions and notes, and the codes were then categorized into themes. Afterwards, we arranged themes into a thematic network, which we explored and described, and then summarized, and finally produced interpretative patterns. To strengthen the analysis, we also created analytical memos (24). Quotes were extracted from transcriptions and notes and translated into English. We then structured the results section based on the thematic analysis, analytical memos and our research questions. Each theme is illustrated using verbatim quotes with a participant ID and brief description to demonstrate the breadth of sample.

Results

Sample characteristics

We recruited and interviewed 22 patients in total (10 men and 12 women), with an age range of 30-71 years. Nine patients came from the north, three from the center, and ten from the south of the West Bank. Fourteen people had stage 4 cancer, and eight people had stage 3 cancer. Time since diagnosis ranged from one week to 14 years. Five interviews were conducted in an inpatient ward, while the rest were with patients attending daycare. Moreover, we interviewed three lead oncologists in the governmental hospitals that have oncology units located in the north, center and south of the West Bank (assigned to us by the Ministry of Health).

Main findings

The analysis identified three main themes: 1) Obstacles to cancer care attributable to Israeli military occupation; 2) Health system challenges; 3) Service delivery and quality.

Obstacles to cancer care attributable to military occupation

One of the main obstacles to cancer care is obtaining Israeli permits to enter Palestinian East-Jerusalem, particularly for radiotherapy treatment. This service is only available in the Palestinian-led hospital in East-Jerusalem, with Palestinian health care centers on the West Bank not allowed to obtain or operate such treatment by Israel. Additionally, some patients seek advanced diagnostic services in East-Jerusalem that are not available in Palestinian governmental hospitals, such as nuclear scans. Participants' complaints about Israeli permits included delays in obtaining them or refusal, for instance, because of so-called "security" related reasons:

> "… *I do not receive permits from a security point of view* (i.e. denied on the basis of 'security' by the Israeli military). *I tried before and it did not work….I tried to apply for a permit from the Israelis to go to "A" hospital* (the Palestinian led East-Jerusalem hospital) *for a checkup, the Israeli authorities did not agree, the Israeli interrogator interrogated me and told me I am not allowed.*"

(Interview 11, male, 58 years old, rural, north WB)

Another participant shared his experience of being unable to get the permit usually given to patients because he already had what is called a commercial permit which does not allow him to cross the usual East-Jerusalem crossing. Instead, he has to go another way. This prolongs his travel to East-Jerusalem and separates him from his son, who must pass through the usual East-Jerusalem crossing alone.

> *"By God, these permits are burdensome and taxing, burdensome and taxing…. Even though I have a commercial permit, they issued a permit for my son and they did not issue me a permit, not allowed. (With) my commercial permit, (I have to) go into the tunnel (a different crossing from his son), they said let the boy in and I was not allowed. The Israeli soldier at the checkpoint said: you should go down and around to Bethlehem (in the south) to the checkpoint there, and the Israeli army checkpoint was so congested with workers (Palestinian workers wanting to cross to work in Israel) and I should have been there with my son at 7.30 am."*
> (Interview 7, male, 54 years old, rural, south WB)

Some participants with a Jerusalem identity card (ID), which is considered by Israel an Israeli ID and allows free passage between the West Bank and Israel, including East-Jerusalem reported being unable to access care in East-Jerusalem. A Palestinian woman who has a Jerusalem ID and is married to a man with a West Bank ID had her Israeli health insurance terminated as she now resides in the West Bank.

> *"My health insurance was cut [stopped]. If I want to go and renew my health insurance, it would take me months and I do not know what will happen to my health state."*
> (Interview 3, female, 38 years old, urban, south WB)

Another patient, who lives in Bethlehem in the south of the West Bank but has a Jerusalem ID, preferred to access treatment in a Palestinian governmental hospital because she was concerned about the travel time and high transportation costs to reach treatment centers in Jerusalem.

> *"They get you tired when you have to go out at 6 am and reach Jerusalem at ten and pay 100 Israeli shekels for transport, and you want food, and you want drink, and you get tired before you sit on the chair for Israeli hospital treatment. Here in fifteen minutes, I reach the hospital and the doctors."*
> (Interview 8, female, 50 years old, rural, south WB)

Patients also reported interruptions in accessing diagnostic and treatment services due to Israeli delays in providing supplies to the Palestinian hospitals, such as medical materials needed for nuclear medicine in addition to the chemotherapy drugs.

> *"Now I have to get a nuclear image/scan in Hebron, but the material did not arrive from Israel."*
> (Interview 8, female, 50 years old, rural, south WB)

> *"There are some days when the medication (chemotherapy) is there and at other days the medications are not there so they are obliged to postpone giving medications to patients until medications arrive. We also faced this because this medication comes from Israel, and Israel gives them the medication according to the number of patients they have. It does not give them the medication in large quantities, only based on the number of patients who need it, meaning if they have 800 patients, so only 800 doses of medication."*
> (Interview 10, male, 48 years old, urban, south WB)

> *"Last week, I didn't get my chemotherapy treatment. I came, and they (at the hospital) told me that there are no medications, so they postponed my session for two days and gave me two doses to make up for it."*
> (Interview 18, female, 46 years old, rural, north WB)

Health system challenges

In the following sections, we discuss the Palestinian health system challenges and service delivery and quality.

Diagnostic services

One of the main problems of cancer care on the West Bank is the lack of advanced diagnostic services at Palestinian governmental hospitals. Some patients reported that even when the diagnostic services are available in governmental hospitals, they are sometimes not functioning, or it takes a long time to make an appointment or to get the scan report. Moreover, nuclear scans are offered only in the one hospital in East-Jerusalem and one governmental hospital in Hebron in addition to a few private hospitals.

> *"If we want to send a message to someone or to those responsible in the governmental hospital, there must be MRIs and CT scans operational, and not having to come to do these tests and they tell you today we cannot because the machine is out of order…if a machine is out of order in a government hospital which serves all of Bethlehem and Hebron and there is only one machine?! A hospital with an oncology unit and you cannot get a nuclear scan done! You have to go to either "B" hospital or "A" hospital…A hospital with an oncology unit does not have a colored CT scan… I came to "C" hospital to do a CT, I may do it today and after week or two weeks I will get the scan report."*
> (Interview 5, male, 33 years old, rural, south WB)

This frustration with waiting to receive care, especially scans, was described by another participant:

> *"In this hospital, if you want a scan, you have to wait a month to have your turn if you do not have wasta (connection)… radiation yes, it is available but you go and find that the machine is out of order, you may need one month, two months to be able to have the image."*
> (Interview 6, male, 45 years old, rural, south WB)

Due to the shortage of advanced diagnostic services in Palestinian governmental oncology departments, patients are referred to other governmental hospitals or the Augusta Victoria hospital in East-Jerusalem or private hospitals that are contracted by the Ministry of Health to receive these services. Participants who must go through a bureaucratic, lengthy, referral process view delays in receiving treatment as disease progresses, in turn causing additional strain and frustration.

> *"From March till August, I was going from a physician to another till they do the CT scan for me…then we knew in October when they took the biopsy that I am in stage 4."*
> (Interview 12, male, 57 years old, urban, north WB)

At times, due to referral delays, some patients choose to pay for diagnostic services in private hospitals rather than going through the lengthy referral process. It is important to note that for many patients, this was a significant expense, albeit one that they viewed as necessary in order to improve their treatment outcomes.

> *". Almost all the tests are at my expense… for example the doctor today told me I must do a test using my insurance, but I would have to wait two or three days, so I am obliged to do it at my expense."*
> (Interview 9, female, 65 years old, urban, south WB)

In addition to delays, other patients reported problems which were related to ineffective or wrong diagnoses. At times discrepancies in advice or diagnoses would push patients and their families to seek care in other hospitals, often at their own expense. For some, it also affected their confidence in the care that was provided to them and for many, it was a source of stress. Below, we can see the experiences of two men.

> *"We went to the hospital emergency department, and a surgeon came to us and said that these tests indicate that I do not have anything. But how nothing? I have something. The doctor said you do not have anything…. He told me throw away this medication and that medication, and of course he wrote me other medications. My son began to scream and said no, my father we will get a CT scan at our expense."*
> (Interview 7, male, 54 years old, rural, south WB)

> *"For laboratory exams in Ramallah they told me that the biological treatment does not work with me, so we went to "A" hospital in Jerusalem and they took a biopsy to Israeli labs, and told me that one of the biological treatments works with me, so we came here (to this Palestinian hospital on the West Bank) and told them and I began treatment because the biological medication was here at this hospital on the West Bank. I took six sessions and then the medication was cut (no longer available), so they transferred me to the East Jerusalem hospital for the six remaining sessions, and I finished them and came back here."*
> (Interview 6, male, 45 years old, rural, south WB)

Oncology surgery

Some governmental hospitals offer this service, while referrals are provided for some specific procedures. However, the referral process is sometimes confusing to patients who face delays similar to referrals for diagnostic services. Delays in referral for surgery had a negative consequence on patients' health, compounded by the complications of having a Jerusalem ID and living in the West Bank as this patient illustrates:

> *"I took six chemotherapy sessions at "A" hospital, and went to the doctor and did a nuclear test and my situation was excellent… but was told I needed an operation… But because I have a Jerusalem ID, I had to go back and forth to obtain a referral to the Palestinian hospital, it took me time. And the situation became bad, the growth went around the pelvis and it made it difficult to have an operation……It is due to their neglect…"*
> (Interview 3, female, 38 years old, urban, south WB)

A patient described the referral issues she encountered when undergoing head and neck surgery to remove a tumor. She finally went to a Palestinian government hospital and refused to leave until the surgery was completed because further delay would worsen her condition.

> "*This doctor pushed me to that doctor, and that pushed me to that… they said there are no surgeons in the West Bank hospitals, your operation should be done at "A" hospital (in East Jerusalem). We went to Ramallah for a referral, and they told us that the doctor responsible for referrals is traveling… Either this is a game, or they making a mockery of people…"*
> (Interview 19, female, 48 years old, rural, north WB)

In addition to the above surgery related difficulties, another patient reported on his experience when he had surgery in a governmental hospital to remove a tumor in the colon. He was asked to bring a device needed for the surgery at his expense. He was told that his surgery would have been postponed for three months if he could not bring the device. Following his colon surgery, he also needed a colostomy bag with its base in addition to needles, and he purchased them from private companies because the Palestinian Ministry of Health did not have them.

> *"These bags are not available at the Ministry of Health and every day I need two… I can only find them from companies which sell medical equipment, and you buy the bag with the base for 35 ILS daily, and they do not cover any of the costs."*
> (Interview 21, male, 36 years old, rural, center WB)

Furthermore, some patients decided to seek surgical treatments in private hospitals because of referral delays or other problems such as physicians' strikes or when they needed immediate medical intervention that could not wait.

> *"I came and found that surgeons were on strike… so I did not want to wait, I did both operations at my expense…."*
> (Interview 4, female, 47 years old, rural, south WB)

Other than the financial difficulties that the patients face in accessing health care, some interviewees especially those who do not live close to treatment centers elaborated on the transportation difficulties and financial burden related to reaching treatment centers:

> "*Transportation, financially, is expensive and tiring. We are patients, we should have priority, we are cancer patients, and we should have transport and everything available to us."*
> (Interview 2, female, 59 years old, urban, south WB)

> *"I come from a southern town with a private taxi, and they take 150 ILS every day…. To be honest, financially you cannot expect to have 400-500 ILS available to come and go, in addition to hospital expenses. You do not have that kind of money."*
> (Interview 7, male, 54 years old, rural, south WB)

Chemotherapy treatment

Interviewees stated that this treatment is generally available at oncology hospitals. Most participants reported that they were informed of the treatment plan in terms of the number of chemotherapy treatments.

Some participants stated that there is a lack of information provided to patients by health professionals regarding their treatment that also applied to the side effects of the chemotherapy treatment.

> *"The chemotherapy I took made blisters in the mouth and dryness in the palms…. And slight nausea but the doctor did not tell me hair would fall…."*
> (Interview 5, male, 33 years old, rural, south WB)

Patients also reported experiencing delays in beginning their chemotherapy sessions, and were bothered by the long waiting time they have to endure till they receive their treatment, and by being asked to come on another day.

> *"When we were upstairs at the hospital, we would come at 8 am or before, and the medication would come to us at 3 pm or 4 pm… at 8 am they come and take tests, and your tests take about an hour to come out, so around 10 or 11 you should get your medications … but I do not get my medication until 3 or 4 pm… a whole day is lost."*
> (Interview 6, male, 45 years old, rural, south WB)

> "*You do the tests and you wait and you stay a long time while you wait between the tests and the treatment."*
> (Interview 15, female, 30 years old, rural, north WB)

Service delivery and quality

Consultations

In addition to the variations of information shared by the oncologists, there were also differences in the consultation time given to the patients by oncologists. Some patients' views were positive, feeling that oncologists work within their full capacities given the high number of patients. However, at the same time they suggested improvements related to the Palestinian Authority's investment in health.

> *"The government should take into consideration that one cannot do more than one's capacity. They have a lack of doctors…. They should employ more people, but to have one doctor for an entire district like this district, who will he be able to see? Even the doctors are oppressed, they are right and they are wrong, but in the end, they are oppressed…"*
> (Interview 7, male, 54 years old, rural, south WB)

Other participants complained about the available time for interaction with the oncologists. This prompted some patients to seek consultations with oncologists at their private clinics due to the limited time available for them at the hospital.

> *"with doctors it is difficult, if you want to talk to them, you need wasta [connections], they do not answer…if you go to the*

> *doctor's private clinic he answers you… here at the governmental hospital, he cannot see you at all, too busy…. if you want to talk to the doctor, you need to go to the clinic and pay 100 ILS, he would sit with you for an hour and laugh with you….”*
> (Interview 11, male, 58 years old, rural, north WB)

With regard to nurses, most participants expressed their appreciation for the nurses, particularly those who work in daycare treatment, acknowledging that the nurses are overworked. Nevertheless, less positive feedback was reported by some participants for the nurses responsible for inpatient wards.

> *“Some nurses are the sweetest you like to see them 24 hours a day, some nurses you do not accept a glance from them, not all of them… only 1% of them… By God this night no one came to us, no one, even when the IV drip was finished.”*
> (Interview 2, female, 59 years old, urban, south WB)

Infrastructure

Complaints about the lack of system capacity also extend to the infrastructure of the treatment facilities, especially in the inpatient ward of the oncology hospitals. One of our oncologist interviewees confirmed that the inpatient ward in the hospital he works at has only 20 beds and is overloaded. He noted that they sometimes admit cancer patients to other wards. As we see below, some patients reported delays in being admitted to the rooms and waiting for a bed to become available.

> *“I come and I sit on a chair for a long time before they find a place for me in the inpatient ward.”*
> (Interview 2, female, 59 years old, urban, south WB)

> *“The size of the patient-load (cases) is large… meaning that when I come to register at the hospital, I wait in line for a bed to be empty or for space. I was supposed to sleep at the hospital on Thursday, but it was not possible because there was no space, so we postponed until Sunday.”*
> (Interview 10, male, 48 years old, urban, south WB)

Most participants also reported lack of cleanliness in the rooms such as dusty surfaces, un-sanitized equipment, and dirty bed sheets. They mentioned that the rooms are overcrowded with patients beyond their capacity, toilets are shared, some beds are broken, blankets and pillows are insufficient, and there is no space for accompanying family to sleep. Some were bothered by the noisiness of visitors and the lack of privacy.

> *“I get upset because of the lack of cleanliness, because of the general services… we ask and nothing happens. This is how the floor is[pointing to the floor], no cleanliness, they do not wipe the floor. Here there is no cleanliness, and we (the patients) clean.”*
> (Interview 2, female, 59 years old, urban, south WB)

> *“The oncology section on the third floor, I do not know if you have been there or saw it…. Terrible… rooms for two have three patients other than companions… pressured, no privacy, cleanliness is almost non-existent… there is no space for companions to sleep…. they sleep on the floor if they obtain a cover… sometimes there is no pillow for you (the patient), not for your family (accompanying you).”*
> (Interview 6, male, 45 years old, rural, south WB)

Timeliness and integration

Fragmentation of services was a common concern. For example, patients demanded easy access to receive prescribed medications and other treatment-related services such as blood testing given that it is difficult for them to go to multiple centers for different health care needs.

> *“Most of my treatment is here in this building, and the blood tests are in another building…. For sure it would be more comfortable for one if they were in one place instead of going up and down, going and coming… this is tiring.”*
> (Interview 20, female, 57 years old, rural, center WB)

Drug availability, pain and palliative care

In general, nearly all interviewees reported that the unavailability of medications at the Palestinian oncology hospitals is a significant difficulty. Painkillers, laxatives, vitamins, and gastrointestinal medications were among the reported missing medications. Therefore, the patients pay for these medications out of pocket, which create additional financial burdens for many patients and their families.

> *“Pain killers I buy from my own pocket, they are found in the market, but not available with the governmental insurance. I need stomach medications because what they give me for my stomach is not as effective as other medications which I buy at my personal expense outside the hospital….”*
> (Interview 6, male, 45 years old, rural, south WB)

Patients in pain were the ones who emphasized the shortage of painkillers the most, indicating that they get inconsistent supplies of painkillers medications. Furthermore, some noted that paracetamol is usually administered to treat their intolerable pain, which they found to be inadequate.

> *“Pain is terrible … there is a pain killer which is close to morphine, a strong pain killer that I used to take in the East*

> *Jerusalem hospital, but it is not available here of course…I do not know if they just did not give it to me, they gave me this medication but it did not work with me."*
> (Interview 6, male, 45 years old, rural, south WB)

> *"A painkiller, paracord that needs a prescription. Yes, the doctor wants to give it to me to use when necessary. He tells me to take one pill and if needed to take two pills…first, I took paracord and benefited from it and then I stopped benefiting… they (at the hospital) give me the new medication (Paracetamol 325). Maybe the two first hours the pain goes and then it doesn't work."*
> (Interview 12, male, 57 years old, urban, north WB)

> *"I'm in a lot of pain. Every day a certain pain is not the same pain from the first day to the last day…. The doctor wrote Panadol and told me that I can take it whenever I need. I sometimes take 4 or 6 pills a day and there is a pain that remains. I told the doctor and he told me that this is normal, and it is a period and that I have to endure it."*
> (Interview 15, female, 30 years old, rural, north WB)

The experiences of patients reveal that there is a systemic problem with pain management. There are inconsistencies in the availability of medication, in prescribing practices, and in the training of the health staff. One of the oncologists we interviewed confirmed the medication issue. He noted that despite the importance of appropriate pain killers to the quality of life of patients, most painkillers medications are not available and those that are available are in low supply.

> *"The problem is that cancer patients are treated as if they will die and everyone forgets about them. They forget that these patients are in pain regardless of their disease."*
> (Oncologist, male, south West Bank hospital)

Moreover, palliative care is seen as "missing" in cancer care in the West Bank.

> *"There are no clear guidelines or protocols with cancer care generally, and palliative care specifically at the MOH. There is no clear structure for palliative care, nor is there a dedicated team. There is a need for home visits, especially with the end-of-life patients and psychosocial support but there is currently no structure for it within the current system."*
> (Oncologist, male, center West Bank hospital)

In line with this, another oncologist said:

> *"There is no palliative care team or department in our hospital. Emotional and psychosocial care is not available: the oncologist does the job of talking and communicating with the patient and their family."*
> (Oncologist, male, south West Bank hospital)

Psychological support

The need for professional psychological support was deemed very important by most interviewees, even though they acknowledged receiving support from their families. Some of the reported psychological impacts due to the illness include nervousness, bad temper, feeling incapacitated, and overthinking. Many patients highlighted the importance of high morale and good psychological wellbeing as a key part of their treatment.

> *"I wish they would sit with me and tell me what is happening… or what you can do… such things are a must, but here, none."*
> (Interview 20, female, 57 years old, rural, center WB)

As the quote above shows, many patients noted that this aspect of care was largely missing. While many would say that they are in good spirits in general, when we asked about their care needs, they would frequently mention the need for psychological support.

Discussion

This study describes the difficulties that patients with advanced-stage cancer experience in accessing oncology services in the West Bank from the point of seeking a diagnosis. The findings reveal that cancer patients encounter multiple barriers in accessing oncology services throughout their treatment journey, underlining difficulties Palestinians in general face in accessing health care (16–18). Some of these challenges are shared with other conflict-affected areas (5, 7), while others are specifically related to prolonged Israeli military occupation and its effects on the capacity of the Palestinian health system to deliver comprehensive cancer care.

One of the significant challenges encountered by cancer patients is the unpredictable, lengthy process of obtaining Israeli permits to access cancer care in East-Jerusalem not available on the West Bank. The delays or refusal are consistently confirmed in World Health Organization reports for patients seeking Israeli permits, including cancer patients (20, 22). The refusal or delay of Israeli permits results in delays in diagnosis and treatment, negatively impacting health outcomes of cancer patients (17, 20). Additionally, interruption of cancer treatment, related to delays from the Israeli side in providing chemotherapy-related drugs and diagnostic materials are major blockages in the cancer pathway. Interruption of chemotherapy treatment is an ongoing challenges for cancer care in the oPt (17, 19) and experienced in other conflict-affected areas (7).

Cancer patients face challenges in accessing advanced diagnostic services such as nuclear scans, CT scans, and MRIs, which are unavailable at governmental hospitals, not functioning, or inaccurate in some cases. Earlier studies were in line with these findings which confirmed that nuclear medicine and PET scans are not available at

Palestinian governmental hospitals and patients are referred to East Jerusalem or Israel to obtain such services (12, 13, 19).

Moreover, our study showed that cancer patients face barriers in accessing surgical oncology services. These barriers included a lack of guidance to the patients on where to seek their surgeries. This sometimes leads patients to go to multiple hospitals in search of the needed surgery as a result of not being provided by the appropriate referral. Our finding is consistent with earlier research results stating that the oPt lacks specialized centers in oncology surgery, and the existing surgery services are not well-structured (13).

Additional referral barriers in accessing diagnostic and surgery services were also reported by the participants. Problems included delays in getting referral approval from the Palestinian Ministry of Health which negatively affected the health condition of some patients. Timely approval for cancer care referrals is a persisting challenge (17, 25, 26). While some participants waited for the referral approval, others were forced to receive treatment at their own expense which added a financial burden on the patients and their families. Out-of-pocket costs for cancer patients and their caregivers in low and middle-income countries account for an amount that equals 42 % of their annual income (27).

Another significant issue is the consistent shortage of medications at the governmental hospitals that patients are required to take home for their treatment. This is a persistent issue (12, 28). Specifically, the lack of pain medications highlights the absence of a palliative care program in cancer care, confirmed by the oncologists participating in the study. Palliative care is an essential health service within Universal Health Coverage (29) and is cost effective (30). Yet, people with advanced cancer in conflict- affected areas are especially in need of palliative care as they report compounded trauma, that of living in wars and conflicts and that of enduring the symptoms and treatments of their cancers at the same time (29, 31). Indeed, it is concerning to note the absence of palliative care and the distress due to uncontrolled pain among cancer patients in the West Bank.

Concerning other deficiencies in health services, the oncologists' lack of communication and limited consultation time with patients was one of the important problems noted by patients. In accordance with our findings, an Indian study found that almost half of the studied cancer patients required information related to their treatment without being able to receive such information (32).

The poor infrastructure of the treatment facilities was also among the cancer patients' concerns. Prior studies have noted that health system challenges for cancer patients might be partially explained by the Israeli military occupation and economic crisis of the Palestinian Authority in financing the health care system in general, including cancer care (19).

In summary, barriers to accessing cancer care in the West Bank are structural and due to the constraints imposed by the Israeli military occupation, while some are related to the Palestinian health system's shortage of resources which relate to living under Israeli occupation as well as failures in adequate management of the healthcare systems. Patients called for significant improvements in services, including comprehensive diagnostic services; obtaining timely referrals to services; and providing all oncology pathway services in the same place. Other recommendations included increasing numbers of health staff (especially oncologists and nurses); having a consistent supply of medications; expanding inpatient wards and making improvements in infrastructure and cleanliness.

Finally, cancer patients accessing care in chronic conflict-affected settings (such as is the case of the oPt) will continue to suffer if the root causes of these access constraints persist. Palestinians need to obtain their right to health, which means that in the absence of freedom, justice and a fair political solution to the Palestine-Israeli conflict, a fragmented and underdeveloped health system will not be able to sustain cancer services nor guarantee their adequacy.

Data availability statement

The datasets presented in this article are not readily available. Requests to access the datasets should be directed to SM, smitwalli@birzeit.edu.

Ethics statement

Ethical approval was granted by the Research Ethics Committee at the Institute of Community and Public Health, Birzeit University (ref number 2020(3 – 1) and at Kings College London (ref number HR-20/21-18199). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RG, WH, and SM conceptualized the research idea, and designed the study. RH read and commented on the draft paper. SM conducted the field work, analyzed transcripts and wrote the draft paper, and finalized the article. WH participated in the field work and writing of the draft paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The state of cancer research in fragile and conflict-affected settings in the Middle East and North Africa Region: A bibliometric analysis

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Background: Cancer represents a disproportionate burden in LMICs, especially conflict-affected countries in the MENA region. Research output on cancer fails to match the growing burden in the region. This bibliometric study aims to examine the status and trends of cancer research in fragile and conflict-affected settings in the MENA region from 2000 to 2021, while also incorporating economic and demographic indicators as additional factors of analysis.

Methods: The Web of Science databases were searched for publications related to cancer research in Iraq, Lebanon, Libya, Palestine, Syria, and Yemen from January 1, 2000, to December 31, 2021. The retrieved publications were screened based on preset eligibility criteria and the final list was analyzed using the Bibliometrix Package in R to generate the annual scientific production and citations, journals, institutions, authors, collaborations, keywords, and title co-occurrence. Each country's annual scientific production was analyzed against its annual GDP per capita.

Results: A total of 4,280 documents met the inclusion criteria in this research. The annual number of publications revealed a significant increase over the past 20 years. These publications were mostly published in international journals that had impact factors rated in the 3rd or 4th quartiles. The overall contribution of researchers from Fragile and Conflict-Affected Settings (FCS) to cancer research was 6.5% of the MENA cancer research productivity, despite comprising around 23% of the total MENA region's population. Lebanon had the highest publication productivity at the country level, followed by Iraq and Syria. GDP per capita was not significantly correlated with cancer research across the countries under investigation. At the institutional level, the American University of Beirut was the most prolific institution and had the highest number of collaborations and the widest range of cooperative partners. Most first authors were male researchers.

There is an interest in cancer expression, prevalence, diagnosis, and management in terms of commonly researched topics.

Conclusion: This study underscores the need for a concerted effort to improve cancer research outcomes in FCS, which can be achieved through targeted research, increased investment in research infrastructure and capacity-building initiatives, and greater regional and global collaboration.

KEYWORDS

cancer research, bibliometric, conflict settings, Arab world, MENA region

Introduction

The global burden of cancer is disproportionately higher in low- and middle-income countries (LMICs) compared to high-income countries (1–4). It is speculated that by 2035, two-thirds of the world's cancer cases will arise in LMICs, which include many countries in the Middle East and North Africa (MENA) region (5). To address this burden, it is important to establish regional and national cancer control plans, strengthen cancer surveillance systems, build clinical and research capacity, and promote cancer research (2). Locally driven and high-quality cancer research is essential to understand the challenges and barriers to the cancer care continuum and address them in effective, sustainable, and context-specific approaches.

The MENA region's capacity to conduct research is limited compared to other regions. The recurrent and endemic nature of conflicts and political and economic instability in many MENA countries has resulted in numerous systemic challenges to healthcare research, including cancer research. Currently, ongoing conflicts in Iraq, Libya, Palestine, Yemen, and Syria, and the resultant mass displacement, have led to the worst humanitarian crisis since World War II (6). In 2021, 18% of all forcibly displaced people worldwide originated from the MENA region (7). With its fragile health system, Lebanon currently hosts the world's highest number of refugees per capita following the Syrian crisis (8). Regional conflicts and crises, as well as Lebanon's civil war, Israel's Second Lebanon War, and protracted internal struggle have all had an impact on its politics and socioeconomic situation (9).

Although health research in active conflict settings is crucial, it is often deprioritized as the focus shifts to resolving conflict, delivering humanitarian assistance, and managing forced displacement (10). Insufficient spending on research, poor research and health infrastructure, fragmented health systems with underdeveloped disease registries, and limited collaboration with the global research community undermine the capacity to conduct locally relevant health research in these contexts, particularly cancer research (2, 3, 11). In addition, the lack of research culture, which can be attributed to cultural norms in some countries, negatively impacts cancer research despite its importance and relevance to local challenges (12, 13). Our knowledge of the causes of cancer, our ability to control it, and how it is impacted by conflict would advance considerably if the clinical, basic, environmental, lifestyle and ethnic determinants of cancer were thoroughly investigated (14).

Despite the challenges mentioned above, the MENA region has been actively contributing to cancer research over the past two decades (15–18). However, and to the best of our knowledge, studies using bibliometric methods to analyze the knowledge output and trends of research on cancer in Fragile and Conflict-Affected Settings (FCS) in the MENA region are limited. Against this backdrop, we conducted a bibliometric study of published cancer research between 2000 and 2021 in FCS in the MENA region: Iraq, Lebanon, Libya, Palestine, Syria and Yemen. Our study investigated the trend of publications over the study period and the characteristics of published research, including the authors' institutional affiliations and collaborative landscape. Demographic and economic indicators were also considered as we compared research output across the study countries.

Methods

Source of data

Scientific publications focusing on cancer research in Fragile and Conflict-Affected Settings (FCS) in the MENA region, as defined by the World Bank (19) were searched in the Web of Science (WoS) database on June 30, 2022. WoS is the most relevant, prominent, extensive, and reliable database for literature retrieval and analysis (20, 21). Data on the study countries' sociodemographic and economic indicators were retrieved from the World Bank's DataBank (22).

Search strategy

A search strategy (Supplemental Table 1) was developed using an extensive list of cancer-related keywords compiled from previous studies, reviews, practical reporting, and meta-analyses to search for titles, and abstracts listed under WoS oncology categories and published in oncology-specific journals. Then, the six FCS (Iraq, Lebanon, Libya, Palestine, Syria, and Yemen) were entered as country affiliations. Four indices were used: Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts and Humanities Citation Index (A&HCI), and Emerging Sources Citation Index (ESCI).

Inclusion criteria

Cancer research publications with at least one of the authors from FCS in the MENA region were included. Publications that did not primarily relate to cancer were excluded. The period of the index date was from January 1, 2000, to December 31, 2021, with the language restricted to English. The document types included were original articles, article data, and article early access. All other types of articles including review articles, case reports, book chapters, and letters to the editor were excluded (Supplemental Figure 1).

Data management and selection process

Full metadata of the articles identified was downloaded in text format and then imported into an excel file. Two reviewers independently screened the titles and abstracts of retrieved publications and discrepancies were resolved by discussion with a third reviewer. A full-text review of all included references was also conducted independently by the two reviewers. A second full-text review was performed on the discrepant articles to make the final decision for inclusion/exclusion.

Data extraction and analysis

The analysis of the final list of publications was completed using the Bibliometrix Package (http://www.bibliometrix.org/), which is an R statistical software package for comprehensive science mapping analysis (23). The raw data exported from R was transformed into graphic and tabular using the Flourish software (24) to generate the annual scientific production and citations, journals, count, affiliations, corresponding authors' countries, the gender distribution of authors by countries, collaboration patterns, universities' collaborations, and author's keywords and title co-occurrence. The gender of the authors was determined using the gender API (gender-api.com), which uses the author's first name and country of origin as inputs. Authors with no scores or scores <90 and first names shorter than 2 letters were filtered out. The impact factor (IF) and quartiles (Q) of journals were derived from the Journal Citation Reports (JCR; Web of Knowledge) in October 2022 (25).

Ethical approval

The study did not require the submission of an IRB application since the researchers used publicly available information and did not involve any interactions with human participants.

Statistical methods

Data from *WoS* were exported to *Excel* and then to *PRISM version 9* for analysis, where relevant. Categorical data were expressed as percentages. Data on the study countries' growth domestic expenditure on research and development could not be obtained from online public resources. Therefore, we used the countries' growth domestic product (GDP) in the current US$ as a proxy for their economic positions and analyzed the trend of publications from each country against its annual GDP per capita, as reported in the World Bank's public databases (26). We performed linear regression analysis to assess the statistical significance of the increasing trend in annual publications between 2000 and 2021. The model included the number of publications each year (as the dependent variable) and the year (as the independent variable). We performed a similar analysis to assess any statistically significant correlation between each country's GDP per capita and yearly publications over the study period. $P<0.05$ was considered to indicate statistical significance in both models.

Results

Publications analysis

Our search for cancer research publications in FCS countries in the MENA region between 2000 and 2021 yielded 5,064 publications, out of which 4,280 were included, based on the eligibility criteria (Supplemental Figure 1). The annual number of publications significantly increased ($P<0.0001$) from 16 in 2000 to 853 in 2021 (Figure 1). The data indicated an inconsistent rising trend in the number of publications, with an average annual change rate of approximately 22% over 13 years (2000-2013). From 2013 to 2021, the number of publications increased steadily, reaching a peak in 2021 (Supplemental Figure 2). The overall contribution of authors from FCS to cancer research productivity in the MENA was 6.5% (data not shown). Notably, the average annual citations per publication significantly increased from 2000 to 2021 ($P<0.0002$), as presented in Figure 2. The yearly average article citation ranged from 1.51 and 3.19 between 2000 and 2014, with a sharp increase to 6.86 citations in 2015 and a peak of to 8.25 citations per publication in 2017, followed by a decline to around 2.12 citations in 2020 (Figure 2). On average, the total number of citations per publication was around 18.1 (Supplemental Table 2).

Analysis of sources

The retrieved documents were published in 1,514 sources, including journals and books among others. The *International Journal of Surgery Case Reports*, with an impact factor (IF) of 0.690 in 2021, was the most used source for publication of cancer research in FCS (53 publications; 1.23%). This was followed by *PLOS One* (IF 3.752; 48 publications; 1.12%), the *Saudi Medical Journal* (IF 1.422; 45 publications, 1.05%), *Scientific Reports* (IF

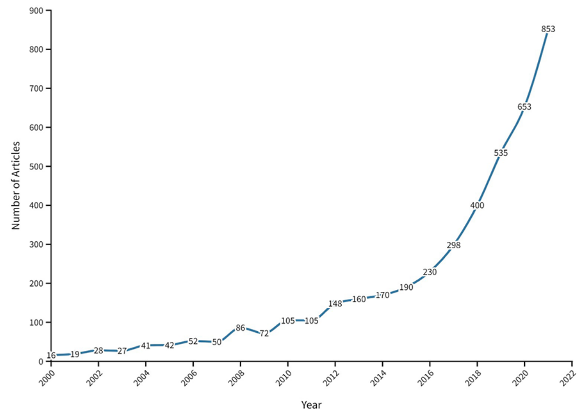

FIGURE 1
Annual number of cancer research publications in FCS in the MENA region from 2000 to 2021.

4.996; 44 publications; 1.02%), and the *Iraqi Journal of Hematology* (37 publications; 0.86%) (Figure 3, Supplemental Table 3). In our study, the top 20 sources published 14.6% (n=626) of the research manuscripts, 41.21% of which were Q2 journals. Only one Q1 journal, the journal of *Cancer*, had a few publications (n=26, 4.15%). Among the top 20 sources, four were based in the MENA region, and the journal with the most publications focus on case reports.

Analysis of countries and institutions

Lebanon was the leading country in terms of the number of publications on cancer research, with a total of 3,966 publications and 12,509 citations, and an average article citation of 11.86. Iraq followed with 2,574 (2,888 citations, average article citations of 3.55), then Syria with 602 (825 citations, average article citations 4.10), Yemen 389 (672 citations, average article citations 10.03), Palestine 358, and Libya 341 publications (818 citations, average article citations 12.21) (Figure 4).

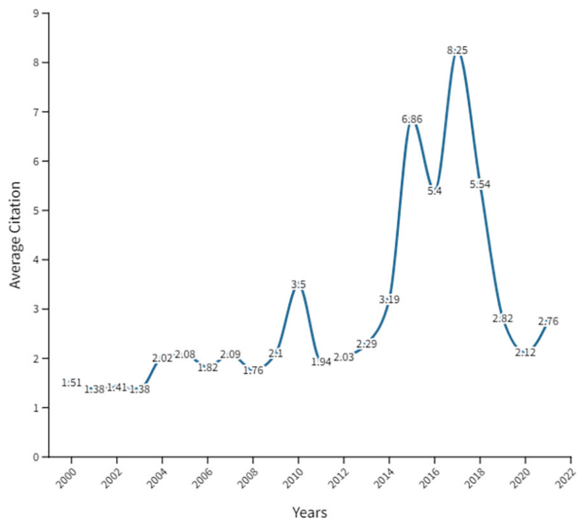

FIGURE 2
The average annual citations of cancer research publications in FCS in the MENA region from 2000 to 2021.

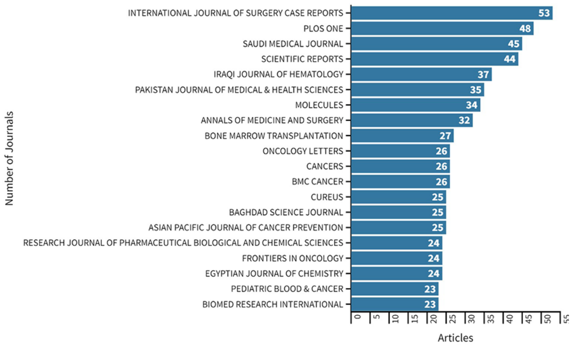

FIGURE 3
Top 20 most relevant sources by the number of publications on cancer research in FCS in the MENA region from 2000 to 2021.

The GDP per capita in the six countries displayed a high level of fluctuation between 2000 and 2021. Nevertheless, published cancer research steadily increased over the same period. Lebanon had the second-highest median GDP per capita ($6,733) after Libya ($8,590), followed by Syria ($5,157), Iraq ($4,610), Palestine ($2,516), and Yemen ($943) (Supplemental Figure 3). There was no significant correlation between the median GDPs per capita and scientific publications on cancer for the six countries collectively or any of the individual countries. As an example, Lebanon, the highest contributor among the study countries, had a correlation coefficient of –0.01 (p value= 0.86) between the number of yearly publications (dependent variable) and annual GDP per capita (independent variable) between 2000 and 2021.

The retrieved publications were published by authors from 6,816 different institutions. The top 20 institutions, selected and listed based on the number of publications, included the American University of Beirut (Lebanon; 1,953), followed by the Lebanese University (Lebanon; 422), the Saint Joseph University of Beirut

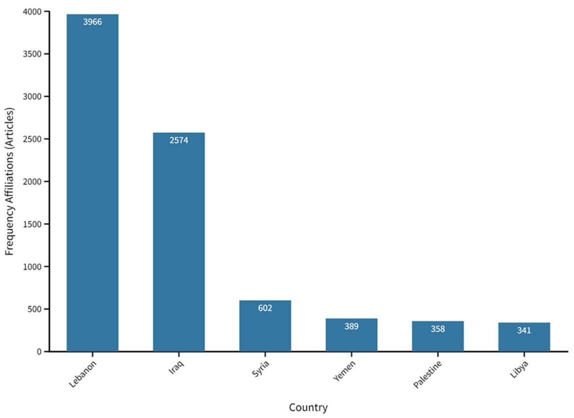

FIGURE 4
Country production from 2000 to 2021.

(Lebanon; 295), the University of Baghdad (Iraq; 274), and the Lebanese American University (Lebanon; 217) (Figure 5). Four of the top five institutions are from Lebanon.

Analysis of authors and gender distribution

From 2000 to 2021, there were a total of 29,246 authors who contributed to the 4,280 publications on cancer research in FCS, with an average of 6.83 authors per document (Supplementary Table 1). There were 100 (0.3%) single-authored publications and 29,146 (99.7%) multi-authored publications. The top corresponding authors from FCS who published on cancer research were from Lebanon, Iraq, and Syria. Most of their publications (62.5%, 82.7%, and 72.6%, respectively) were single-country publications (SCP) (Figure 6). Around 37% of the corresponding authors were neither from MENA nor FCS (data not shown). A sizeable portion of the first authors (n=1,838 42.9%) of the dataset were from 71 non-FCS countries, mainly the USA, France, England, Saudi Arabia, and Malaysia (Figure 7A). Among the first authors from FCS (n=2,442, 57.1%), 67.6% (n=1,652) were men and 28.8% (n=703) were women, while the gender of the rest was unknown (n=87, 3.6%) (Figure 7B). The female-to-male gender ratio was below 3 in only Lebanon and Libya (Figure 7C).

Analysis of collaborations

To further examine the collaborative landscape of cancer research in FCS in the MENA region, an analysis was conducted on the countries' partnerships. Three main collaboration clusters were recognized in Figure 8. The first cluster consisted of Lebanon, the USA, France, Spain, Italy, Canada, Germany, and Syria with Lebanon demonstrating strong collaborations with USA and France. The second cluster included Iraq, Iran, Malaysia, Finland, China, India, Australia, Ethiopia, and the United Kingdom with nonspecific linkages. The third cluster included Saudi Arabia, with its main collaborations being with Egypt and Yemen. These clusters spotlight the cooperative research partnership on cancer in FCS.

Authors' keywords and co-occurrences

In general, keywords convey the major idea and subject matter of an article, while their co-occurrence indicates their degree of association and relevance. This study identified around 9,560 keywords, with 162 high-frequency keywords, occurring ≥10 times and forming two clusters, namely "cancer" and "expression" (Figure 9). The top-ranked keywords were "breast cancer", "cancer", "apoptosis" and "cytotoxicity" (Supplementary

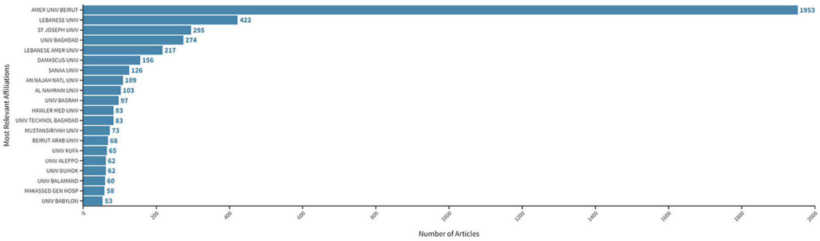

FIGURE 5
Most relevant affiliations per article on cancer research in FCS in the MENA region from 2000 to 2021. From top to bottom: American University of Beirut, Lebanese University, Saint Joseph University, University of Baghdad, Lebanese American University, Damascus University, Sanaa University, An-Najah National University, Al Nahrain University, University of Basra, Hawler Medical University, University of technology Baghdad, Mustansiriyah University, Beirut Arab University, University of Kufa, University of Aleppo, University of Duhok, University of Balamand, Makassed general hospital, University of Babylon.

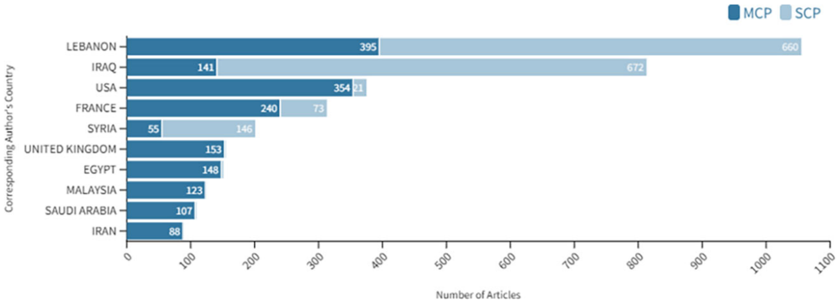

FIGURE 6
Top corresponding authors' countries on cancer research in FCS countries in the MENA region from 2000 to 2021. SCP stands for single-country publication. MCP stands for multiple-country publication.

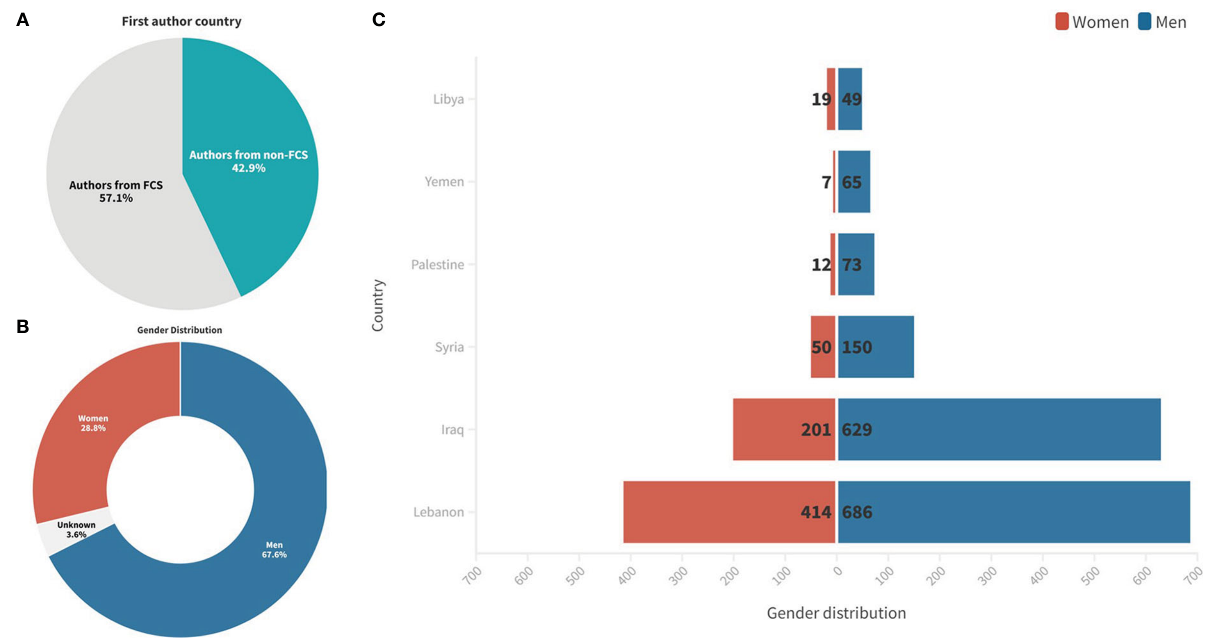

FIGURE 7
(A) Percentage of first authors from FCS compared to non-FCS. Gender distribution of first authors **(B)** and **(C)** by FCS.

Figure 4) occurring 329, 183, 156, and 105 times, respectively (data not shown). The first cluster, consisting of interconnected keywords related to "expression", focused on basic research, and included co-occurring keywords such as apoptosis, growth, cells, activation, proliferation, mechanisms, and others. The second cluster contained interconnected keywords related to "cancer" and "apoptosis" and included keywords related to prevalence, diagnosis, and management such as carcinoma, therapy, chemotherapy, risk, diagnosis, epidemiology, management, and others.

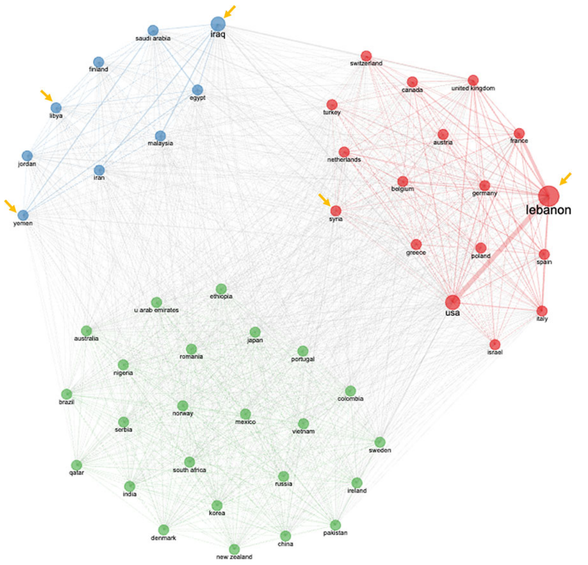

FIGURE 8
Country collaboration on cancer research in FCS in the MENA region from 2000 to 2021. The dimensions of the rectangles symbolize the number of cooperative partners, while the font size of the countries shows the number of their collaborations. Additionally, the closeness of the countries' partnership is reflected by the thickness of the lines. Arrows indicate the FCS countries included in this study.

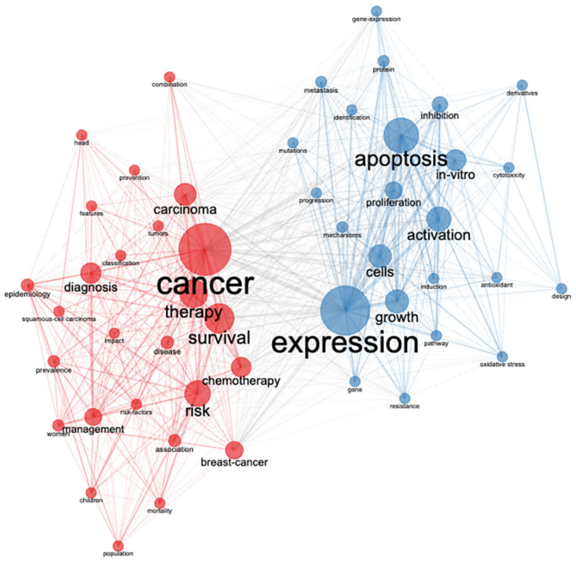

FIGURE 9
Co-occurrence network of most frequently used author keywords on cancer research in FCS in the MENA region from 2000 to 2021. The rectangle size reflects the total number of highly cited articles, while the color and thickness of the lines reflect the link clustering and strength, respectively.

Discussion

Armed conflicts and insurgencies have severely undermined the research capabilities of several MENA countries. Ranging from chronic underfinancing and poor infrastructure to deficient research culture (15, 18, 27), the challenges health researchers face in fragile and conflict-affected settings are numerous (11, 28). Aiming to identify opportunities for improvement, our study aimed to map out published cancer research and highlight the characteristics of published research across 6 countries affected by conflict in the MENA region.

The study found that there has been a consistent rise in the total number of cancer publications in the six FCS investigated from 2000 to 2021. This trend may reflect the growing concern about cancer as a major public health problem. Nevertheless, this increase is relatively small compared to other countries in the region and worldwide. Additionally, the annual citation rate and regional contribution are relatively low, suggesting a diminished capacity to produce quality research. This could be because researchers lack motivation or support from their institutions in most of these countries. Most publications focused on cancer expression, prevalence, diagnosis, and management. Therefore, targeted research on these topics could help to fill gaps in knowledge and provide insights that can be used to inform cancer control strategies and improve patient outcomes in FCS. Importantly, despite being home to 23% of the total MENA region's population and constituting 10% of the region's GDP in current US dollars in 2020 (the latest year reported in the World Bank's database), the six countries represented only around 6.5% of the MENA region's research productivity. The studies that were conducted were often collaborative, with the majority involving non-MENA countries as indicated by the countries of the first and last authors. Furthermore, the shortage of funding for authors and the high publication costs could negatively impact research productivity, particularly in conflict-affected settings where resources are already limited. Overall, this highlights the urgent need for greater investment in research infrastructure and capacity-building initiatives, and for funding agencies to provide more support for cancer research in FCS.

The need for more robust study designs that can provide higher quality evidence is highlighted by the high number of case reports published in the *International Journal of Surgery Case Reports*, a journal focused on case reports. The research dataset was mostly published in international journals that had impact factors rated in the 3rd or 4th quartiles, except for one journal (the *cancer* journal, 1st quartile), which may reflect the compromised quality and capacity of research being conducted. Furthermore, four of the top 20 publication outlets were journals from the MENA region i.e., Saudi Arabia, Iraq, and Egypt. These findings align with a previous study showing that the most publications (40%) from the Arab world in the last decade appeared in Q4 journals with only a few publications (0.7%) in the highest quartile score (Q1) journals (26). Increasing investment in research infrastructure and capacity-building initiatives is crucial to improve the quality of scientific material produced in the FCS. Additionally, proper acknowledgement of the contributions of authors from LMICs in the authors' list is essential, as undervaluing or overlooking their efforts can perpetuate disparities in research recognition and funding.

The majority of publications in cancer research came from institutions in Lebanon, Iraq, and Syria with Lebanon being the most productive country over the analysis period. Surprisingly, our study found no significant correlation between a country's GDP per capita and its cancer research productivity. Despite having the second-highest GDP per capita, Lebanon exceeded other countries in terms of published cancer research which may be due to active collaboration with foreign researchers and the availability of research infrastructure provided by academic medical centers in Lebanon with strong ties to international academic institutions. These centers, such as the American University of Beirut Medical Center and Hotel Dieu de France, are affiliated with renowned private universities, like the American University of Beirut (AUB) and Université St-Joseph (USJ) (29, 30) that rely on international funding schemes to support their research activities (31, 32). Increasing collaboration and knowledge-sharing across institutions and countries in the region could be an effective strategy to address the gaps in cancer research. The high research productivity in Lebanon may also be due to the country's physician density, which was 2.1 physicians per 10,000 people in 2018, compared to other countries like Iraq, Libya, Syria, and the West Bank and Gaza (World Bank). It is worth noting that private universities represent over 90% of the higher education institutions in Lebanon (32), but more research is needed to effectively evaluate the impact of private ownership on academic institutions' scientific productivity.

Our results reveal that there is a significant gender disparity in cancer research in fragile and conflict-affected settings in the MENA region, with around 70% of the first authors being men. This underrepresentation of women in cancer research is consistent with the UNESCO Institute for Statistics (UIS) data from 107 countries, covering the years 2015-2018, in which women made up 33.3% of researchers globally (33). Regionally, in non-conflict settings, Tunisia is the only country where women researchers outnumber men (56% of Tunisian researchers are women), while some countries have made notable strides towards gender equity in research in a short period, including Algeria (from 35% in 2005 to 47% in 2017), Egypt (from 36% in 2007 to 46% in 2018), and Kuwait (from 23% in 2008 to 53% in 2018) (34). Importantly, gender stereotypes and biases, family responsibilities, unequal access to funding, unconscious bias in hiring and promotion, workplace culture, discrimination, and harassment maybe impact women's representation in research (35), which is further compounded in conflict-affected settings due to political instability, security insurgencies, and weak women-empowering policies (36, 37). Addressing these issues will require policymakers' attention, and promoting gender equity in cancer research, such as supporting female researchers and addressing biases in the research process, may help to enhance the quality and diversity of research in the region and globally.

The study highlights some gaps and limitations that need to be addressed in future research. The search strategy was restricted to the WoS database and excluded articles written in Arabic which may have led to an underestimation of the total number of published documents.

Another limitation is the restriction to the Web of Science database, which excludes other data sources such as Scopus, Google Scholar, Index Medicus, or Microsoft Academic Search, which may have led to an incomplete view of the research output in FCS. Additionally, bibliometric studies concentrate on the research publications' methodology and designs rather than the importance of their findings. Due to the vast amount and span of articles analyzed, it was not possible to analyze the impact factor and citations of each paper. Finally, due to concurrent conflicts and publication barriers, the study results may not accurately reflect the scope and goal of research in some FCS. Therefore, future research should account for the local context and challenges faced by researchers in conflict-affected regions.

Conclusion

Despite an increase in cancer research in conflict settings it still falls behind other countries in the MENA region and globally. It is crucial to identify the barriers and challenges to cancer research in conflict settings, expand funding, increased investment in research infrastructure and capacity-building initiatives, and encourage collaborative research to improve both the quantity and quality of research output. This study provides an in-depth understanding of cancer research output in MENA region conflict settings, which can inform the development of evidence-based policies and interventions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

ZS contributed to the conception and design of the study, and data analysis. YY and MH contributed to the data acquisition and analysis, TF and ME did the analysis and interpretation of data. LJ did the graphics. TF, ME, and MK drafted the manuscript. ZS, DM, AT critically revised and oversaw the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1083836/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) bibliometric study flowchart.

SUPPLEMENTARY FIGURE 2
The percentage change in the number of cancer research publications in FCS in the MENA region from 2000 to 2021.

SUPPLEMENTARY FIGURE 3
The number of publications per 100K people on cancer research in FCS per country and the median GDP per capita (current US$) between 2000 to 2021.

SUPPLEMENTARY FIGURE 4
Word cloud for top keywords of cancer research in FCS in the MENA region from 2000 to 2021. The importance of these single words is reflected by the font size or color.

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The burden and scope of childhood cancer in displaced patients in Jordan: The King Hussein Cancer Center and Foundation Experience

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Introduction: Jordan hosts one of the highest numbers of refugees per capita in the world, with the Syrian crisis leading to an influx of displaced persons to the already vulnerable population. However, limited resources and a lack of cancer-care strategies have made it difficult for refugees in Jordan to access quality cancer care. The King Hussein Cancer Center (KHCC) and Foundation (KHCF) have played a pivotal role in providing financial and medical support for displaced children with cancer, treating 968 non-Jordanian children with cancer between 2011-2022, with a median age of 6 years. Of these, 84% were fully funded by KHCF, and nationalities included Syrians (29%), Palestinians (26%), Iraqis (23%), and Yemenis (17%). Cancer diagnoses included solid tumors (44%), leukemia (23%), lymphoma (13%), bone sarcomas (9.5%), and retinoblastoma (9.1%). The median cost of treatment was JOD 18,000 (USD 25,352), with a total estimated cost of JOD 23.8 million (USD 33.5 million). More recently, in partnership with St. Jude Children's Research Hospital (SJCRH), two successive humanitarian funds (HF) were established to optimize cancer care for displaced children in Jordan.

Results: Between February 2018 and September 2022, 51 children were fully treated on KHCC-SJCRH-HF, with a median age of 6 years and nationalities including Syrians (80%), Iraqis (6%), and Yemenis (8%). The most common cancer diagnoses were leukemia (41%), lymphoma (25%), solid tumors (24%), retinoblastoma (6%), and brain tumors (4%). Of these, 94% are alive and 51% are still receiving coverage. The median coverage for patients was JOD 21,808 (USD 30,715), and the total cost of treatment on KHCC/KHCF-SJCRH/American Lebanese Syrian-Associated Charities HF1 and HF2 was JOD 1.44 million (USD 1.97 million) and JOD 1.18 million (USD 1.67 million), respectively.

Conclusion: This experience highlights the high burden of displaced children with cancer in Jordan, and the importance of local foundations like KHCC/KHCF and partnerships with international partners like SJCRH in providing lifesaving humanitarian initiatives and quality cancer care. Innovative cancer-care delivery models and sustainable financing are essential to ensure continuous coverage and access to cancer care for displaced persons in Jordan.

KEYWORDS

Syria, Jordan, refugees, humanitarian response, childhood cancer, displaced children, access to health care, public health

Introduction

Refugees constitute a population with unique vulnerabilities, and addressing their needs requires extensive support and places substantial burdens on hosting countries and the global community. Over the past decades, the number of refugees seeking refuge has been on a steady increase (1). Conflicts in countries such as Iraq, Palestine, and Yemen have led to increased displacement in urban areas. In 2011, the Syrian crisis had a profound impact on neighboring countries, many of which were unprepared for the scale of the situation (2).

Jordan, a country with a population of 11 million located in the Middle East and bordered by Syria to the north, has extensive experience in handling refugee crises and has well-established mechanisms in place to maintain the wellbeing of refugees within the country. Although considered by the World Bank as an upper-middle-income country, 13% of the population lives below the poverty threshold (3). Jordan boasts a modernized healthcare system, with a total expenditure per capita for healthcare of 334 US$ (2019), constituting approximately 7.58% of the gross domestic product (1, 3).

Despite its struggling economy, depleted resources, security threats, and enormous sociopolitical burdens, Jordan hosts the second-highest refugee population worldwide, with 89 refugees per 1,000 inhabitants. According to the United Nations High Commissioner for Refugees (UNHCR), 1 in 14 people in Jordan is a refugee (4). Jordan hosts approximately 1.4 million refugees who have escaped conflicts in Syria since 2011. The most recent UNHCR data from 2022 show that Jordan has 762,877 refugees, with 88.7% being Syrians, 8.6% Iraqis, 1.7% Yemenis, and 0.7% Sudanis (5). The actual number of Syrians in Jordan is still debated as there is a persistent gap between the registered number by the UNHCR and the number reported by National Census reports (6). Additionally, many Syrian refugees remain unregistered through the UNHCR. Currently, 82.4% of displaced Syrians reside in the municipal areas of Jordan (5). Additionally, according to the UNHCR, there are approximately 2,242,579 registered Palestinian refugees, in addition to 750,000 to 1 million registered Iraqis who have fled to Jordan before the arrival of Syrian refugees (6), many of whom continue to have restricted access to vital needs, primarily healthcare (1).

Humanitarian assistance focuses on traditional priorities such as the provision of healthcare services to address communicable diseases (7). However, the burden of non-communicable diseases (NCDs) among refugee populations is growing (8), representing substantial emerging challenges in humanitarian responses in both refugee and host communities. The increasing incidence of NCDs among refugee and host communities presents challenges to the provision of quality healthcare (8) as they require more sophisticated diagnostic and management capacities than many communicable diseases. Furthermore, delays in diagnosis and therapy and avoidable complications can result from a lack of access to diagnostic and therapeutic modalities for NCDs (9). The global health and humanitarian community's response to the increasing incidence of NCDs, including cancer, among millions of refugees fleeing to host countries, has been relatively slow (7). Cancer represents a significant health challenge in refugees and host communities (10, 11) as it is a main cause of mortality, and cancer care delivery requires vigorous and wide-ranging health systems delivering multidisciplinary diagnostic and therapeutic interventions (7, 12). Additionally, for refugees, cancer care necessitates a long-term commitment to the medical system (13).

Jordan's healthcare system is a mix of public and private healthcare providers, with the Ministry of Health responsible for regulating the public healthcare sector (14). Public healthcare is available to all Jordanian citizens and residents, while private healthcare providers offer high-quality medical care for a fee. The government provides free cancer treatment to all Jordanian citizens, regardless of their socioeconomic status or insurance coverage. The King Hussein Cancer Center (KHCC) in Amman is a world-renowned cancer treatment center that provides state-of-the-art cancer care to patients from Jordan and around the world.

We describe the impact and feasibility of collaborative efforts, the prioritization approach, the strategies of sustenance, and the results of quality cancer care among displaced children treated at the KHCC. Our report reviews our experience in Jordan and gives a deeper understanding into the extent of the humanitarian refugee crisis, pertaining to childhood cancer. It also underscores the need for accurate cancer registration, which will assist in producing the estimates of fiscal resources required to provide quality cancer care and informing humanitarian funding planning and resource allocation. It also highlights the need for upscaling the local and humanitarian efforts to integrate cancer care in their planning.

Methodology

The KHCC has a robust department of pediatrics that provides fully funded cancer care for Jordanian children. However, since the start of the Syrian crisis in 2011, there has been an influx of displaced cancer patients, particularly Syrian children, seeking treatment at the KHCC. To address the financial needs of these patients, the KHCC and King Hussein Cancer Foundation (KHCF) have established several funds to provide financial assistance for cancer care for displaced children in Jordan. These funds can be applied for by families and by referring physicians.

King Hussein Cancer Center/King Hussein Cancer Foundation goodwill funds

Goodwill funds (GWFs) were established to provide financial assistance to a considerable number of displaced children with cancer annually. These funds cover the costs of treatment, transportation, accommodations, and food coupons. However, the needs of these patients are ongoing including financial constraints, the disruptions of therapy, and the lack of social support, leaving many displaced patients left behind. The patients eligible for enrollment in these funds are all nationalities of children under 18 years old who are newly diagnosed with cancer and have not received any prior treatment. These funds, however, provide treatment coverage for relapsed/refractory cases ranging from advanced therapy to palliative care. Medical care provided for displaced children at the KHCC is comparable to those applied to Jordanian children. Since the start of the Syrian crisis, the GWFs have been used to cover the costs of cancer care for displaced Syrian children treated at the KHCC through strategic partnerships and focused fundraising efforts.

King Hussein Cancer Center/King Hussein Cancer Foundation–St. Jude Children's Research Hospital/American, Lebanese Syrian associated charities humanitarian funds

In response to the growing numbers of displaced children with cancer referrals, the Humanitarian Fund (HF) was established in 2017 as a collaboration between KHCC/KHCF, St. Jude Children's Research Hospital (SJCRH), and American, Lebanese Syrian Associated Charities (ALSAC). The HF provides funding for a specified number of patients over a period of 2 years, including full treatment for some patients and partial support for others such as diagnostic work-up and surgery. To ensure the sustainability of the program and optimal utilization of funding, eligibility criteria were established, including a documented refugee status, a newly diagnosed curable cancer, commitment to treatment adherence, therapy per standard-of-care, and the provision of follow-up information. The management of this fund is overseen by a joint KHCC/KHCF-SJCRH team, and regular administrative follow-up meetings are held to track the program's development and adjust as necessary.

Overall, the KHCC and KHCF have established several funds to provide financial assistance for cancer care for displaced children in Jordan, with a focus on, but not limited to, highly curable cancer patients. These funds have been successful in providing treatment for a significant number of patients, and the collaboration with SJCRH/ALSAC has expanded the resources available for this population. However, the needs of these patients are ongoing, and many displaced patients are left behind. Further support is needed to ensure that all displaced children with cancer have access to the care they need.

Results

Patient nationalities and enrollment

Data analysis for the period from 2011 to June 2022 at a median follow-up of 77 months (0.9–146) from the KHCC hospital–based cancer registry (Supplementary Figure 1) revealed 2,779 fully registered Jordanian children with cancer (Figure 1A), with a median age of 7 years [3, 13 interquartile range (IQR)], and 968 displaced non-Jordanian children (Figure 1A) with a median age of 6 years (2,12 IQR). The date of the last follow-up was June 2022. Figure 1B describes the displaced patients' nationalities. Cancer diagnosis and staging for displaced children were similar to Jordanians and include solid tumors (n = 413; 44%), leukemia (n = 223; 23%), lymphoma (n = 119; 13%), bone sarcoma (n = 90; 9.5%), and retinoblastoma (n = 86; 9.1%) (Figure 2). The patients' underlying cancer characteristics are described in Table 1. Cancer staging for Jordanian *vs.* displaced children is described in Figure 3.

The data from KHCF records between 2011 and June 2022 indicate that 809 displaced children were fully covered for cancer treatment. These represented 84% of displaced children registered in our KHCC cancer registry, leaving 159 children who were funded through other sources. Of those covered by the KHCF, 38% (n = 307) still have active coverage, 52% (n = 423) have completed therapy, and 9.4% (n = 76) are deceased. Still, no accurate survival data, however, could be established on non-Jordanian displaced patients as a significant number could not be traced after completing therapy.

Among the non-Jordanian displaced children fully recorded on the KHCC cancer registry, 278 Syrian children were registered (Table 1). The patients' characteristics were compared to 2,779 Jordanian children who were fully treated during the same period (Table 1).

Humanitarian Funds (HF1) and (HF2)

Per the KHCC-SJCRH/ALSAC partnership, two consecutive funding programs were established to provide cancer care for displaced children including a prioritization scheme along with a continuous assessment of resource utilization. The first program (HF1) covered the costs of full cancer treatment for 27 displaced children with cancer (diagnostic evaluations and specific interventions: surgery, radiation, or chemotherapy) over a 2-year

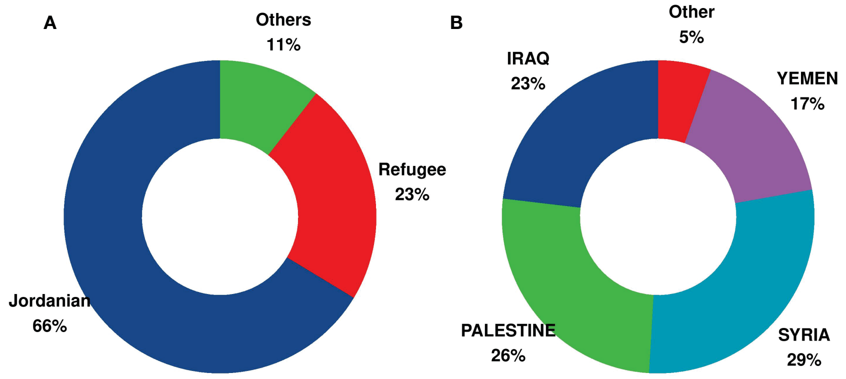

FIGURE 1
Percentage of Jordanian and non-Jordanian displaced children with cancer treated at the King Hussein Cancer Center (KHCC). **(A)** Percentage of Jordanian and non-Jordanian displaced children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022. **(B)** Nationalities of the displaced children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022.

period (2018–2020). Once the HF1 funds were consumed, the second program (HF2) was applied to cover another 2-year period (2021–2023). The HF2 program has the same eligibility and is planned steady accrual over a 2-year period; it has enrolled 24 patients to date and is still ongoing.

King Hussein Cancer Center–St. Jude Children's Research Hospital HF1 and HF2 patient characteristics

Between February 2018 and September 2022, 51 children with cancer were eligible for KHCC/KHCF-SJCH/ALSAC HFs and were diagnosed and fully treated at the KHCC. Median age, 6 years; IQR,5–9; 65% (n = 33) were males. Nationalities included Syrians (n = 41; 80%), Iraqis (n = 3; 6%), and Yemenis (n = 3; 8%). The most common cancer was leukemia (n = 21; 41%), lymphoma (n = 13; 25%), solid tumors (n = 12; 24%), retinoblastoma (n = 3; 6%) and brain tumors (n = 2; 4%). Of those 94% (n = 45) patients are alive and 51% are still on treatment and receiving coverage.

Because of funding restrictions, off-therapy screening was not sustained beyond the completion of treatment on HF1 and HF2. Further follow-up was covered by the KHCF GWFs. Treatment planning, however, was not impacted by patients' nationality, and all accrued patients received curative treatment regimens, surgical procedures, and radiation therapy. Follow-up data were collected for all patients who completed therapy or were still receiving first-line treatment on HF1 and 2.

Cost of treatment of displaced children with cancer

The median coverage (IQR) in JOD and US$ for displaced patients who were fully treated for cancer (n = 809) from KHCF records (between 2011 and June 2022) was 18,000 (5,000, 37,000)

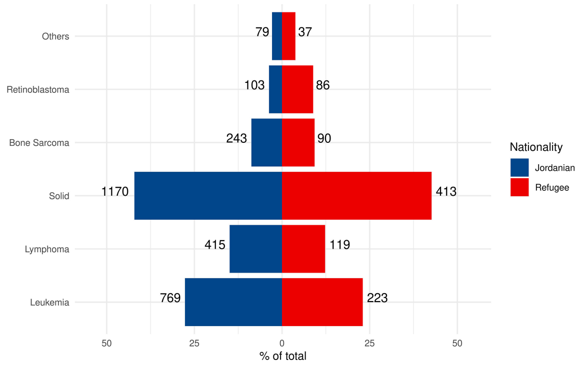

FIGURE 2
Comparison of the distribution and percentages of cancer diagnosis categories among Jordanian *vs*. non-Jordanian children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022. Column **(A)** Distribution, frequency, and percentages of childhood cancer categories among Jordanian *vs*. non-Jordanian children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022. Column **(B)** Distribution, frequency, and percentages of childhood cancer categories among Jordanian *vs*. non-Jordanian children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022.

TABLE 1 Patients' and cancer characteristics among Jordanian and non-Jordanian displaced children with cancer treated at the King Hussein Cancer Center (KHCC).

Characteristic	Jordanian, N (%) N = 2,779[1]	Non-Jordanian Displaced Children N (%) N = 968[1]
Age (years)	7.0 (3.0, 13.0)	6.0 (2.0,12.0)
Gender		
Male	1,532 (55)	555 (57)
Female	1,247 (45)	413 (43)
Displaced Nationalities		
Syrians	———	278 (29)
Palestinians		251 (26)
Iraqi		224 (23)
Yemeni		162 (17)
Others		53 (5)
Cancer Classification		
Bone sarcomas	243 (8.9%)	90 (9.5%)
CNS	9 (0.3%)	2 (0.2%)
Leukemia	769 (28%)	223 (23%)
Lymphoma	415 (15%)	119 (13%)
Retinoblastoma	1,170 (43%)	413 (44%)
Solid tumors	103 (3.8%)	86 (9.1%)
Others	28 (1.0%)	16 (1.7%)
SEER Stage*		
In-situ	0 (0%)	0 (0%)
Localized	653 (26%)	354 (36.6%)
Regional	500 (20%)	176 (18.1%)
Distant	1,324 (53%)	430 (44.4%)
Unknown	12 (0.5%)	8 (0.8%)
Status		
Alive	2,156 (78%)	948 (88%)
Dead	623 (22%)	20 (12%)

* Adolescent and young adults 2020 classification (https://seer.cancer.gov/ayarecode/aya-2020.html).
Data source from the KHCC Cancer Registry for the period 2011–2022.
KHCC, King Hussein Cancer Center; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival; IQR, interquartile range.

and 25,352 (7,042, 52,112), respectively. On the other hand, the median coverage (IQR) in JOD and US$ for displaced patients treated on KHCC/KHCF-SJCRH/ALSAC HF1 and HF2 was 21,808 (10,496–46,522) and 30,715 (14,783,65,523), respectively. With a total cost of treatment on KHCC/KHCF-SJCRH/ALSAC HF1 and HF2 was 1.44 million JOD, US$ 1.97 million, and 1.18 million JOD, 1.67 US$ million—to date), respectively. Table 2 describes the median cost of treating displaced children with cancer, per diagnosis, at the KHCC (in JOD and US$) between 2011 and 2022.

Patient outcomes

Kaplan–Meier survival estimates were generated by defining the date of diagnosis as the starting point and death from any cause as the endpoint. Mortality data were sourced from the medical chart or cancer registry records that are linked to national mortality records by social security numbers. While this approach is considered reliable for Jordanians, it may be less accurate for refugees who may have departed from the country or lacked a valid social security number, potentially leading to inflated survival estimates. The

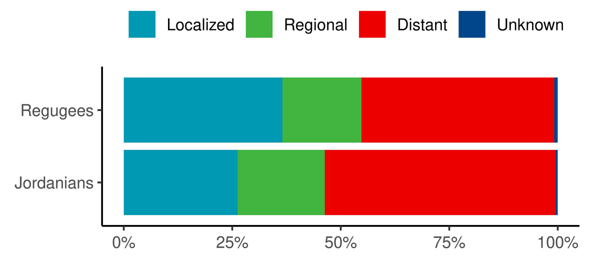

FIGURE 3
Comparison of the Surveillance, Epidemiology, and End Results (SEER) Histologic Staging of Cancer among Jordanian *vs*. non-Jordanian children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022. Cancer categories include leukemia*, solid tumors, sarcomas, lymphomas, CNS tumors, and retinoblastomas. *Leukemias are included in distant staging. KHCC, King Hussein Cancer Center; SEER, Surveillance, Epidemiology, and End Results.

estimated 1- and 5-year overall survival of displaced non-Jordanian children are 90.1% +/− 0.6% and 78.9% +/− 0.9%, respectively (Figure 4). This outcome was slightly but significantly better ($p = 0.037$) than Jordanian patients.

Discussion

Our report highlights the impact and effectiveness of advocacy efforts, partnerships, and financial coverage provided for the treatment of displaced children with cancer in Jordan. The data, collected from the records of the KHCC and KHCF between 2011 and June 2022, highlight the increasing burden of childhood cancer among displaced children in Jordan. The data indicate that comprehensive cancer care was provided to 809 non-Jordanian children with cancer, with Syrians, Palestinians, Iraqis, and Yemenis being the most common nationalities. The most common cancers were solid tumors, leukemia, brain tumors, and lymphoma.

The ongoing war in Syria and the subsequent influx of refugees have placed significant pressure on the local health system in Jordan. Cancer and cancer therapy are increasingly recognized as significant burdens due to their economic, social, and health implications (15), particularly in low- and middle-income countries (LMICs) like Jordan.

The report also highlights the inadequate funding allocated for cancer treatment for displaced patients in the Middle East, similar to other reports (16). The majority of pediatric applications for cancer treatment made to the UNHCR in Jordan are approved, compared to less than half of adult applications (16). The main justification for application rejection is a poor prognosis.

The WHO estimates that 400,000 new cases of childhood cancer are diagnosed annually, with LMICs accounting for 84% of childhood cancer cases (17). Although childhood cancer is highly curable, the costs of care exceed what displaced families can afford (15). The KHCC currently treats the majority (85%) of new childhood cancer cases in Jordan. The report suggests that the number of displaced pediatric cancer patients in Jordan exceeds that highlighted in the report as a significant number remain underdiagnosed or do not seek medical attention due to various reasons.

The report also highlights the success of the collaborative efforts and robust partnership between the KHCC/KHCF and the SJCRH/ALSAC in optimizing the care and providing financial coverage for cancer treatment through the establishment of the HFs (HF1 and HF2) for displaced children. The results show that the updated patient outcomes treated through these funds are favorable and comparable to Jordanian patients. The collaboration between the KHCC/KHCF and the SJCRH/ALSAC was critical for the success of these efforts in addressing the humanitarian crisis in Jordan. Similar results from the region address displaced pediatric cancer patients treated in Lebanon (18) and Turkey (15). Approximately 100 displaced Syrian children are diagnosed with cancer in Turkey annually (15) (the third-highest refugee burden after Lebanon and Jordan, 3.6% of the Turkey population). The government covered 212 displaced children with cancer for full treatment (18) with outcomes similar to Turkish children. Likewise, Saab et al. (18) described the collaboration for displaced children with cancer in Lebanon established through SJCRH/ALSAC support *via* HFs to deliver quality cancer care (full and partial treatment) to 311 non-Lebanese children using prioritization strategy with encouraging outcomes (78%).

Our report has several limitations including brief follow-up time (35% of patients are on active therapy), the fact that the lack of follow-up data with a significant number of displaced patients could not be traced, and the limited number of patients in each diagnosis subsets, which limits comparisons with expected outcomes. Additionally, precise long-term outcome data on displaced children with cancer treated by KHCC/KHCF funds could not be accurately established since a significant number of patients could not be traced after completing therapy. Additionally, our study may not accurately reflect the entire number of displaced children in

TABLE 2 Cost of treating displaced children with cancer at the KHCC (in Jordanian dinars and US dollars) between 2011 and 2022.

Diagnosis	Median (IQR) in JOD	Median (IQR) in US$
Leukemia	35,212 (16,345, 69,083)	49,947 (23,184, 97,990)
Lymphoma	25,000 (9,088, 44,562)	35,461 (12,891, 63,208)
CNS	17,000 (7,000, 31,785)	24,113 (9,929, 45,086)
Solids	13,800 (5,000, 28,075)	19,574 (7,092, 39,823)
Retinoblastoma	9,550 (1,457, 17,700)	13,546 (2,067, 25,106)
Bone sarcomas	20,306 (7,500, 51,000)	28,803 (10,638, 72,340)

IQR, interquartile range; JOD, Jordanian dinars; CNS, central nervous system.

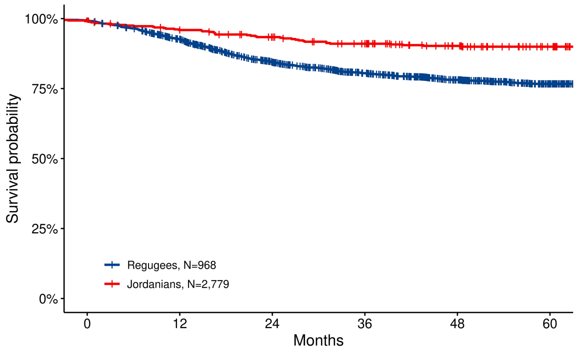

FIGURE 4
Overall survival for Jordanian and displaced non-Jordanian children with cancer treated at the KHCC and fully registered on the KHCC Cancer Registry for the period 2011–2022. Survival in displaced children with cancer is favorable and comparable to Jordanian children. This can be due to a younger age group, less metastatic patients—or reflecting referral bias, and the possibility that mortality registration is missed for some patients as they do not have a national identification. KHCC, King Hussein Cancer Center.

Jordan as it includes only refugees registered with the UNHCR. Moreover, survival among displaced children with cancer is high; this should be interpreted with caution. Likely explanations include referral bias (accepting a younger age group, less metastatic, a better prognosis, and less sick patients), and the possibility that mortality registration is missed for some patients as they do not have a national identification. Moreover, it was shown that Jordanian patients have more cases diagnosed in the late stage; this is mostly explained by selection bias.

Despite these limitations, this report offers the only data addressing the burden and characteristics of displaced children with cancer in Jordan, a population that is challenging to enumerate, evaluate, and follow-up over time. The underlying cancer diagnosis for which displaced children are treated in Jordan is also described with cost data given, which can provide the baseline information for the international community to assess and prioritize funding and respond with well-informed and structured programs and interventions. Moreover, these initiatives are well aligned with the Global Initiative for Childhood Cancer led by the WHO and SJCRH aiming to integrate childhood cancer into national cancer control planning (19).

In conclusion, this report highlights the significant burden of childhood cancer among displaced children in Jordan and the inadequate funding allocated for cancer treatment for displaced patients in the Middle East. It also highlights the success of collaborative efforts, partnerships, and financial coverage provided for the treatment of displaced children with cancer in Jordan through the establishment of the HFs. These insights can inform further multistakeholder-coordinated action plans for addressing the humanitarian crisis in Jordan and other similar contexts.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

RR: patient enrollment, budgeting, data collection and analysis, and the drafting of the manuscript. IS: patient enrollment, program budgeting, data collection and analysis, and the drafting of the manuscript. SJ: programs, budgeting, the review of the manuscript. MN: patient enrollment, budgeting, and the editing of the manuscript. CR-G: programs, budgeting, and the review of the manuscript. AM: programs, budgeting, and the review of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research in this report was conducted in the absence of any commercial or financial relationships that could be established as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1112788/full#supplementary-material

SUPPLEMENTARY FIGURE 1

Flow chart of children with cancer treated at KHCC and fully registered on the KHCC- Cancer Registry between January 2011- June 2022; these include Jordanian and displaced children with cancer. The chart illustrates the different funds covering the cost of treatment of displaced children with cancer.

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Providing person-centered palliative care in conflict-affected populations in the Middle East: What matters to patients with advanced cancer and families including refugees?

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Introduction: Universal health coverage highlights palliative care as an essential component of health services. However, it is unclear what constitutes person-centered care in populations affected by conflict, as they may have specific concerns in the dimensions of physical, emotional, social, and spiritual wellbeing. This study aimed to identify what matters to patients with advanced cancer and family caregivers in Jordan including refugees, to inform appropriate person-centered assessment and palliative care in conflict-affected populations.

Methods: Cross-sectional face-to-face, semi-structured interviews were conducted at two sites in Amman. Adult patients with advanced cancer and family caregivers were purposively sampled to maximize diversity and representation. Interviews were digitally audio recorded, anonymized, and transcribed verbatim for thematic analysis.

Findings: Four themes were generated from 50 patients (22 refugees; 28 Jordanians) and 20 caregivers (7 refugees; 13 Jordanians) (1). Information, communication, and decision-making. Truth-telling and full disclosure from clinicians was valued, and participants expressed concerns that information was not shared in case patients would disengage with treatment. (2) Priorities and concerns for care and support. Participants' top priority remained cure and recovery (which was viewed as possible). Other priorities included returning to their "normal" life and their "own" country, and to continue contributing to their family. (3) Role of spirituality and Islam. Most participants had strong faith in God and felt that having faith could comfort them. For refugees whose social network was fractured due to being away from home country, prayer and Quran reading became particularly important. (4) Unmet support needs of family caregivers. Family caregivers were affected physically and emotionally by worrying about and caring for the patients. They needed support and training, but often could not access this.

Discussion: Truth-telling is highly valued and essential to achieving person-centered care and informed decision-making. This study also reveals specific concerns in conflict-affected populations, reflecting the experience of prior losses and fracturing of existing social networks and support. The role of religion is crucial in supporting refugee communities, and consideration should be paid to the needs of patients and caregivers when caring for a patient at home without access to their communities of origin and the support they accessed.

KEYWORDS

palliative care, needs, experiences, oncology, Jordan, qualitative, refugee "crisis"

1 Introduction

By 2060, there will be an estimated 16.3 million people experiencing serious health-related suffering and dying with cancer annually, and this number will rise more quickly in low-income countries (407% increase), lower-middle income countries (169% increase), and upper-middle income countries (96% increase), compared to high income countries (39% increase) from 2016 to 2060 (1, 2). Jordan faces unique and complex challenges in health care due to refugee influx and rising cases of cancer. It has the second-highest ratio of refugees to citizens of any country in the world, creating an immensely complicated refugee crisis (3). In Jordan, cancer is the second leading cause of death (4). According to the most recent data from the Jordan Cancer Registry, 8152 cancer cases were reported for the year 2016, of which 5999 cases (73.6%) were from Jordanians and 2153 (26.4%) from non-Jordanians including refugees. Out of the 19,676 recorded mortalities, 3084 (16.2%) were due to cancer (5). Cancer burden in Jordan is a challenge, and the national cancer control should place a high priority on developing an endorsed National Cancer Control Strategic Plan (6).

Palliative care is a multidisciplinary approach aimed at improving pain and other symptoms and optimizing quality of life among people with life-threatening illness. It is a global human right (7, 8) as well as being a powerful adjunct to oncology that adds distinct value to the physical, emotional, social, and spiritual well-being of patients living with cancer (9). Integrating palliative care into the trajectory of standard oncologic care early has shown clinical effects on alleviating symptom burden, enhancing understanding of illness and prognoses, and improving both quality of life and overall survival for patients (10). Palliative care should be provided as a crucial health service, according to universal health coverage (11). It was explicitly recognized as one of the comprehensive services needed for non-communicable diseases in the WHO global action plan for the prevention and control of non-communicable diseases 2013–2020 (12, 13). However, palliative care and pain management have received the least attention in the global health agenda. The goals of the Lancet Commission report on palliative care and pain relief can be achieved by identifying and managing the specific needs, pain and other symptoms, and concerns of patients with advanced cancer including refugees (14).

A population-based analysis of adult death registry data from the Jordanian Ministry of Health shows that the annual mortality rate rose from 6792 in 2005 to 17,018 in 2016 (151% increase). In Jordan, hospitals accounted for 93.7% of all fatalities, while both Jordanians and non-Jordanians had a rise in hospital deaths from 2005 to 2016 (82.6%–98.8% and 88.1%–98.7%, respectively) (15). The need of palliative care is rapidly increasing; however, palliative care is not routinely available across Jordan (4, 16). In addition, Jordan is experiencing difficult healthcare issues as a result of the influx of refugees from numerous regional conflicts, notably Syria. The lowest expenditure of cancer care for Syrian refugees is estimated approximately 2.09 million euros annually (17). Using diagnosis-specific cost information from the King Hussein Cancer Foundation, it is projected that 869 Syrians are diagnosed with cancer each year in Jordan, costing roughly 15.6 million Jordanian dinars (US$22.1 million) for their treatments (18).

Access to cancer treatment is poorer for refugees and immigrants than for other Middle Eastern citizens (19). Prior to, during, and after displacement, they frequently encounter stressful and traumatic situations (20–22), as well as a heavy burden of physical, emotional, mental, and financial obstacles (23). Up until recently, humanitarian emergency and crisis did not include palliative care, which provides holistic care and support to people who are experiencing serious health-related suffering (24). What matters to patients with advanced cancer and their caregivers from refugee population in Jordan has not been explored. A systematic review indicated a lack of evidence on palliative care needs and interventions in humanitarian crises, difficulties in providing palliative care particularly in the context of limited resources and guidelines, and the importance of contextually appropriate care (25). The COVID epidemic revealed both potential and deficiencies in the palliative care response to health system need to provide better care at the end of life (26). In addition, it is unclear what constitutes person-centered care in populations affected by conflict, as they may have specific concerns in the dimensions of physical, emotional, social, and spiritual wellbeing. This study aimed to identify what matters to adult patients with advanced cancer and family caregivers in Jordan including refugees, in order to inform appropriate person-centered assessment and palliative care in conflict-affected populations.

2 Methods

2.1 Study design

We explored the unique needs, specific experiences of, and preferences for palliative care from the viewpoints of patients with advanced cancer and family caregivers in Jordan using a qualitative cross-sectional design through individual interviews. The guidelines of the Consolidated Criteria for Reporting Qualitative Research (COREQ) were adhered to (27). COREQ is a 32-item checklist for explicit and comprehensive reporting of in-depth interviews and focus groups.

2.2 Setting and participants

The study took place at two sites in Amman, Jordan: a comprehensive cancer center that manages around 60% of the country's cancer cases and a public hospital that offers some supportive care. The eligible participants in this study included patients who were ≥18 years old with advanced cancer and received care at one of the study sites, and informal caregivers who are defined as "unpaid, informal providers of one or more physical, social, practical, and emotional tasks. In terms of their relationship to the patient, they may be a friend, partner, ex-partner, sibling, parent, child or other blood or non-blood relative" (28). People from Jordanian and refugee populations who met the inclusion criteria were invited to participate in this study. Patients deemed too unwell to be contacted by healthcare professionals, and those unable to speak Arabic or English were excluded from the study. In order to maximize variation in age, gender, place of origin, and primary diagnosis, participants were purposively sampled. Patients and informal caregivers were recruited and interviewed separately.

Oncologists, palliative care physicians, nurses and other healthcare professionals who were working at the two sites during the study period helped to identify and first approach the eligible patients and family caregivers. They received a study training session which covered the topics of the eligibility criteria, how to identify and approach potential participants, and informed consent process. Then they applied the knowledge and skills learned from the training to screen eligible patients including both inpatients and outpatients and provide them with information sheets. The dedicated research team contacted those who expressed their interest in taking part in this study, gave them more information about this study, and responded to any question they had. Similar consent process was adopted for recruiting caregivers. 24 hours or longer were given to all potential patients and caregivers if they desired more time to consider their participation. Written consent (or an ink thumb print if unable to write due to disability, weakness, or illiteracy) was obtained from those who decided to participate. All study materials including information sheet and consent form were translated from English into Arabic using forward/backward translation to enhance accuracy.

2.3 Data collection

Between October 1, 2018 and May 31, 2019, the research team conducted in-depth semi-structured interviews with participants in their preferred time and locations. The interviewers (SA, GA, WA, and LA) have a wealth of knowledge and experience in both qualitative research and palliative care. Before participants gave their consent, the interviewers had no relationship with them. The development of topic guides for patients and caregivers was informed by a review of the research evidence on the experiences of refugees in Jordan (21, 22, 29, 30), and the needs of palliative care in humanitarian emergency and crisis settings (24, 25). The topic guides were then improved through regular discussion among wider cross-national research team members.

The topic guide for the patient participants covered (a) the experiences of having a terminal illness, facing death, and receiving support from family; (b) personal priorities, needs, and concerns, (c) the needs, experiences, and preferences of patients with advanced cancer in terms of palliative care (such as family needs, religious/spiritual needs, trauma/displaced experience/challenges as refugees, preferences for advance care plan, decision-making, and communication); and (d) what would make care more patient centered. Apart from these, the needs and concerns of the family caregivers themselves, as well as their experiences with providing care for a person with advanced cancer, and opinions on the quality of care were also explored. Data were collected until we reached information power (i.e., no new themes were identified in line with the study aim). Each interview was digitally audio recorded and the interviewer took field notes if needed.

2.4 Data analysis

These interviews were anonymized, transcribed verbatim by GA, and then translated from Arabic into English by AA. The researcher from the United Kingdom (UK) (PG) and the researcher from Jordan (SA) jointly coded the data in QSR NVivo 10, which were then analyzed using thematic analysis. To establish a coding framework, the two researchers independently examined seven transcripts. They then used that framework to analyze the remaining transcripts. As the data collection process continued, the data were simultaneously transcribed, translated, and analyzed. The categorization and comparison of interview data allowed for the discovery of recurrent themes and sub-themes in the dataset. Themes that overlapped were combined under descriptive names, while themes with few quotations were investigated. The data were continually examined during this process to learn more about the connections and relationships between the themes. Researchers discussed the themes and sub-themes when they were emerging to increase reliability and dependability.

2.5 Ethics and project management

The Research Ethics Committee at King's College London (HR-17/18-7243), King Hussein Cancer Center (18KHCC70), and the Jordanian Ministry of Health (MOH REC 1800110) granted relevant ethical approvals. The study complied with the Declaration of Helsinki (31). Throughout the study, the research team upheld the study's integrity, patient privacy, and data confidentiality. The UK and Jordanian members of the steering committee regularly met to discuss the study's overall direction and review its progress.

3 Findings

3.1 Participant characteristics

A total of 71 eligible people were approached and invited to participate in the study, of which only a native Jordanian declined. No difference was identified in the overall response rate or willingness to participate in the study between native people and refugees. 70 participants (50 patients with advanced cancer, 20 family caregivers) were interviewed including 29 refugees (22 patients, 7 caregivers) (Table 1). Patients ranged in age from 26 to 75, with an average age of 54 years. They were of six nationalities (Iraqi, Jordanian, Libyan, Palestinian, Syrian, Yemeni). Refugees' duration of stay in Jordan ranged from 6 months to 50 years. All the participants were Muslim except one patient who was Christian. The length of interviews varied from 12 to 97 min (Mean=60). All participants answered the questions in the topic guide. Only in two interviews conducted with the patients, their family caregivers also joined the interviews to accompany the patients but made no or limited contribution to the actual discussion.

3.2 Themes

Four main themes were identified (1): Information, communication, and decision-making; (2) Priorities and concerns for care and support; (3) Role of spirituality and Islam; and (4) Unmet support needs of family caregivers. These four main themes and ten sub-themes are presented in Table 2 and supported by direct quotations from the interview participants below. A unique combination of three letters and four numbers was used to represent each participant (such as P or C indicating the type of participants - patient or caregiver, followed by KH or AL indicating the study site and then four digits indicating participant numbers).

TABLE 1 Participant characteristics (n=70).

	Patients (n=50)	Caregivers (n=20)
Mean age in years (range)	54 (26-75)	42 (19-67)
Gender		
Male	20	7
Female	30	13
Primary diagnosis of the patients		
Breast cancer	20	5
Colorectal cancer	9	5
Lung cancer	5	3
Gastric cancer	3	1
Lymphoma	2	0
Gallbladder cancer	1	1
Bladder cancer	1	1
Pancreatic cancer	1	0
Parotid gland adenoid cystic carcinoma	1	0
Prostate cancer	1	0
Myelofibrosis	1	0
Ovarian cancer	1	0
Rectal cancer	1	0
Skin cancer	1	0
Anal cancer	1	0
Acute lymphocytic leukaemia (ALL)	1	0
Brain tumour	0	1
Liposarcoma cancer	0	1
Orbital tumour	0	1
Sarcoma cancer	0	1
Cancer stage of the patients		
III	13	2
IV	36	18
Unstageable	1	0
Number of people to live with		
Live alone	3	0
1-5	36	12
6-10	10	2
11-15	0	1
16-20	0	1
Unknown	1	4
Care for a sick family member?		

(Continued)

TABLE 1 Continued

	Patients (n=50)	Caregivers (n=20)
Yes	7	3
No	1	0
Unknown	42	17
Number of children < 18 years of age		
None	29	8
1-3	16	7
4-8	4	2
Unknown	1	3
Nationality		
Jordanian	28	13
Syrian	11	3
Iraqi	4	0
Libyan	4	1
Palestinian	2	2
Yemeni	1	1
Refugees' duration of stay in Jordan		
≤2 years	7	2
3-5 years	2	1
6-7 years	8	1
≥8 years	2	0
Unknown	3	3

3.2.1 Theme 1: Information, communication, and decision-making

Information needs

Most participants believed that the patients had the right to know everything about their condition.

"I want to know which stage the disease have reached. Is it bigger? Is it smaller? Maybe it's gone! But they just prescribe me meds and painkillers." (PKH0014, Jordanian)

The patients emphasised the importance of face-to-face consultations and valued hearing the opinions of more than one medical doctor. Mutual trust was described as a fundamental aspect of the doctor-patient relationship. Building strong trust-based relationships with the patients could help to achieve their optimal health outcomes and care experiences.

"I prefer coming in person. I am already coming here so I felt that it is better to consult them face to face. Patients' lives are precious, so there should be more than one opinion involved. A doctor can make mistakes, but when it is more than one doctor, the chance of making mistakes is smaller." (PKH0018, Jordanian)

When the patients were informed about their condition and treatment plan, they felt that their worries and anxiety were reduced, and they had more trust in the clinicians treating them (e.g., PKH0020, refugee; CKH0008, refugee).

"If I have a question, I would ask the doctor. He's the one responsible for my case so he would be more helpful. I think patients would prefer to have information directly from their doctor rather than online." (PKH0024, Jordanian)

"A doctor is a person who cares about their patients and not see them as a source of money and still care because the reward of the doctor is not the money, the reward is that God would bless that money and effort. A patient life is trusted in the hands of a doctor and that's why they should be accurate as this is a serious disease and should attend to the patient's complaint." (PKH0034, refugee)

Most participants expressed the view that doctors played an important role in information giving. They believed that doctors were good sources of information (but not nurses). Heads of department were seen as being more knowledgeable and respected. The health care system is reportedly embedded in a hierarchical culture and structure where the voice of doctors and senior managers is often given more importance than others. Both patients and caregivers considered that receiving positive information could boost patient spirits and make a significant difference in their physical and psychological wellbeing, even though later it was honesty that was valued.

"… he (the patient) would listen to a doctor rather than a nurse. Because he likes to hear the information from the source, so when it is from these two doctors, he listens because I think they're the head of department. Because they told him from the beginning that everything was ok and because they gave him a morale boost. He

TABLE 2 Themes and sub-themes.

Themes	Sub-themes
Information, communication, and decision-making	Information needs Honest communication Informed decision-making
Priorities and concerns for care and support	Getting back to normal and managing pain Social support and financial challenges Being able to contribute to their family and society
Role of spirituality and Islam	Strong faith in God Believing in God or taking medications
Unmet support needs of family caregivers	Caregiver burden Support and training needs

trusts the doctor more than he trusts his son, because his son might lie to him to make him feel better and he knows that his son's love will prevail, but the doctor will answer his questions so he will trust the doctor more." (CAL0014, refugee)

Honest communication

Participants commented that lack of honest communication and disclosure was not valued and although prayer was very important, it should not be used as a euphemism for breaking bad news. They also expressed concerns that information was often not shared in case it would cause patients to disengage with treatment.

"I remember asking the nurse in Saudi Arabia about my mother's condition and she told me there was nothing we could do but pray. She should have told me about her condition, I am her companion, I can handle it, but what she said meant she was going to die." (CAL0016, Jordanian)

"Maybe they don't provide adequate information because they worry about the patient's feelings and to ensure they accept the treatment. If you tell a patient their body is no longer responding to the treatment, they might decide on pulling the plug on the whole thing." (PKH0024, Jordanian)

However, some participants highlighted that clinicians would need to know their patients well enough to be able to assess whether their patients could accept bad news and judge when would be the appropriate time to communicate this news to their patients. Patients reported that communication must be personalized and raised the importance of clinicians correctly judging whether to communicate with patients directly or *via* family. A few participants expressed the views that clinicians should only inform the family of 'bad news' as a way to protect the patients.

"The doctor should also be smart enough and know that some patients cannot tolerate certain news so the doctor should have an insight. He should know I am a nosy person and wanting to know every single detail, otherwise I won't receive treatment, whereas other patients cannot tolerate such news and he should inform his family instead." (PKH0017, Jordanian)

"She should tell the family, but I am against telling the patient. He would be crushed regardless of how strong his faith is … In my opinion, patients shouldn't be told they are terminal, or that they are not to be given chemotherapy anymore. They should leave that to God. I wished I had met his doctor, but I didn't, I wanted to tell her she shouldn't have told him whatever she told him." (CKH0011, refugee)

Informed decision-making

Other participants also explained their preference of being informed about different treatment and care options beforehand and getting timely advice. This would help them to make informed decisions.

"They should tell him everything they intend to do and give him the chance to make decision, even regarding the type of painkiller he wishes to be on. They should tell him about possible complications. The symptoms I experienced from the chemo really burdened me. I didn't know anything when I took the first cycle, so I advise anyone who is sick to tell their doctors to explain to them before taking any step." (PKH0027, Jordanian)

In addition, timely access to information and internal team communication was crucial to patients and they valued this as a marker of quality care.

"We have seen the palliative doctors three or four times since the admission. They come and talk to him (the patient) then they talk to us outside. If it happens that I don't catch the palliative doctor I can always go see him on the second floor and ask him … They are great when it comes to follow-up. Even the nurses. They have good communication between each other and if anything comes up they immediately contact the patient…" (CKH0007, refugee).

3.2.2 Theme 2: Priorities and concerns for care and support

Getting back to normal and managing pain

Among our sample of patients with advanced disease, their priorities included cure and recovery (which was viewed as possible), returning to their "normal" life, and to continue contributing to their family (e.g., CAL0001, Jordanian).

"I wish I could go back to my normal life … I want to be active again. I can beat the disease, I just need to feel better and at ease, so I can beat this disease faster." (PAL0040, refugee)

"I have a family that I am responsible for, I might be an old man, but I still care about them and I still hold myself accountable for them. This responsibility makes me worried, of course it does, whom would I worry about if it wasn't my kids? Myself?" (PAL0045, refugee)

Some participants stated that managing pain was a top priority for them. Family was still often a dominant theme when discussing pain.

"I want my pain to calm down so that I can be there for them … I want to reduce the pain so I can be around them again. Go out with them on the weekends." (PKH0011, Jordanian)

Social support and financial challenges

For all refugees, they expressed the view that they would like to receive cancer treatment in Jordan and hoped they could return to their home country eventually.

"We have two homelands; one that lives in us, and another in which we live in. Jordan is our home which we live in, respect, and appreciate. We are ready to fight for it. As for our home that lives in us, we hope one day we will return to it. The disease made me stronger. I don't think about my disease. I believe that this illness doesn't make my life any shorter … So my lifespan has nothing to do with this disease." (PAL0010, Jordanian)

Some refugees raised concerns that they could not afford medication and treatment any longer and that they were experiencing financial challenges. Any financial aids that could help them to get medication and cover basic living expenses would be a priority.

"There isn't any money. I wish they would help us with the pain and lower the price of the medication." (PAL0002, refugee)

"I worried about my kids. Financially, I want them to be covered, but my financial status is below zero. We rented two rooms in a house that leaks when it rains and has no heating." (PAL0037, refugee)

"Its life and the hardships we're facing. I am burdened financially and mentally. I cry constantly because our life is sad, and we suffer financially. It is the money, the loss of my daughter and my illness. Yes, because we don't have any money." (PAL0009, refugee)

Being able to contribute to their family and society

A few participants mentioned that they did not worry about their own disease but were more concerned about their family and other people. Family roles and responsibility mattered most to many participants. They had a sense of needing to put things "in order" and plan ahead. This links strongly to the theme about honest communication about their conditions.

"I am not worried about the disease, but I want to make sure my kids have a good future. My son is 26, if he had gotten married, wouldn't I be seeing his kids already? Seven years ago, I thought I was going to die because I had cancer, so I wed my other son, he was 22 years old at the time." (PAL0044, Jordanian)

Furthermore, their priority was to be able to continue to help others and contribute to society.

"When I was going to surgery, the doctor asked me if I was afraid of anything, and I told him "What would I be afraid of? The Prophet said my people live sixty to seventy years, and I have already passed the limit by 5 years". He started laughing. Why would I be scared? I see this disease as a blessing, not a curse … I help people. There is nothing better than helping people. When you help people, you feel that you exist. This is a person's value in the society. You can't put a price on helping people out. In the association, we help out orphans and people in need." (PAL0010, Jordanian)

3.2.3 Theme 3: Role of spirituality and Islam

Strong faith in God

Most participants expressed their strong faith in God and felt that having faith comforted them and helped to prevent worries, anxiety, and depression (e.g., PAL0002, refugee; PKH0032, refugee; PAL0041, refugee; PAL0037, refugee; CAL0013, refugee).

"I feel relieved when I pray, it's like my burden were taken away. I love praying … I have more faith and trust in God because he is with me and he answered my prayer, he never forgot about me. It makes me strong, and my faith grows stronger, it gives me strength … If I let desperation into my life, I will feel worse. I already have the disease so why make it harder for myself? I pray, I strengthen my faith and be optimistic. Those around me grant me strength. I am optimistic and I believe I will get out of this, and that God will cure me." (PAL0038, refugee)

"We are all believers, but when you are in this condition, you feel like you need to stick to your prayers and all the forms of worship, I became more adherent to them. I know they all love me and pray for me, but it is God who will cure me, I always ask him to strengthen me, and that's when I feel that he loves me, I like to think that he is putting me through this as a form or redemption from my sins or to get me closer to him…" (PAL0040, refugee)

"I pray, praise be to God. I always read the Quran and rarely skip a prayer, I do it as much as I can. I pray in the mosque and go to Jumaa Prayers [Jumaa Prayer is a special prayer held at noon time every Friday, it includes a short lecture and a prayer. It is similar to Sunday services in Christianity]." (PAL0006, refugee)

Believing in God or taking medications

Furthermore, participants believed that a cure for their illness would be in the hands of God, and that they could leave matters to God and God's mercy would exceed all, even though they also valued the use of medications.

"I am not concerned about the progression of the disease because I have faith in God. Sometimes I worry that my pain would be unmanageable, but I think increasing the morphine would help with that. Like I said before, I am content with whatever God has written for me. Life and death are a godly matter…" (PAL0007, refugee)

"I talked to him (my son) over the phone, and I started to read some Quran to him when I came here and he felt better … I believe in what God said in the Quran; "And we send down of the Qur'an that which is a cure and a mercy to the believers". It is all about believing. If you believe the Quran will cure you, then it will. God grants us immunity when we believe in him, and if this immunity is disrupted, all the medications in the world will not help … We do what we can do and leave the rest to God. We try to make all causes come and leave the rest up to God. We knock every single door, believing it will eventually come up to God … I don't believe it is serious because I have faith in God that there isn't a disease without a cure. It could be something very simple. We just have to take every measure and pray to God to cure him. I know a stage 4 cancer is serious, but I know God's mercy exceeds all." (CAL0013, refugee)

Participants highlighted that their social network was fractured due to being away from their home country, and prayer and Quran reading became the most comforting and meaning thing they could do.

"God is all I have. What can I possibly do? I go out and sit by myself. I cry a little, then I leave things in the hands of God. If was in Syria, I would be surrounded by my family and relatives, but here I have no one. He (my son in law) reads from the Quran and prays. Some people started praying or reading Quran after him getting diagnosed, but nothing changed for him because he already did that even before his diagnosis. These last days he likes to read from the Quran when he's alone." (CKH0007, refugee).

3.2.4 Theme 4: Unmet support needs of family caregivers

Caregiver burden

Participants described family members having *"their world turned upside down"* (PKH0020, refugee). They worried about the patients, became sleepless, and reduced the time they spent away from home and stopped socializing with others (e.g., CKH0008, refugee). Patients were aware that their family members knew more about their conditions than them, which reconfirmed that families were often informed instead of the patients. This brought a great burden to family caregivers.

"They (family caregivers) know I am sick, and they know I have the disease. They know more than I do because they ask the doctors. They worry about me. They worry I might feel sad or anything.

They are more informed about my illness … my disease affected the family…" (PAL0037, refugee)

Family caregivers often lost social and working life due to their caring role and had to manage the mental health of the patient. They also often suffered from their own poor health.

"I used to be out of the house most of the time, I would stay at home for a maximum of one to two weeks, but since my mother got sick, I am staying with her. It all depends on how well you accept the fact that this is fate, and you can't change it. It is tough for her, she thinks anything told to her is because she is dying, she becomes very sensitive and angry in an intolerable way." (CAL0016, Jordanian)

"I stopped going out after he got sick. I don't visit people anymore … There is nothing else I can do. I can't physically take care of him, I am an old lady and I have diabetes." (CAL0004, Jordanian)

Support and training needs

Family caregivers felt sad when they saw how the disease had changed their loved ones but there was nothing they could do to help. When they received bad news, family caregivers had to conceal or give a positive interpretation of poor prognosis, and this brought a psychological burden on the family.

"There was nothing I could do. He's a 23-year-old boy and my daughter's fiancé, surely that would make me upset. I felt sorry for my daughter who comes with him every day. I didn't tell her that the cancer had spread in his entire spine … I am trying to spread some positivity in the air because she spends her time crying … What do I do? I talk to her and try to cheer her up. I tell her "Let's have a cup of coffee" or "let's go do some grocery shopping". I try to change her mood. I'm not fine myself. It hurts me to see how he was and how he is now. I cry a lot, but not in front of him. There is nothing we can really do." (CKH0007, refugee)

"It has a psychological impact, of course, when you see your own son not able to go to the bathroom, of course you'll feel bad. When he is a young man at that age and to be this disabled, it kills you to see your son like that. It kills me to see my son helpless … My own son who was my rock, to see him being destroyed like this. He was really helpful to me, he carried them on his shoulder, and to see him like this. He was a pillar in this family." (CAL0013, refugee)

They were affected physically and emotionally by worrying about and caring for the patients. Family caregivers need support and training but often could not get it. They felt guilty when they saw their relatives suffering but could not help.

Not just courses on how to deal with a sick person and talk to them, I believe these are skills that should be passed on to all people surrounding the patient because when a person gets sick, all of those around them are also sick … When you see a person going through so much pain and you can't do anything about it, that makes you feel guilty. When you have parents who are at an advanced stage, it is nice to provide guidance to accept it and explain to them that there is nothing they can do. This is very important, because providing support to the family at such a stage is very important. (PKH0017, Jordanian)

Some young caregivers stopped education because of their caring role. Even the children in the family having patients with advanced cancer, tried to offer help beyond their age (e.g., PAL0040, refugee).

"I stopped studying. I failed high school because I only wanted to help my mother. She kept encouraging me to study and I told her I only wanted to be around her and help her." (CAL0001, Jordanian)

This was a real challenge for young children when they were seeing very sick parents but being told they were well.

"I tell them he's well. No, because they see him at home and how weak he is, sometimes he can't get out of the bed or can't eat. They cry sometimes and say "I don't like seeing daddy like this"." (CAL0003, Jordanian)

4 Discussion

This study reveals the importance of honest communication, community support and spiritual care for people with advanced cancer in Jordan and highlights the impact of the unmet needs of family caregivers. Open and effective communication about their cancer illness, treatment plan, and appropriate spiritual and psychosocial support have been identified in our study as the things that matter most to patients and family. Yet, these aspects of care are often underserved or overlooked.

Health literacy is crucial in health care, particularly in the context of cancer where patients and family caregivers experience clinical uncertainty and suffer overwhelming physical, psychological, social, and spiritual symptoms, and financial burdens (32, 33). Research shows that effective person-centered communication between health care providers and patients can improve patients' health literacy, which also leads to enhanced health outcomes (34–36). An adequate level of health literacy is required to make informed decision, and several studies have reported that most cancer patients express a willingness to have their diagnoses and prognoses fully disclosed and show preference for participation in treatment decisions. However, according to the family caregivers interviewed in this study, patients' knowledge of their diagnosis and prognosis could have a negative impact on how their illness progresses in the future and lead to stress, despair, hopelessness, and low self-esteem in patients. Therefore, they preferred nondisclosure of information (37, 38). These findings were corroborated in a multicentre cross-sectional qualitative study in India, which demonstrated that while clinicians were motivated by professional values to disclose cancer related information, they experienced pressure from family members to conceal information (39).

Despite the fact that the majority of patients expressed a preference of face-to-face consultations for full disclosure of their cancer diagnosis and prognosis, family members frequently make decisions in many non-Western societies (40–42) and non-disclosure is more likely to occur in "family-centric" Asian cultures (43). A systematic review of 53 studies which explored prognostic disclosure in cancer care using different communication methods and interfaces found that cancer patients usually know their diagnosis, and to some extent, their prognosis, even though their clinicians and family members do not disclose information (44). In our study, some participants expressed the views that clinicians should know their patients well to be able to judge whether to communicate with patients directly or *via* family, particularly when breaking bad news. Patients often hesitated to ask questions and were not involved in decision-making process, which potentially led to patients' poor insight into their disease, lack of consent to treatment, and limited access to palliative care. In addition, there was a clear hierarchy within the team in terms of information giving and communication. Our findings suggest that patients strongly trusted the oncologist and people in senior leadership roles (such as Director of the Department), and doctors were seen as good sources of information instead of nurses.

How the patients and their families who were interviewed view disease, suffering, and death and dying processes is greatly influenced by spirituality and Islam (45, 46). According to a systematic review, patients and their families accepted their diagnoses because they believed that Allah (God) planned their destiny and path. They developed coping mechanisms by engaging in Islamic practices such as praying to Allah and reading the Qur'an (the holy book of Islam) which brought them hope, internal peace and comfort (47). It is reconfirmed by our findings in this study indicating that patients and family caregivers became closer to God and performed prayers particularly in the context of advanced cancer and when they were experiencing pain. They believed that Allah has more power than medication and could give them the strength to conquer everything.

Some of the participants in this study are refugees (n=29) who experienced compounding trauma related to war and disease and were receiving cancer care in Jordan. They reported that their social support network was fractured, therefore, religious practice and prayer were described as even more important for them, which has been published in a separate paper (23). A cross-sectional study with 95 palliative care outpatients has shown that spiritual wellbeing had a positive correlation with quality of life and the dimensions of physical, emotional, and functional wellbeing. In addition, it was associated with being less uncertain, more satisfied with one's decision, and feeling more informed and supported (48). It is crucial to determine the role and influence of spirituality in palliative care, however, evidence is limited on the perceptions of spirituality among Muslim patients with advanced illness and their families.

Financial challenges were also identified as key issues refugees were experiencing in our study and they often could not afford health care costs and basic living expenses. It is recognized that migrants usually undergo a difficult integration process to live in the hosting community. This process involves the cultural and economic adaptations (49). Our findings indicated that accessing to and receiving cancer treatment and palliative care under the hosting healthcare system added another layer of complexity into the life of refugees. In addition, the relationship between migrant patients and health care providers may be impacted by cultural differences (50) and communication barriers (51). For example, clinicians may be reluctant to discuss health conditions and care with migrant patients as communication may take more time and effort. Refugees may consider that communication with their clinicians results in stereotyping, so become less likely to share their feelings, needs and concerns with them (52).

Cancer patients particularly refugees in Jordan often experience unmet multidimensional needs, symptoms, and concerns. Person-centered care is considered as an essential component of high-quality healthcare for people with palliative care needs across the globe (53). In a cross-national, cross-sectional qualitative study, interdependency and collectivism have been highlighted in relation to person-centered care, including "the benefits of social support systems, the value of interpersonal harmony, the interdependence of a person's and their loved ones' well-being, and the value of group-based learning, peer-to-peer support, and care in the community". According to this study, in order to provide person-centered care, the healthcare system must have certain structural components in place such as partnerships with community-based workers and professional training in person-centered care values (54).

In this study, a lack of ability to engage in family responsibilities due to illness and treatment was identified as a priority concern of the patients. Continuing "responsibility" to family was seen as important. A few participants mentioned that their priority was to be able to continue contributing to their family and that they were more concerned about their family and other people than about their own disease. Evidence suggests that caring for a loved one who is nearing death is often physically and emotionally intensive. In addition, family caregivers of patients with advanced cancer frequently experience high level of distress, depressive, and anxiety symptoms, which highlights the critical need of psychological and emotional support for both patients and their family caregivers (55–57).

However, family caregivers' own needs are often unidentified, unmet, and neglected. The level of care burden can be persistent or increasing over time, particularly in the care situation of refugees with advanced illness where they have two homelands, one which lives in them and another which they live in. As a result of being cut off from their wider social support network due to being abroad, caregivers experienced heightened anxiety and responsibility (23). In addition, our study reveals that children wanted to be involved but were often shielded and excluded by adults throughout parental life-limiting illness. Children's experiences of caring for a dying parent were reported emotionally taxing and the required heavy caregiving responsibilities may have had an impact on their academic performance. This is consistent with the findings of a review ensuring that the voices of children whose parents have terminal diseases are heard and acted upon (58).

Prior studies have suggested that staff shortages and budget constraints in Jordan (especially at public hospitals) make it difficult to identify palliative needs of patients and provide holistic care (59). These findings can help improve access to palliative care by structuring assessment and services. A regular holistic needs assessment with standardized instruments such as the Integrated Palliative care Outcome Scale (IPOS) is required for early identification and intervention of symptoms and concerns (60). Adequate training including symptom management, communication, psychosocial and spiritual care is important for healthcare providers to strengthen their capacity to deliver dignified and person-centered cancer and palliative care. In addition, to make it easier for family caregivers to balance paid work with caregiving responsibilities and lower the risk of burnout during the trajectory of an illness and after death, greater support is required. Families should be trained and given the skills to care for their loved ones with advanced cancer.

5 Strengths and limitations

To our knowledge, this is the first qualitative study to determine what matters to patients with advanced cancer and family caregivers in Jordan including both host Jordanian and refugee populations. It not only emphasizes the importance of identifying and addressing multidimensional needs of patients and their families, but also provides recommendations of how person-centered and culturally appropriate palliative care could be better implemented to improve outcomes. We recruited the participants from two study sites – a specialist cancer center and a public hospital, enabling that highly diverse experiences and needs of people from different backgrounds have been represented and captured. Cross-national collaboration has also made it possible to acquire, analyze, and interpret data from a variety of cultural perspectives.

A study limitation is a relatively small sample size of refugee population for family caregivers (7/20, 35%). The responses to the topic guide may have been more diverse and in-depth if there had been more refugees from caregiver participants. Additionally, more patients with breast cancer and family caregivers (n=20 patients and 5 caregivers, 36%) and Syrians (n=11 patients and 3 caregivers, 20%) were interviewed than the other groups, which might have made it harder to compare and contrast the viewpoints from other groups. Future research should explore the needs and experiences of cancer and palliative care among patients with other cancer conditions than breast cancer and refugees from a variety of original countries.

What matters to people with advanced cancer and their families is unique and context specific. It is not appropriate to immediately extrapolate data generated from Western countries to Muslim-majority nations like Jordan, where 95% of the population follows Sunni Islam (61) and there is the second highest share of refugees per capita globally - most affected by the Syria crisis (3). Further investigation is needed to understand its cultural and spiritual assumptions, and the population with the underpinning evidence generated should be scrutinized.

6 Conclusion

Our study gathered first-hand information about the multidimensional and unique needs of patients with advanced cancer and families such as communication and information needs, and explored the role of spirituality and Islam, and the impact of unmet family support. It provides a robust evidence base to inform culturally appropriate cancer and palliative care in Jordan. Truth-telling is highly valued and essential to achieving person-centered care and informed decision-making. This study also reveals specific concerns in conflict-affected populations, reflecting the experience of prior losses and fracturing of existing social networks and support. Religion plays a crucial role in supporting refugee communities, and consideration should be paid to the needs of patients and family caregivers when caring for a patient at home without access to their communities of origin and the support they accessed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study involving human participants was reviewed and approved by the Research Ethics Committee at King's College London (HR-17/18-7243), King Hussein Cancer Center (18KHCC70), and Jordanian Ministry of Health (MOH REC 1800110). The patients/participants provided their written informed consent to participate in this study.

Author contributions

RH and PG conceptualized and designed the study, with input from SA, AM, AG, RS, and OS. SA, GA, WA, AA, and LA were involved in data collection, transcription, and translation. PG and SA jointly analyzed and interpreted the data. PG wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Communication and information sharing with pediatric patients including refugees with advanced cancer, their caregivers, and health care professionals in Jordan: a qualitative study

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Introduction: Effective communication in pediatric palliative cancer care is an important aspect of practice to enhance patient- and family-centered care, and to optimize decision-making. However, little is known about communication preferences practices from the perspectives of children, caregivers and their health care professionals (HCPs) in the Middle Eastern region. Furthermore, involving children in research is crucial but limited. This study aimed to describe the communication and information-sharing preferences and practices of children with advanced cancer, their caregivers, and health care professionals in Jordan.

Methods: A qualitative cross-sectional study was conducted using semi-structured face to face interviews with three groups of stakeholders (children, caregivers and HCPs). Purposive sampling recruited a diverse sample from inpatient and outpatient settings at a tertiary cancer center in Jordan. Procedures were in line with the Consolidated criteria for reporting qualitative research (COREQ) reporting guidelines. Verbatim transcripts were thematically analyzed.

Findings: Fifty-two stakeholders participated: 43 Jordanian and 9 refugees (25 children, 15 caregivers and 12 HCPs). Four major themes emerged: 1) Hiding information between the three stakeholders which includes parents who hide the information from their sick children and ask the HCPs to do so to protect the child from distressful emotions and children who hide their suffering from their parents to protect them from being sad; 2) Communication and sharing of clinical versus non-clinical information; 3) Preferred communication styles such as use of a companionate approach by acknowledging patients and caregivers' suffering, building a trustful relationship, proactive information sharing, considering child age and medical status, parents as facilitators in communication, and patients' and caregivers' health literacy; 4) Communication and information sharing with refugees where they had dialect issues, which hindered effective communication. Some refugees had unrealistically high expectations regarding their child's care and prognosis, which posed challenges to communication with staff.

Discussion: The novel findings of this study should inform better child-centered practices and better engage them in their care decisions. This study has demonstrated children's ability to engage in primary research and to express preferences, and parents' ability to share views on this sensitive topic.

KEYWORDS

pediatric, palliative care, cancer, refugees, communication, information sharing

1 Introduction

Around 300,000 cases of children worldwide are diagnosed with cancer each year (1, 2). Although around 80% of those patients are cured in high income countries, this drops to 20% in low- and middle-income countries (3). Cancer is a leading causes of death among children (4), and will become the leading cause of serious health-related suffering for any age at the end of life globally (5). In the Eastern Mediterranean region, cancer is the third leading cause of death for children aged 5-14 years (6). In 2015, nearly 245 new Jordanian pediatric patients were diagnosed with cancer, and it was estimated that about 62 new pediatric Syrian refugee patients in Jordan were diagnosed with cancer (6).

Tailoring effective communication according to cancer patients' preferences and needs, during cancer treatment trajectory, is considered as a crucial component of patients' centered care. It was correlated with patient adherence to treatment, decision making, and satisfaction with care and had shown a noticeable impact on patients' quality of life (7). Effective communication between patients, family and HCPs requires a humanitarian touch, compassionate connection, interdisciplinary team collaboration, and coordination and follow up to meet patients, family, and HCPs needs (8).

Palliative care is now established as an essential health service within Universal Health Coverage. Effective communication and information is essential to sharing information about diagnosis and prognosis and for informed decision-making when cure is unlikely. Good communication can improve children's health related outcomes positively (2, 9, 10), enable children to better cope better with their disease, treatment, end-of-life care and relapse (11, 12) and for the families when curative therapy is unsuccessful and families are grieving (8).

Evidence to date regarding communication and information sharing in pediatric palliative care settings has mainly originated in Western cultural settings (13). The existing evidence in this field has focused on parents sharing cancer diagnoses with their children (14), and adolescents' experience of their diagnosis (15). The pediatric palliative care research literature has not recruited child refugees (16). Similar research among adult refugees with advanced cancer revealed specific issues relating to compounded trauma and fractured social networks (17).

This study aimed to describe the communication and information-sharing preferences and practices of children with advanced cancer, their caregivers, and health care professionals in Jordan.

2 Materials and methods

2.1 Study design and settings

We conducted a qualitative cross-sectional study with semi-structured face-to-face interviews. It was conducted within inpatient and outpatient clinics of a tertiary cancer center serving

>60% of adult and pediatric Jordanian patients with cancer and patients from surrounding countries (18).

GA, WA and SA (senior researchers and instructors at adult palliative care department) conducted the Jordanian interviews with three groups of stakeholders (children, caregivers, and HCPs). The consolidated criteria for reporting qualitative research (COREQ) guidelines were followed (19). The research questions were: 1) What are their communication and information sharing practices and preferences? 2) What are the communication challenges in this population and what might be the best practice? Primary data for these questions was collected to improve child- and family-centered care and palliative care through local health policies, clinical guidelines, and local practices in Jordan and regionally.

2.2 Research study participants

Inclusion/exclusion criteria for each population were as follows:

Children and young people (hereafter "children") aged from 5-18 years with advanced cancer (Stage III or IV as determined by their treating clinicians) who had been seen by palliative care team at least once. Parents or main caregivers of children who met the inclusion criteria.

Children or caregivers who were unable to communicate, to speak Arabic or English, or those were unable clinically to provide assent/consent (written and/or verbal) were excluded.

Health care professionals (HCP) with at least 6 months' clinical experience of managing children with advanced cancer (doctors, psychologists, social workers, child life specialists and nurses).

We purposively sampled the populations by gender, age, child diagnosis and HCP profession. The aim was to recruit participants till reaching data saturation with respect to the study aim.

2.3 Recruitment and ethical considerations

Eligible participants were identified and approached by one of the three clinically experienced trained Jordanian researchers (GA, SA and WA) with the support of the pediatric palliative care nurse coordinator (SA). Each population sample was recruited and interviewed using a customized interview topic guide, information sheet and consent form. Furthermore, for children the topic guides, information sheets and assent forms were designed appropriately for their age and developmental stage (5-7, 8-10, 11-16 and 17-18 years, in line with ongoing research in this population (20–22).

If the participant agreed to participate, they were asked to sign a consent form. An assent form was also obtained from children 5-18 years old following their parents' approval (23). A distress protocol was used to reduce potential harms (24).

Ethical approval was obtained from both: Kings College London (Study Reference: HR-18/19-8838) and King Hussein Cancer Centre (Study Reference: 18 KHCC 162) prior to any study recruitment.

2.4 Data collection

GA, WA and SA conducted and digitally audio recorded the interviews in Arabic language using appropriate topic guide (decided with the family). Interviews were conducted at a private convenient place and time, after obtaining informed consent/assent forms from the participants. However, due to COVID-19 restrictions, five interviews were conducted by telephone following further institutional review board approvals.

The interviews were carried out between April 23rd 2019 and July 29th 2020. Qualitative methods training workshops were held with local research team (led by RH PG OS). The interviewers had no previous knowledge or relationships with any participants prior to the consenting or interviewing process. The main caregivers who participated in this study were not related to any recruited child participant.

The interview topic guides were developed by the core project team members following review of relevant literature. The interviewers started the interview by building a rapport with the participants, then used the topic guide's open-ended questions. For example, they played and drew with children before and during the interviews to encourage them to interact, to answer the topic guide questions, and to complete the interviews effectively. The questions mainly focused on children's concerns, needs, preferences and challenges in relation to the four palliative care domains of physical, social, psychological, and spiritual (25).

Before the end of each interview, the interviewer summarized the information back to participants for clarification and any further data was added to enhance data credibility (24). The majority (n = 23) of pediatric patients (especially those 15 years old or below) were accompanied by their caregivers during the interviews, and the caregivers were permitted to assist the child in the interview when needed.

2.5 Data analysis

Descriptive analysis of sample characteristics was followed by two local researchers (GA and WA) transcribing interviews verbatim. Transcriptions were pseudonymized, translated into English language by two local professional translators, then the two local researchers did a data quality check on the translation for accuracy, then imported to NVIVO 12 PRO software. The joint research team (Jordan and UK) applied the six phases of inductive thematic coding (Table 1). Frequent virtual meetings were held, and the thematic framework was refined during an iterative process by rearranging, adding, and deleting some generated themes and codes after discussion and agreement of the full team (26). The proposed coding framework was then presented to the wider research team for review, refinement and approval. The final approved framework was used by (GA and SB) to analyze the whole data after discussion and agreements of the teams on the findings' interpretations.

TABLE 1 Six phases of thematic analysis.

Phase 1: familiarization process	• 'repeated reading' of the interview transcripts before analysis • Transcription of the recoded interviews by GA and WA
Phase 2: developing initial codes	• Initial coding developed by the research team members (SB, GA, WA, FA, SY). • Frequent virtual meetings were done, and the codes was refined after discussion and agreement of the involved research team members
Phase 3: identifying themes	• The codes and the coded data extracts were sorted and collated into possible selected broader themes and GA developed the initial thematic map
Phase 4: themes refinement	• Themes were reviewed by the involved research team members for possible modification. Some themes were deleted, merged into one theme, or one theme have different ideas that had been divided into more themes.
Phase 5: themes explanation and naming	• Each theme was refined by taking into consideration the overall picture to be clearly defined and named.
Phase 6: generating final report	• writing up the finalized research report using analytical narrative approach that was supported by representative quotes taken form the participants interview transcripts

3 Results

3.1 Participant characteristics

52 interviews were conducted. Of those, 43 were Jordanian and 9 were refugees. 100% of those who were approached were recruited. Their demographics are reported in Table 2.

Median duration of interviews (minutes) was as follows: children=28.5 (range=16-62); caregivers=39.5 (range=27-80); HCP=50 (range=37-116).

3.2 Main findings

Four major themes emerged: 1) Hiding information between the three stakeholders; 2) Communication and sharing of clinical (physical) versus non-clinical (social, spiritual, and psychological) information; 3) Preferred communication styles such as use of a companionate approach by acknowledging patients and caregivers' suffering, building a trustful relationship, proactive information sharing, considering child age and medical status, parents as facilitators in communication, and patients' and caregivers' health literacy; 4) Communication and information sharing with refugees where they had dialect issues, which hindered effective communication (Table 3). Themes were supported by quotes with basic demographic description.

3.2.1 Hiding information between the three stakeholders

The three stakeholders shared that they did not share all information with all the other partners, and hide some information from each other. Interestingly, no interviewee mentioned that parents may be hiding the information from the healthcare workers.

Parents and HCPs, upon parents' request, shared they mainly hide bad news, such as cancer diagnosis and bad prognosis, from the sick child to protect them from feeling bad.

> "The next day he told my father, and my parents kept it from me, they kept telling me it was a microbe in the blood and not to be scared. They told me my treatment would take a while, when I was admitted here, they knew I didn't know it was leukaemia." (child, age 16, male, Jordanian)
> "We need the parents' permission to know to what extent we can speak because you are not allowed to talk about everything with the child, or they don't want the child to know that he is in a critical situation and he's near death even though the child usually knows." (Medical HCP, female, 10 years of experience).

Furthermore, some parents stated that they were not sharing the information with their young children because they thought that such young children cannot understand cancer related information.

> "I think they start understanding at the age of 9. My nephew is eight and a half years old, he understands things now, he asks me questions about my daughter, but I don't think younger children can understand. One of our relatives, who is friends with my daughter, is seven years old, and she doesn't understand what cancer is" (Mother of a 3 years old child, age 35, Jordanian)

Some HCPs also reported challenges in sharing information with both children and parents during the same encounter. Staff were often asked by the caregivers to hide certain information (mainly negative information such as bad prognosis or relapse) from the child. HCPs reported they would then ask the child to go out the meeting room or rearrange another meeting with the caregivers alone when they wanted to share negative information. This attitude may affect HCPs' relationship with the child, especially with those who want to know more about their health status.

> "A lot of the time, especially if we have the father and mother, both are present, so we take the- yeah go to the playroom, go dispense the medicine […] Sometimes if it's not possible or the child is asking why we are speaking to the parents alone, we will

TABLE 2 Participant characteristics (N=52).

	Children		Caregivers		HCPs	
	n	%	n	%	n	%
Gender:						
Female	14	56	12	80	9	75
Male	11	44	3	20	3	25
Nationality						
Jordanian	21	84	10	67	12	100
Libyan	1	4	2	13	N/A	
Palestinian	1	4	2	13	N/A	
Syrian	2	16	1	7	N/A	
Children diagnosis classifications						
i. Leukaemia, myeloproliferative diseases, and myelodysplastic diseases.	6	24	5	33	N/A	
ii. Lymphomas and reticuloendothelial neoplasms.	2	8	1	6	N/A	
iii. CNS and miscellaneous intracranial and intraspinal neoplasms.	1	4	3	20	N/A	
iv. Neuroblastoma and other peripheral nervous cell tumours.	0	0	4	26	N/A	
v. Renal tumors.	1	4	1	6	N/A	
vi. Malignant bone tumors.	12	48	0	0	N/A	
vii. Soft tissue and other extraosseous sarcomas.	2	8	1	6	N/A	
viii. Other malignant epithelial neoplasms and malignant melanomas.	1	4	0	0	N/A	
Relationship with children:						
Mother	N/A		11	73		N/A
Father	N/A		3	20		N/A
Grandmother	N/A		1	7		N/A
Healthcare profession:						
Medical staff	N/A		N/A		7	58
Non-medical staff	N/A		N/A		5	42

HCPs, Health care professionals; N/A, Not Applicable, Children diagnosis classification using the International "Classification of Childhood Cancer, third edition: Main Classification Table". Source: (27, p. 1459) Table 1, Medical staff: Nurses and doctors, Non-medical staff: Social workers, psychologist, and child life specialists.

> call the parents for a meeting outside the clinic on a different day if it's possible." (Medical HCP, female, 10 years of experience).

On the other hand, some children also hide information from their parents. They tended to hide their suffering and symptoms from their families to protect them from feeling sad. So, HCPs develop strategies to navigate the conflicting demands and communication needs by going back to see some children when their family are not around.

> "Because sometimes a child can't talk to just anyone, especially his parents. When I talked to you earlier, I felt relieved, but I can't go and talk to my dad, and I can't tell mom everything. If I was to talk to my siblings about it, it would make them sad, and I don't like seeing them sad." (child, age 15, female, Jordanian)

> "We would ask if there is anything about the child; and the mother "no, there is nothing", and I always tried to go back, especially if the patient was inpatient, I tried to find a chance, when the mother is praying or is out to get something, to sit with the boy or the girl and ask them the questions I needed." (Medical HCP, female, 15 years of experience)

Arranging for these additional meetings with parents alone or the child requires extra time and effort for services that are already busy.

> "I think it is too much for him. Dr. X clinic is every Tuesday, he is busy with his clinic patients, and I don't know how much time he has to check on his inpatients" (Mother of a 3 years old child, age 35, Jordanian)

TABLE 3 Communication and information sharing themes and sub-themes.

Themes	Sub-themes
1. Hiding information between the three stakeholders (Children, HCPs and parents)	**1.1 Parental gatekeeping.** • Parents and HCPs, upon parents' request, shared that they hide bad news from the child. **1.2 Children hiding information from their families.** • Children hide their suffering from their families to protect them from feeling sad. **1.3 Hiding information, trust, and treatment compliance.** • Hiding information from children may affect their trust on others and may interfere with their compliance with treatment.
2. Communication and sharing clinical versus non-clinical information	**2.1 Sharing adequate clinical information by the HCPs** for caregivers and children. **2.2 Stakeholders lack awareness of non-clinical issues.** • HCPs are not involved with children and family's non-clinical information. • The three stakeholders are sharing clinical information more than non-clinical ones. **2.3 Communication in other than physical domain is helpful.** Helps in: • venting. • better understanding patients' needs. • better assessment of child's physical issues.
3. Preferred communication styles	**3.1 Preferred way of communication that HCPs need to use when communicating with caregivers and children** • Compassionate and understanding way. • Active listening. **3.2 Effective communication needs a trustful relationship between the three stakeholders** • Trustful relationship need time, experienced staff, and honesty. **3.3 Proactive information sharing by HCPs** • Helps in decreasing the level of uncertainty, better coping and enhancing the feeling of reassurance. • Caregivers want to be proactively informed **3.4 Caregivers and children need for more information/health literacy** • **Health literacy** of children and caregivers need to be taken into consideration during communication and information sharing process because some children and caregivers, with limited health literacy, may need more information to understand things better. **3.5 Collaboration and coordination between staff** • Needed to enhance effective communication • Can be done directly or indirectly though meetings and over phones. • Regular meetings are recommended • Lack of communication and coordination between the staff can affect patients' care. **3.6 Age and developmental stage** • Adapting communication to children ages and developmental stages. **3.7 Medical status** of children should be taken into consideration when communicating with them to ensure effective communication and avoid conflicts. **3.8** According to some HCPs and few caregivers, **caregivers understand their child needs and complains better than HCPs**. • Caregivers/parents can help HCPs in better assessment of the child especially younger ages and those with certain communication limitations. • Few parents cannot understand their child's needs and complaints.
4. Communication and information sharing with refugees	**4.1 Refugees reported similar communication practices, issues and needs like Jordanian** **4.2 Language, dialect issues, and discrimination** • Refugees reported no language barrier and no feeling of discrimination. • Some HCPs and refugees had dialect issues, which hindered effective communication. **4.3 High expectations** • Some refugees had unrealistically high expectations regarding their child's care and prognosis, which posed challenges to communication with staff.

Hiding information from children, especially, teenagers may affect their trust in their parents. They may become doubtful and lose trust in their parents and HCPs which may interfere with their compliance with treatment.

> "But there are the older ones that we consider teenagers those start to lose trust in their parents because they kept [information] from them." (Non-Medical HCP, female, 3 years of experience)
>
> "For example, some young children around the age of 8 and 9 can read what is written on the medication or on the badges and go and Google it. When they figure out what it's for and that they have cancer, they stubbornly refuse to continue treatment – and we have a couple of cases like this. They become so upset from their parents for hiding it from them, they become skeptical of them and think about what else they've been hiding from them. They refuse treatment." (Non-Medical HCP, female, 7 years of experience)

Few HCPs stated that some parents make decisions regarding their children care plans without involving or informing the child, which was also confirmed by some children.

> "They offered to amputate my leg from the hip down. My parents refused, but they didn't tell me about it." (child, age 17, male, Jordanian)

Some children reported being fine with certain information being hidden from them. They preferred that medical HCPs talked to their parents first. They thought that this was helpful and more convenient for them, especially when sharing bad news.

> "I came here and started getting treatment for six months and I didn't know I had cancer. I owe all of this to my parents, it was a very helpful step … I still thank them for it, I tell them it's the best step they've done with me." (child, age 16, male, Jordanian)
> "No, my mom is the one who used to talk to [the doctor], she shouldn't say anything [to me] if it's not good." (child, age 15, female, Jordanian)

However, nearly half of the interviewed children said that they wanted to know more about their illness.

> "When they are talking at the door, I wish I can be a mosquito so I can know what they are saying." (child, age 14, female, Syrian)
> "Interviewer: Would you like if they came and spoke to you? should they come and tell you or speak to your mom and dad first? child: Sometimes they don't tell me. Interviewer: Sometimes they don't tell you. You would like if they can tell you? child: Yes, just for me to know" (child, age 8, female, Jordanian)

3.2.2 Communication and sharing clinical versus non-clinical information

Many caregivers and some children shared that they needed HCPs to share enough information especially regarding treatment plan, disease prognosis and side effects, and that their needs for information were satisfied.

> "They [The HCPs] always provided me with all the full information, and they'd tell me what's happening, what the plan is for the future, and what the possibilities are." (Mother of a 3 years old child, age 26, Jordanian)

In contrast, few parents stated that they did not receive enough clinical information and wanted to know more, especially about prognosis and future plans. They mentioned that hiding information such as disease progression could cause conflicts with HCPs and increase their feeling of uncertainty.

> "A doctor told us that [the child] has an aggressive disease but no one ever told me before that. I confronted the nurse coordinator and asked why he didn't tell me before that he [the child] has an aggressive disease, he said that he did tell me he had and active disease. I told him you didn't say active or aggressive, you didn't tell me anything." (Father of 4 years old child, age 36, Jordanian)
> "I: Do you have enough medical information regarding her situation?
> CG: Well, no, I don't think so. I just know that she's taking chemotherapy and today was supposed to be her 6th cycle but then they told us that she has radiotherapy instead. So today is her first session of radiotherapy […] I like to know everything about my daughter like when she should finish treatment and what happened to the tumor – is it still the same or did it shrink." (Mother of 3 years old child, age 26, Jordanian).

Some caregivers reported that addressing clinical issues was their priority. The majority of caregivers, more than half of HCPs and half of children stated that HCPs, especially doctors, tended to focus more on clinical information and they considered it was not their job to share or interact with non-clinical issues.

> "I think physical issues are the most important. If a symptom is upsetting her, they should check that first. Psychological issues are not really their thing, […] as doctors, they should mainly think about the body, and how different medications are affecting it, or if it is causing any side effects. This is a hospital, not a chapel." (Mother of 16 years old child, age 46, Jordanian)

However, some parents and children reported that sharing non-clinical information could help them to vent and make the HCPs understand their needs better which would be reflected on the child's health status.

> "It is important to ask about the mood, ask them about their likes and dislikes, that should be included, what they feel like doing, whether they want to play or to listen to music, or even dance and sing, or maybe go out. The questions you asked me earlier should be included because it makes some people feel better." (child, age 15, female, Jordanian)
> "They should ask about the mental state. If the parents are in a good place mentally, the child will benefit more from treatment." (Mother of 3 years old child, age 46, Jordanian)

Some HCPs recognized the need of non-clinical information to help in assessing patients' physical issues, such as pain and insomnia. They shared that some physical symptoms may result from non-clinical issues such as social, emotional and psychological problems.

> "Sometimes problems manifest as physical symptoms. Like, if the patients don't want to eat, it may be due to pain but it can also be because the child saw his/her parents fight or is worried

> or upset about something and it's keeping the child up at night. So, not all physical symptoms are cause by a medical pathology, sometimes it's due to psychological or social factors. For example, a child with divorced parent […] never been given enough attention and they always want the medical team to care for them, so they fake the pain." (Non-Medical HCP, female, 1 year of experience)

3.2.3 Preferred communication styles

Being compassionate and understanding were mentioned by some HCPs and caregivers as an important aspect to consider when communicating with caregivers and children. This included using compassionate verbal and nonverbal communication with caregivers and children, acknowledging their suffering and feelings, and giving them adequate time to answer their inquiries.

> "It's unnatural the way she holds all of these children, you feel like she is a human in every sense of the word. She gives you enough time, if you forget any questions, she reminds you of them. She's unreal when you deal with her you wonder why there aren't more people like this … honestly some doctors if they want to hand you the child it's like gum. They don't look at the child or acknowledge him even though it's a child." (Mother of a 3 years old child, age 44, Jordanian)
> "Interviewer: Are you happy with the way the doctors and nurses communicate?
> child: It is perfect.
> Interviewer: How so?
> child: They make me feel at home. They treat me well.
> Interviewer: Do you feel they are compassionate?
> Child: Yes" (child, age 17, male, Jordanian)
> "But the parents are like those drowning who are holding on to a straw, they want anything that might work. He might think it is ridiculous if it was someone's son, but when it's his it's different. And this is something that as a medical staff we must appreciate, we don't belittle anyone who says anything. There must always be a sense of respect and dignity for the other person so that the relationship can remain healthy." (Medical HCP, female, 10 years of experience)

For HCPs, effective verbal and non-verbal communication between the three stakeholders relied on trustful relationships for better interaction, understanding, and information sharing.

> "They have to be on the same page as their child, they have to know what is wrong with their child and not to tell their child lies, because if that child lost trust in the parents, they will be living in their own world. Some healthcare professionals, not many in our center, lack experience and cannot use proper words. Choosing words is very essential with children, as many of our children are too aware for their age." (Medical HCP, female, 3 years of experience)

Some HCPs highlighted the role of experience, time and previously knowing the family and the patient in facilitating effective communication and interactions with them and delivering bad news for individuals.

> "He [the child], for example, has been with us for a long time and then dies as we know his family, or we had a relationship with the patient's family. So, telling them becomes much easier for me. But here is the first time for me, I have known him just for two weeks or a week, and the patient's family is unknown to me, so telling them becomes much difficult for me, but by the time with the period and with the experience that become a little easier for us." (Medical HCP, male, 3 years of experience)

Sharing information proactively, before the event, helps in reassuring the family and the patient, decreases their uncertainty and helps them to cope better.

> "We all changed, it got better, when you have information about something, you feel relieved, you know what to expect." (Mother of a 3 years old child, age 35, Jordanian)
> "I had spots on my lungs. My parents knew about it and they also didn't tell me and I found out, there was this guy named […], God bless him, he told me that those who have it in their bone it can come back to their lungs so it might come back for you, so he gave me a hint so I expected it so when I got it I wasn't shocked" (child, age 15, male, Jordanian)

The findings show that some children and caregivers with limited health literacy need more information and explanation regarding cancer and its related aspects. Some caregivers acknowledged that they would need more explanation to understand things better because they were less educated.

> "I want to get the right result. I did not go to school, if you didn't explain to me what is in this piece of paper, I would never understand a thing even if I stared at it for an entire day." (Father of a 4 years old child, age 38, Jordanian)

Some HCPs and caregivers mentioned that collaboration and coordination between staff were needed for effective communication as it helped in managing families' and children's health-related issues appropriately. Open and regular communication channels were used. Some HCPs reported that they communicated with each other directly face-to-face (e.g., during rounds, clinics, and meetings) or indirectly (e.g. through phone calls, messages, emails, and WhatsApp) as needed.

> "We usually see each other during rounds, we see each other in the clinic. If anything happens, we immediately contact each other through the phone and we also have a WhatsApp group. So, we communicate on all levels as they say. So, if one of the

> parents contacted one of us on duty or someone came during the weekend, she would tell me." (Medical HCP, female, 10 years of experience)

Some HCPs, caregivers and few children mentioned that the use of different approaches of communication upon the child developmental stage, age group and disease progression were helpful for effective communication between the child and both the staff and caregivers. Searching for alternative ways to communicate with children with disabilities (e.g. losing certain communication abilities such as speech or eyesight) resulting from tumor, even when limited, may address some of these challenges. They reported that using children's language and aiding material may facilitate communication with the child. Few parents stated that the use of simple and plain language when communicating with young children may make them communicate and understand their health-related information better.

> "When Dr […] first explained the illness to me, she did it using Lego with trucks, these things […] like some little kids, like when they come to the center this toy idea, these ideas would really help them." (child, age 16, male, Jordanian)
> "I remember having a patient who lost his sight, could no longer speak, and could no longer hear. They were completely dependent on their sense of touch. The only person they could communicate with was their mother. If he was hungry, he'd press on one finger […] the family's biggest issue was being able to communicate with their child, which was very difficult to facilitate. What we try to do is create a tool for the neuro-oncology patients so that they aren't completely incapable of communicating with their family." (Medical HCP, female, 13 years of experience)

Informing caregivers that disease may cause behavioral changes for the child could help HCPs and caregivers when dealing and communicating with the children. It may also help in preventing conflicts and facilitating communication among the three stakeholders.

> "if he [the child] has a brain tumor it changes his behavior. He cannot differentiate if it's ok to say that or not. So it's not that he's impolite, or not to criticize the father, and the behaviors are caused by the tumor. It put pressure on the behavior area, so neither the mother nor the father can let him know what's right or wrong, especially when the child never said any bad word and all of sudden, he does." (Medical HCP, female, 15 years of experience)

Some of HCPs and caregivers reported that caregivers may help in communicating and assessing the child's needs especially younger ones and those who have certain communication limitations. However, these results were mentioned by staff and caregivers only and not by any child.

> "If I cannot communicate with the child, I would ask their parents, if they were sleeping, you'll ask their mom how they're doing, and whether they have eaten or drunk anything that day. All of this gives an impression." (Medical HCP, female, 3 years of experience)
> "Forget about talking, he can't even express himself anymore. He just nods his head or blinks for "yes", he raises his eyebrows for "no" […] we tell them about his symptoms because we can understand him more than the physicians. We're his parents, we can understand what's hurting him, like once he was indicating that his leg hurt him by saying "my weg ow"." (Father of 4 years old child, age 36, Jordanian)

In contrast, a couple of parents verbalized that they found difficulties in understanding their young child's (5 years old below) complaints and needs, which made them feel frustrated and anxious. They related this to the effect of disease progression or child's age.

> "Little children are tough to understand, and I believe this is the greatest challenge in children younger than five years of age. This is my experience, there were nights when I couldn't sleep because I was worried, she might be in pain and I couldn't spot it, so I would keep observing. It was very hard, but it is easier if the child is a bit older." (Mother of a 3 years old child, age 35, Jordanian)

3.2.4 Communication and information sharing with refugees

Most refugees (caregivers and children) were found to have similar practices, issues, and needs in relation to communication and information sharing themes. For example, caregivers felt they understood their child needs and complains better than HCPs.

> "If I ask her [the child] what she feels like eating, I can tell from the way she answers that question if she doesn't feel like eating. I ask her if I brought her food from home would she eat and she says yes, that means she doesn't like the food in the hospital and not that she doesn't feel like eating." (Grandmother of a 5 years old child, age 55, Palestinian)

Refugee children and caregivers reported facing no discrimination or problems regarding a language/dialect barrier between them and their HCPs or their ability to understand or being understood.

> "It wasn't that difficult, we have similar vocabulary, very little difference. We understand what you say" (Father of 2 years old child, age 45, Libyan).
> "Interviewer: Do you face any trouble understanding some of the words the medical team uses? Do you have an issues with

> the dialect or do you understand clearly? *child: No, I understand."* (child, age 17, male, Syrian)

In contrast, some HCPs shared that some refugees had difficulties in understanding their dialect, especially the Libyans and Iraqis. Other HCPs stated that they faced problem in understanding some refugees' dialect words, especially at the beginning when refugees started to come for treatment at the center. However, with time HCPs get more used to different refugees' dialects. They reported that refugees' dialect issues may vary between and within cultural contexts especially for Libyan, Iraqi and Yemeni.

> "When the Libyans first came, it was hard to understand some of the sentences they were saying. I remember having a Yemeni patient who I didn't know how to collect history from, it is probably due to the cultural background of the patient. Other Yemeni patients were easy to talk to, but I can't generalize and say we have a communication issue with them here at KHCC." (Medical HCP, female, 3 years of experience)
> "The Libyans in particular would face great difficulty in interpreting our dialect, sometimes the doctor would come to speak with them, and they can't understand a thing, so this problem needs a solution. I mean, the Syrian dialect is similar to the Jordanian dialect, but the Libyans and Iraqis aren't very familiar with it." (Medical HCP, female, 1 year of experience).

Some of Libyan refugees had misleading information, which created communication challenges for HCPs. Some Libyan caregivers had unrealistically high expectations toward their children's health status though they came to the center with a progressive terminal stage, and expected their child to be cured. This may result in communicational conflicts between the staff and refugees and parents or/and refugees and non-Jordanian parents' dissatisfaction.

> "I mean, the Libyan patients, do you understand how? I mean, the problem is that they do not come to us at the early stage, they are all in complicated stage and end stage, and their situation is complicated, you understand how? And the problem is that they have been told if they go to Al- Hussein Centre, they will be cured, if God's will […] I mean, he is coming with a belief, and you are coming to change their belief […] Therefore, dealing with them is a little more difficult." (Medical HCP, male, 3 years of experience)

4 Discussion

This novel study has revealed communication and information sharing preferences and practices as well as generated recommendations for good practice from primary data collected with children, family members and health care professionals in advanced cancer care in Jordan.

Our study demonstrated the importance and feasibility to involve children participants in palliative care research. It highlighted that children also hide information from their parents to protect them, and that HCPs need to ask whether or not they want to be involved in decision-making or to receive information about their treatment or disease.

We found that hiding information was a frequent practice by all stakeholders. These results contradict WHO recommendations for children's involvement in their health care (28), and the United Nations convention on the rights of child. Furthermore, hiding information from patients may form a moral challenge for HCPs who have to be honest with the patients to gain their trust while respecting families' wishes (29, 30). This trustful relationship built on honesty, is the cornerstone of effective communication (31). Best practices must reflect the religious beliefs of Muslim-majority countries with respect to end-of-life (32).

Our data showed that sharing and addressing enough non-medical information is crucial to enhance patients' and caregivers' satisfaction, high quality patient and family-centered care and improve their mental wellbeing (33; 34). However, HCPs should check patients' and caregivers' preferences regarding information sharing. HCPs should re-check children preferences over time as the children mature and may change their preferences and needs (2). Some children may wish to have full information and be involved in their treatment plan, others may choose not to know and to delegate decisions to their parents.

We found that parents and children in Jordan value compassionate, understanding and proactive communication. They wanted their HCPs to collaborate and coordinate between each other to understand families' suffering and to acknowledge the difficulties they were facing. They wanted to be heard and be given the chance to talk. This concurs with the findings of a systematic review including Eastern and Western studies (2).

Our participants suggested that different approaches of communication could be adapted to fit patients' age and developmental stage. For example, using toys in our sample worked well in facilitating communication and enhancing child understanding (31; 35; 36).

HCPs working with refugees and refugees may face challenges in communication such as dialect differences and potential unrealistic expectations regarding their child's treatment and disease progression. This high expectation may have resulted from the good reputation of the treatment center in the surrounding regions. Previous study with caregivers of children with cancer concluded that communication complexity increased greatly with patients and families from conflict-affected areas (13).

4.1 Strengths and limitations

To the best of our knowledge, this is the first study in the region to describe the views of children and caregivers and their HCPs regarding communication and information sharing in pediatric palliative cancer care. Involving palliative children with terminal diseases in such studies is limited worldwide, especially in low- and middle-income countries (16). Participating stakeholders provided us the opportunity to have more insightful, in-depth data that helped us to meet our study aim and objectives from different perspectives.

The methodological approach used in this study including a variety of interview topic guides, the qualified experienced interviewers, the collaborative approach between the research team in research conduction and analysis and the regular meetings, resulted in producing high quality data. Additionally, the recruitment of a variety of stakeholders, such as a culturally-diverse research team from different countries with various backgrounds (e.g., nursing, public health, and psychology) as well as the different interpretations in this study's initial framework gave our research a culturally and contextually broad perspective and guaranteed data credibility.

Regarding our study limitations, our findings may not be generalizable to the whole region because of the relatively small sample size and the fact that we recruited participants from one cancer institution in Jordan. This may result in excluding participants from another institution (selection bias) who may have different perspectives and experiences of pediatric palliative care. Those with poor engagement in care or greatest distress may not have had the opportunity to engage in the research. Furthermore, parents' religion and socio-economic status were an important issue that has not been addressed in our study. Addressing these aspects may give us a clearer view of parents' religion and socio-economic status and its effect on communication and information sharing in this particular context.

4.2 Contribution to the pediatric palliative cancer care future practice

Communication and information sharing in pediatric palliative care settings is an essential component of care to enhance patients' and families' quality of life and enhance the patient-centeredness of care (2, 9, 10). However, concurrent relevant stakeholders' views (children, families and health care professionals) are rarely collected together, and refugee families have been rarely reported. Our findings emphasize the need to respect patients' and caregivers' rights and preferences, to know how and when to share information in line with cultural and educational backgrounds.

We need to improve stakeholders' (including public) awareness regarding palliative care holistic approach, team roles and services, and the importance of addressing clinical and non-clinical information and issues. Enhanced HCPs training regarding communication and information sharing with children and caregivers in pediatric palliative cancer care settings is required. There is also a need to develop a suitable child-centered outcome measure that assesses child's and family's needs and concerns including communication and information sharing. In addition, refugees deserve particular attention and support taking into consideration addressing any issues related to their dialect and child treatment misconceptions.

5 Conclusion

Communication and information-sharing is a core aspect of quality cancer care for children with advanced disease. The findings of this study can guide evidence-based, culturally appropriate and acceptable care in advanced disease. Thus would put the child and the family at the center of decision making and support, and enable health care professionals to have confidence in initiating relevant discussions. Conducting a multi-center study in culturally homogeneous settings, focusing on communication and information sharing, is recommended.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Kings College London (Study Reference: HR-18/19-8838) and King Hussein Cancer Centre (Study Reference: 18 KHCC 162). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

The study was conceptualized and designed by RH, PG and OS, with input from SA, OS, GA and WA. GA, WA, and SA recruited participants and collected data. GA and WA worked on the interview transcriptions. GA, SB and WA jointly analyzed and interpreted the data. GA wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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War and oncology: cancer care in five Iraqi provinces impacted by the ISIL conflict

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War and cancer have been intertwined in Iraq for over three decades, a country where the legacies and ongoing impacts of conflict have been commonly associated with both increased cancer rates as well as the deterioration of cancer care. Most recently, the Islamic State of Iraq and the Levant (ISIL) violently occupied large portions of the country's central and northern provinces between 2014 and 2017, causing devastating impacts on public cancer centers across central and northern Iraq. Focusing on the five Iraqi provinces previously under full or partial ISIL occupation, this article examines the immediate and long-term impacts of war on cancer care across three periods (before, during, and after the ISIL conflict). As there is little published data on oncology in these local contexts, the paper relies primarily upon the qualitative interviews and lived experience of oncologists serving in the five provinces studied. A political economy lens is applied to interpret the results, particularly the data related to progress in oncology reconstruction. It is argued that conflict generates immediate and long-term shifts in political and economic conditions that, in turn, shape the rebuilding of oncology infrastructure. The documentation of the destruction and reconstruction of local oncology systems is intended to benefit the next generation of cancer care practitioners in the Middle East and other conflict-affected regions areas in their efforts to adapt to conflict and rebuild from the legacies of war.

KEYWORDS

cancer, oncology, conflict, Iraq war, Mosul, Islamic State, political economy, therapeutic geographies

1 Introduction

War and cancer have long been intertwined in Iraq, a country where the legacies of conflict have been commonly associated with both increased cancer rates as well as the deterioration of cancer care (1–4). In addition to studies that explore the toxic remnants of war and potential impacts on cancer incidence (5–7), a growing body of research has explored the destructive impact of successive US-led wars on various aspects of cancer care, including cancer control (2), radiation oncology (3, 4), pediatric cancer care (8), and palliative cancer care (9). Protracted conflict has placed enormous burdens on cancer patients, many of whom have responded to the war-related deterioration of public oncology by travelling across provinces and international borders to pursue treatments in high-cost private centers (10, 11). These cross-border therapeutic geographies have generated catastrophic expenditures for families already suffering from displacement and the loss of livelihoods (12).

In this turn towards studying war and cancer care in the Iraqi context, what is notably lacking is an examination of how conflict generates different impacts on local cancer systems and hospitals depending on local particularities. The impact of war on oncology in Iraq has been examined as a general phenomenon at the national level. Though advances in oncology have been documented in specific areas of the country (13, 14), namely southern Iraq and the Kurdish region, no study has attempted to interrogate locally specific dynamics in the areas directly impacted by the Islamic State of Iraq and the Levant (ISIL) through a comparative political economy analysis. This lack of attention to local particularities has left policymakers and cancer practitioners with few tools to understand why oncology is relatively durable during conflict in some localities and not in others, and why oncology is rebuilt relatively quickly in some localities and not in others. Focusing on the five Iraqi provinces that were fully or partially overtaken by ISIL between 2014 and 2017, this article aims to shed light on how conflict generates locally distinct shifts in the distribution of cancer services, the availability of essential cancer pharmaceuticals and supplies, and the pace of oncology reconstruction. In addition, the article focuses on public oncology hospitals but avoids a strict public/private dichotomy. Indeed, war generates gaps in care filled by procedures or pharmaceuticals purchased in the emerging private sector or the black market.

The primary focus of this article will be on the conflict period related to the rise and fall of the ISIL (2014-2017) and the reconstruction efforts in its aftermath (2017-2022). ISIL violently occupied large portions of the country's central and northern provinces between 2014 and 2017, causing devastating impacts on a once robust healthcare system that was already severely damaged from the compounding effects of the first Gulf War, the UN embargo of the 1990s, and US-led invasion in 2003 and subsequent years of international military presence (15–17). The provinces most directly impacted throughout the ISIL period were Nineveh, Anbar, Kirkuk, Salah al-Din and Diyala (Map 1). The paper tells the story of oncology under conflict for each of the five provinces.

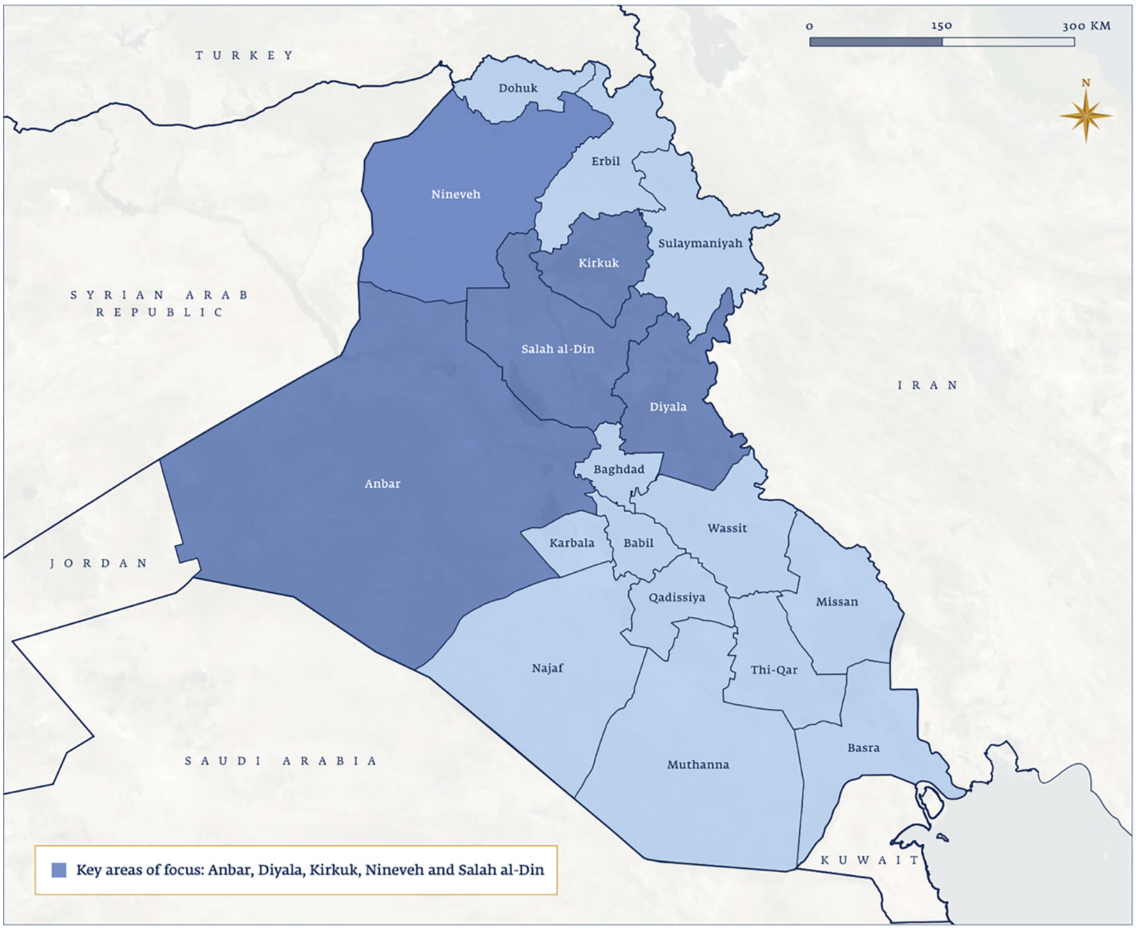
Relying on the accounts of oncologists who served during the ISIL period, the picture of oncology that emerges is geographically specific and highlights the unevenness of both conflict's destructive impact and reconstruction's benefits. For example, the ISIL conflict eviscerated oncology in some regions of Iraq while temporarily enhancing oncology resources in others; similarly, the reconstruction of cancer services has transpired rapidly in some provinces and languished in others. Understanding the factors that drive these varied outcomes in the distribution of care and the pace of reconstruction efforts can help shed light on the Iraqi situation and similar contexts where conflict is reshaping oncology, such as Ukraine (18). Importantly, the documentation of oncology under war is intended to benefit the next generation of cancer care practitioners in Iraq and other conflict-affected regions, who can learn from understanding how cancer services responded to previous periods of conflict.

2 Methods and limitations

This study examines the immediate and enduring impacts of conflict on oncology in the five provinces fully or partially occupied by ISIL between 2014 and 2017. Working chronologically across three periods (before, during, and after the ISIL conflict), the research elucidates the evolving impacts of war on the human resources, facilities, and available therapies necessary for cancer services. The chief aim of the analysis is to show the dynamic relationship between conflict and oncology in each of these provinces. In addition, a political economy lens is applied to interpret the results (19), particularly the data related to progress in oncology reconstruction. This is because conflict generates immediate and long-term shifts in political and economic conditions that, in turn, shape the rebuilding of medical infrastructure.

This article limits the scope of the analysis to the impact of war on the core infrastructural components of cancer care (e.g., the availability of pharmaceuticals, diagnostic tools, treatment facilities, and human resources). The crucial relational dimensions of cancer care (e.g., patient-doctor communication, levels of coordination and trust among all stakeholders, and patients' perceptions of the quality of care) are not foregrounded in this analysis as these lines of inquiry would require an extensive, qualitative study centered around patients' voices and experiences. The authors intend to publish such a patient-centered account in a forthcoming article.

This is a mixed methods paper primarily based on qualitative interviews and the lived experience of oncologists working in the affected provinces. An authorship team comprised of six Iraq-based oncologists from the five provinces was assembled (2 oncologists from Anbar; 1 from Nineveh; 1 from Salah al din; 1 from Diyala; and 1 from Kirkuk) in addition to three international colleagues with either research or practitioner experience in Iraq and the wider MENA region. During 3 group meetings in 2022, the authorship team shared and contrasted accounts of the three periods examined. A series of follow-up semi-structured interviews were conducted with each member of the Iraq-based authorship team. The combined authorship team analyzed the interview data collectively to generate further insights and points of comparison.



MAP 1
Provinces included in the study: Anbar, Diyala, Kirkuk, Nine-veh, Salah al-Din.

This data from the perspective of oncologists was supplemented by an earlier dataset collected in 2016 and 2017 during the height of the ISIL conflict, consisting of qualitative interviews with 40 cancer patients undergoing treatment in the public oncology hospitals of Erbil, Sulaymaniyah or Kirkuk who had fled one of the five provinces examined due to the rise of ISIL (10 from Nineveh; 10 patients from Anbar; 5 from the ISIL-occupied areas of southern Kirkuk; 10 from Salah al-Din; and 5 from Diyala). Though the core findings of the study are derived from the perspective of oncologists due to the focus on tracking shifts in cancer care infrastructure, the limited inclusion of the patient data in the analysis was necessary to verify or complicate the accounts of the co-authors/oncologists, particularly when assertions were made regarding the implications of shifting oncology capacity for patients' access to cancer services.

3 Results

In the following sections, the interview data has been used to develop key trends in the evolving impact of conflict on the essential infrastructures of cancer care (e.g., facilities, pharmaceuticals, equipment, human resources) at the provincial level, focusing on (a) the status of oncology before the ISIL period; (b) the transformations of oncology during the period of severe conflict conditions (2014-2017); (c) the efforts and ongoing challenges to rebuilding cancer care between 'liberation' in 2017 and the present up to the time of writing in 2023. Three provinces (Nineveh, Anbar and Kirkuk) are explored in-depth. These three provinces receive extensive attention due to the significantly larger oncology infrastructure. On the other hand, Salah al-Din and Diyala are examined in an abbreviated fashion due to the relatively recent and limited development of oncology in those areas. Table 1 summarizes the findings from the 5 provinces.

3.1 Nineveh province (Mosul)

3.1.1 Overview of trends: cancer and conflict

3.1.1.1 Advanced oncology capacity before ISIL

During the 1980s, Nineveh gradually developed comprehensive public oncology services, including radiotherapy, and became the second largest hub for oncology in the country behind Baghdad.

TABLE 1 Summary of findings: Cancer care in five provinces affected by the ISIL conflict.

	Before ISIL (Before 2014)	During ISIL (2014-2017)	After ISIL (2017-present)
Nineveh	Public oncology services began in 1979 and remained relatively comprehensive (including radiotherapy) over the course of multiple wars. Prior to 2014, there were 3 oncology centers and 8 specialists.	Nineveh witnessed a gradual deterioration of oncology services during the first 2 years of ISIL rule due to the disruption of supply lines; later oncology facilities were bombed/destroyed during liberation battles.	Specialists returned (11 total), but the province has witnessed a slow reconstruction of public oncology facilities. Services are currently limited to chemotherapy and basic diagnostics, with no functional radiotherapy.
Anbar	A single oncology unit was established in Ramadi in 2008 but saw slow progress (only 1 specialist), with a narrow range of cytotoxic and hormonal therapies.	The province witnessed a total shutdown of the Ramadi oncology unit after the ISIL takeover of the city, as all oncology nurses and staff were forced to flee.	Anbar witnessed a remarkably rapid reconstruction and expansion of oncology services (9 specialists, 2 centers). Anbar is becoming an oncology hub, but radiotherapy remains unavailable.
Kirkuk	A single oncology center was established in 2007 and services were steadily expanding (5 specialists by 2013). Radiotherapy was unavailable.	As ISIL failed to take over the capital of the province, Kirkuk's oncology center became a haven for the displaced. Government funding increased to cover displaced cancer patients; thus, the availability of cancer drugs expanded during the conflict.	With supplementary war-time government support removed, Kirkuk witnessed a regression to pre-2014 levels of pharmaceuticals. Radiotherapy remains unavailable.
Salah al-Din	Limited oncology services were initiated in the provincial capital of Tikrit in 2008 under the direction of one oncologist. Radiotherapy was unavailable.	Tikrit's oncology center was shut down as ISIL took over the city. Makeshift oncology services were delivered in Samarra city at minimum capacity throughout the ISIL occupation of Tikrit.	Cancer services have returned to Tikrit at limited levels, but the local government recently announced plans for a new oncology center. Radiotherapy remains unavailable till end of 2022.
Diyala	The province lacked oncology services. Patients sought cancer treatment in Baghdad, Sulaymaniyah, or Kirkuk.	No oncology services.	In the aftermath of liberation, a small oncology department was created in 2018 (1 oncologist). Chemotherapy approval was obtained in 2019, and a cancer center is currently under construction. Still, no radiotherapy.

Cancer patients travelled to the provincial capital, Mosul city, from across northern/central Iraq. Despite the devastating impacts of the UN Sanctions (1991-2003) and US-led invasion and occupation on oncology (2003-2011), public oncology services remained comprehensive, boasting one of the few working radiotherapy machines in the country. A single new linear accelerator (linac) eventually replaced the two outdated cobalt radiotherapy machines.

3.1.1.2 Gradual deterioration of oncology capacity during ISIL

ISIL took over Mosul city in June 2014. Though medical supply lines from Baghdad were soon cut, oncologists relied upon existing pharmaceutical stocks and equipment to maintain adequate cancer services for approximately one year. By the summer of 2015, the oncology apparatus began suffering from mass shortages in chemotherapy agents and the inability to maintain radiotherapy equipment. As a result, cancer services became very limited. In 2016-2017, liberation battles resulted in the cessation of oncology services; oncology facilities were ultimately bombed and destroyed.

3.1.1.3 Slow reconstruction of oncology capacity after ISIL

Oncology services have commenced in makeshift facilities, but reconstruction of the public oncology facilities has proceeded at a glacial pace. Services are limited to chemotherapy and basic diagnostics, with no functional radiotherapy. An emerging private sector has started to fill the gaps in public services, creating additional costs for a population suffering from the war-related loss of livelihoods.

	Before ISIL	During ISIL	After ISIL
Oncologists	8	3	11
Oncology facilities (public)	3	1	Makeshift temporary facilities
Radiotherapy machine	1	0	0

3.1.2 Cancer care before ISIL

The Iraq-based oncologists contributing to this study all concurred that Mosul once represented the pinnacle of cancer care in Iraq. Since 1979, Mosul city has been home to the Specialized Oncology and Nuclear Medicine Hospital (SONMH). During the 1980s, Mosul developed comprehensive cancer services and became an oncology referral hub for Nineveh and nearby provinces (e.g., Erbil, Dohuk, Salah al-Din, Kirkuk). However, during the UN sanctions of the 1990s, severe restrictions on the import of chemotherapy agents and cobalt source replacement dramatically reduced the continuity and quality of care. In addition, the US-led invasion of 2003 ushered in a period of heightened political instability and insecurity in the province, compelling many medical professionals from Mosul to flee the country. As the intensity of the fighting reached a high point in 2006 and 2007, the relative stability of the nearby semi-autonomous Kurdistan Region – and its emerging oncology system in Erbil, Dohuk and Sulaymaniyah – led to a slight reduction in cross-provincial referrals to Mosul city.

Despite the challenges related to conflict and political instability, oncologists in Mosul city endeavored to maintain advanced public cancer services. In 2013, the year before the takeover of Mosul city by

ISIL, public oncology services in Mosul included three centers (SONMH, Hematology Center, and Pediatric Oncology Center), which jointly had a capacity for over 60 beds, a pain and palliative care clinic, a colostomy care clinic, a radiotherapy department with a fully functioning linac, and a thyroid gland outpatient clinic. In sum, oncology services in pre-ISIL Nineveh were at a level of sophistication that far exceeded any other provinces examined in this paper. Mosul city was a national hub for oncology services.

3.1.3 Cancer care during ISIL

The deterioration of oncology transpired gradually throughout the ISIL occupation of Mosul city. In June 2014, ISIL swiftly took over the entire city of Mosul, including the area where oncology services are located. Mosul's highly experienced oncologists, who had endured repeated war and violence, treated this situation like any other. For the first several months of the ISIL occupation, cancer drugs generally remained available from the previous year's stock of pharmaceuticals (e.g., Herceptin, Avastin, Erlotinib, Sunitinib, Pazopanib, etc.). ISIL did not actively obstruct basic cancer care delivery during the initial months. But problems were looming on the horizon.

Cut off from replenishing supplies from the Baghdad-based Ministry of Health (MoH), oncology hospitals were already witnessing severe shortages in chemotherapy and equipment by the spring and summer of 2015. The linac machine ultimately ceased functioning; the gamma camera stopped working; analgesics required for the palliative care clinic were no longer available. The public stock of chemotherapy agents was increasingly scarce and was almost empty by the beginning of 2016. Smuggling routes allowed chemotherapy agents to enter local circulation in Mosul's pharmacies and the black market (at a cost that exceeded the ability of most patients). The cooling systems required to transport biological therapies were unavailable. By 2016, only three of the eight oncology specialists remained in the city, and the care they could provide was limited to the administration of chemotherapy purchased on the private market. Many patients attempted to flee the province and gain access to oncology centers elsewhere, but the exit routes were expensive and dangerous.

The commencement of the liberation battle in October 2016 injected new challenges in the delivery of oncology. The battle proceeded in two stages. First, the Iraqi Army and Coalition forces liberated the eastern side of the Tigris River as ISIL fighters retreated to the western side – the side of the city's leading hospitals, including the SONMH. Mosul residents on the liberated eastern side were now effectively cut off from local cancer care, and many attempted to travel to Erbil with the help of WHO ambulances. Meanwhile, cancer services on the western side quickly became untenable. ISIL saw the medical apparatus as a strategic asset from the standpoint of providing care to wounded fighters, but oncology was regarded as irrelevant to sustaining a fighting force.

As the battle intensified, ISIL fighters expelled all doctors and staff from the SONMH, repurposing the facility as a military fortress. Oncologists and oncology nurses were then forced by ISIL to work in the surgical hospital to provide general medical services and serve as human shields against Coalition airstrikes. Ultimately the battle over the western side of Mosul city resulted in the aerial bombing of much of the medical infrastructure, including the hematology center and the SONMH. The once famous oncology apparatus, in operation continuously since 1979 through multiple periods of war and sanctions, was reduced to rubble in early 2017.

3.1.4 Cancer care after ISIL

After the battle's conclusion, the destruction on the western side of the city made any notion of reconstituting oncology services a distant prospect. Most of western Mosul's buildings, houses, roads, electricity lines, and water treatment channels had been destroyed by aerial bombing and mortal shelling. The eastern side was relatively untouched by the effects of aerial bombing, however. Therefore, the decision was made to install a makeshift oncology unit on the eastern side. For several months, a small group of oncologists had two small rooms underneath a staircase and one bed for the administration of chemotherapy. In early 2018 they were able to expand this temporary facility into 10-15 beds and a patient lobby, and in 2020 they were able to expand further to 50 beds. But these expansions were made possible by installing temporary cabins repurposed from internally displaced people (IDP) camps, which are poorly ventilated and developed leaks that could not withstand the winter rains. Recently they moved out of the caravans into yet another temporary facility, which remains far too small to meet capacity. As a result, patients undergoing chemotherapy are stacked together tightly. None of the advanced technologies (e.g., gamma camera, linac machine) have been restored, and neither have the specialized clinics (e.g., pain clinic, colostomy clinic, palliative care clinic) been reconstituted.

To the time of this writing in December 2022, less than 20% of the SONMH has been completed. The impact of these severe limitations is that Mosul's historical position as a center for oncology in Iraq has become increasingly diminished. As advanced diagnostics are only available in Dohuk, Erbil, and Baghdad, and radiotherapy in the latter two, these cities are now supplanting Mosul in the referral chain. Whereas Mosul attracted patients from across northern and central Iraq until 2014, today, most patients are local. Human resources are one bright spot. 11 oncologists are now serving in Mosul, compared to 8 in the pre-ISIL period. While this increase could furnish the ground for a bright future of oncology in Mosul, the status quo is unsustainable from the standpoint of infrastructure. Future generations of medical graduates will look elsewhere as long as oncology in Mosul is associated with makeshift delivery conditions. The discussion section will explore the political economic factors that have contributed to the slow pace of oncology reconstruction.

3.2 Anbar Province

3.2.1 Overview of trends: cancer and conflict

3.2.1.1 Minimal oncology capacity before ISIL

In 2008, the first oncology unit was opened in Ramadi Teaching Hospital. Cancer services remained limited during the subsequent years due to ongoing conflict and political instability in the province.

3.2.1.2 Curtailment of oncology capacity during ISIL

In January 2014, ISIL took over Fallujah, the first Iraqi city to fall. In May 2014, ISIL took over half of Ramadi city, but the Iraqi military prevented ISIL from entering the area where the oncology unit is located. Limited cancer services continued. In April and May 2015, ISIL completed its takeover of Ramadi city, resulting in the shutting down of the oncology unit as specialists and nurses were forced to flee the city.

3.2.1.3 Rapid expansion in oncology capacity after ISIL

Ramadi was liberated by the Iraqi military in February 2016. By May 2016, the cancer unit reopened in Ramadi Teaching Hospital with one specialist. Capacity quickly expanded. In 2018, an expanded oncology unit was opened in Ramadi Teaching Hospital (25 beds, 15 nurse staff, and 5 oncologists). An oncology unit in Fallujah was opened in 2019. In 2020, a fully staffed oncology center was opened in Ramadi (9 oncologists, 3 radiologists, 50 beds, and nearly 60 nurses).

	Before ISIL	During ISIL	After ISIL
Oncologists	1	0-1	9
Oncology facilities (public)	1	0-1	2
Radiotherapy	0	0	0

3.2.2 Cancer care before ISIL

Oncology is a recent development in Anbar province. According to the interviews with the Iraq-based oncologists conducted for this study, historically residents of Anbar sought cancer treatments outside the province in the public oncology centers of Baghdad due to the capital's proximity. Despite concerns among citizens about increased cancer incidence potentially stemming from war-related environmental toxins, efforts to initiate oncology services in the province did not begin until 2008 with the establishment a public cancer unit within Ramadi Teaching Hospital. The unit had a capacity for 30 beds and was staffed by one oncologist and 9 nurses. Basic diagnostics and a limited range of cytotoxic and hormonal therapies were administered. A radiotherapy unit was under construction but never completed, meaning that all patients needing radiotherapy had to travel to Baghdad, Mosul, the Kurdistan Region, or abroad. Though cancer services remained minimal before ISIL, one crucial development was that seven oncology residents designated for service in Anbar began their training in 2010 abroad or other provinces. This fortuitous infusion of young trainees before the onset of the ISIL war would bode well for Anbar's eventual reconstruction.

3.2.3 Cancer care during ISIL

Oncologists from Anbar recounted how the province's nascent cancer services were weakened and eventually collapsed during the ISIL war. Due to its multiple borders and permeability to foreign fighters, Anbar was the first Iraqi province to witness major fighting from ISIL and other militant groups. The provincial capital, Ramadi city – where the sole oncology unit was located – was partially overtaken in May 2014. Fortunately, the zone of the city hosting the oncology unit remained under the control of the Iraqi Army for almost 12 more months. Oncology services continued to be operational during that period. But in April 2015, ISIL commenced an onslaught to overtake the remainder of Ramadi. Nurses and the sole oncology specialist fled the city.

By May 2015, the ISIL takeover of Ramadi was complete, and oncology was no longer available in the city. While some previously diagnosed cancer patients could flee to other provinces to continue care, those who were forced to remain in Anbar during ISIL control went without treatment of any kind. Accessing chemotherapy agents and other drugs on the black market or private pharmacies was nearly impossible. Because the Iraqi military regarded the presence of ISIL in Anbar as a major security threat due to its proximity to Baghdad, security forces blockaded virtually all traffic of goods coming in and out of the province. Previously diagnosed cancer patients who survived those dark days in Anbar recall juggling a lack of medications and food and, consequently, the unchecked painful advance of their disease. Most did not survive. The seven oncology residents mentioned previously – all of whom were now displaced to other provinces or countries – did what they could to follow up with displaced patients from Anbar, helping them manage symptoms and clear bureaucratic hurdles in accessing care outside the province. Care outside of Anbar in provinces such as Baghdad, Kirkuk and Erbil were available in public oncology hospitals but nearly always involved significant wait times and expenditures due to shortages and gaps in service, placing a significant financial and practical burden on displaced patients.

3.2.4 Cancer care after ISIL

After the liberation of Ramadi in February 2016, a limited set of oncology services returned to the city with the re-opening of the cancer unit in May 2016. The radiotherapy facility under construction had been destroyed in the fighting. The building housing cancer services had been badly damaged in the bombings and airstrikes, and space was minimal. The oncology unit dealt with dozens of advanced-stage patients who had not undergone adequate treatment during ISIL control – arriving with stacks of reports from multiple hospitals and often very unclear protocols. But conditions would rapidly improve due to favorable post-conflict political and economic conditions (see discussion section). In 2018, the Anbar Directorate of Health announced the opening an expanded cancer unit with 25 beds, 5 oncologists and 15 nursing staff. Then, in 2020, a stand-alone specialized oncology center was established, which replaced the previous cancer unit. The center boasted 9 oncologists, 3 radiologists, 2 laboratory specialists, and 60 nurses. The center has expanded diagnostic equipment, well-stocked chemotherapy agents, and laboratory apparatuses. Private oncology services are also rising in Anbar, including clinics offering chemotherapy, surgical oncology, and diagnostic and interventional radiology. The ongoing lack of radiotherapy continues to force Anbar residents to travel to Baghdad or abroad for that aspect of their treatment, however.

3.3 Kirkuk Province

3.3.1 Overview of trends: cancer and conflict

3.3.1.1 Oncology capacity before ISIL

In 2007, a public cancer department was established within Azadi General Hospital for diagnostics and basic chemotherapy (3 oncologists, 12 beds). Capacity was expanded between 2011 and 2013 (5 oncologists, 60 beds); more chemotherapy agents became available.

3.3.1.2 Partial expansion of oncology capacity during ISIL

As ISIL never took over Kirkuk city, the number of cancer patients expanded as Kirkuk city became home to displaced cancer patients from the ISIL-occupied areas of southern Kirkuk and other provinces. Government funding increased for drugs/equipment to account for the higher patient load, but the cancer unit's human resources did not change. The patient load decreased towards the end of the ISIL conflict due to the forced expulsion of Sunni Arab displaced persons from the city.

3.3.1.3 Stagnation in oncology capacity after ISIL

After the liberation of southern Kirkuk in 2017, Kirkuk's oncology capacity returned to pre-ISIL levels due to the removal of the additional government support provided during the conflict era.

	Before ISIL	During ISIL	After ISIL
Oncologists	5	5	8
Oncology facilities (public)	1	1	1
Radiotherapy	0	0	0

3.3.2 Cancer care before ISIL

According to the interviews conducted for this study, the oncology apparatus of Kirkuk was on a steady rise before ISIL. In 2007, a small public cancer unit with three oncologists and 12 beds was established within Azadi General Hospital in Kirkuk city center. The unit provided a limited range of diagnostics and basic chemotherapy (e.g., Adriamycin, Docetaxel, Paclitaxel, Vincristine). The patient load averaged 20-25 per day. In 2011 the oncology department expanded to occupy an entire floor of Azadi Hospital, and two oncologists were added to the team, totaling five. With the facility's expansion to 50-60 beds, chemotherapy agents increased (e.g., Herceptin, Avastin, Rituximab). As a result, the oncology unit developed a strong enough reputation to attract some referrals from Baghdad, Nineveh, Diyala, and Tikrit in addition to the local patients. By 2013, the oncology unit was receiving 30-45 patients daily. However, there were still serious limitations due to the absence of radiotherapy and scarce access to CT scans. Still, cancer services were on a positive trajectory that outpaced other provinces such as Anbar. This development was crucial for Kirkuk citizens due to the distances required to reach other centers. Before the introduction of oncology in 2007, doctors in Kirkuk referred patients diagnosed with cancer to Baghdad (275 kilometers to the south) or Mosul (175 kilometers to the northwest) for chemotherapy and radiotherapy.

3.3.3 Cancer care during ISIL

ISIL never overtook the urban center of Kirkuk, where the public oncology unit is located. In 2014, ISIL established a presence across the southern areas of Kirkuk province (e.g., Hawija district) but never succeeded in overtaking Kirkuk city. The relative stability in Kirkuk city led to an influx of displaced persons – including cancer patients. During 2014 and 2015, the daily patient load increased dramatically to 120/day. Most displaced patients arriving from the peripheries of the province and neighboring governorates lacked pathology reports and imaging. As there were only 2 CT scans in the city and one MRI machine, oncologists increasingly relied upon a mixture of X-rays, ultrasounds, and blood tests.

Fortunately, the MoH in Baghdad recognized the massive burden of displaced patients and decided to transfer large portions of the pharmaceutical stocks designated for Nineveh, Salah al-Din and Diyala provinces to Kirkuk. Because of this policy, important chemotherapy agents (e.g., Herceptin, Avastin, Cisplatin, Carboplatin) and hormonal therapy remained available throughout the ISIL conflict. Oncologists look back upon the ISIL period as, ironically, the time when crucial medications were most reliably present.

But other aspects of cancer care remained stagnant or worsened during the ISIL conflict. The lack of radiotherapy in Kirkuk created serious challenges during the ISIL period. Kirkuk's oncologists had for many years referred local patients needing radiotherapy to Baghdad, Sulaymaniyah, or Erbil. But after the rise of ISIL, patients were repeatedly turned back at the checkpoints entering neighboring provinces. These rejections were especially common for displaced cancer patients whose places of origin were the districts and provinces then occupied by ISIL. As a hub for many displaced cancer patients, Kirkuk oncologists had to manage the complex and painful therapeutic trajectories of patients who were being denied access to referrals and had to face either curative or palliative care without radiotherapy.

Though the MoH's conflict management of pharmaceuticals was viewed favorably in Kirkuk, other policy decisions during the conflict were more controversial. As Azadi General Hospital became a cross-provincial hub for oncology during the ISIL war, specialists in other disciplines complained that Kirkuk lacked adequate space to manage such an influx of cancer patients. This prompted the MoH in August 2016 to establish a separate unit for oncology in a building 500 meters across the road from the main hospital. While this decision reduced overcrowding at Azadi, some oncologists feel it created onerous physical and administrative barriers to accessing multi-disciplinary consultations and diagnostic services.

Kirkuk's centrality as a conflict oncology hub would become less prominent in the war's later stages. In December 2016, an ISIL attack in central Kirkuk prompted local security forces to expel scores of Sunni Arab displaced persons from the provincial capital on the unfounded pretext that their ongoing presence in the city constituted a security threat and that their cities of origin were now free from ISIL. The forced expulsions immediately impacted cancer patient levels. In the coming weeks and months, the patient load at the newly established oncology center went from 120/day to 40/day. Meanwhile the expelled cancer patients struggled to piece together care in other Iraqi cities or abroad – often at great personal expense.

3.3.4 Cancer care after ISIL

The liberation of southern Kirkuk province in October 2017 generated a final surge of complex and advanced cases in the oncology center. From that point onward, cancer patient levels have gradually returned to pre-ISIL levels (30-40 patients/day). It is now rare to see patients from the neighboring provinces of Anbar, Nineveh, and Diyala in Kirkuk. Kirkuk's loss of its hub-like status is partly a product of the waning of conflict and the return of populations to places of origin. It is also a product of the stagnation in oncology services. Unlike Anbar, which has witnessed a dramatic expansion of oncology services and human resources, Kirkuk levels have remained constant. There were 5 oncologists in Kirkuk before, during, and after the conflict. Only in the past 12 months (2022) have an additional 3 oncologists been added to the team. Pharmaceutical stocks – which again were strong during the conflict years – have regressed. Herceptin, commonly available in 2013 (the year before ISIL) and throughout the conflict (2014-2017), is only rarely in stock. Basic diagnostics such as CT scans remain exceedingly scarce and must usually be acquired privately. There are no plans to establish radiotherapy services in Kirkuk, forcing patients to travel across provinces or borders for treatment relying on personal finances. The discussion section will address the political dynamics undergirding the stagnation of oncology services in Kirkuk.

3.4 Salah al-Din Province

Limited oncology services were initiated in the provincial capital of Tikrit in 2008 under the direction of one oncologist. This oncology unit in Tikrit had minimal capacity and primarily received patients from the capital city and the immediate surrounding districts (e.g., Tikrit, Al-alam, Beiji). Patients from southern regions of the province (e.g., Balad and Dijeil districts) continued to seek cancer care in Baghdad, while patients in the northern regions (e.g., Shirqat, Tuz Khormato) sought care in Mosul and Erbil. When ISIL took over Tikrit in 2014, cancer services in Tikrit were suspended but were soon reopened in Samarra, a southwestern district of the province that had not fallen to ISIL. Oncology services were delivered in Samarra city at minimum capacity throughout the ISIL occupation of Tikrit. Oncology services were reconstituted in the capital city by the beginning of 2016, now with two oncologists. Cancer services have remained limited between the time of liberation and the present. However, to the surprise of the local medical establishment, the provincial government recently announced plans for a new oncology center that would include a linac machine. Why the provincial government (not the MoH) has decided to take the lead on this initiative remains unknown. If completed, the center would be the only oncology facility in the post-ISIL territories with a working linac machine.

3.5 Diyala Province

Diyala did not have oncology services of any kind before ISIL nor during the conflict. In the aftermath of liberation, a small department was created in 2018 under the supervision of one oncologist. At the time, the department lacked the approval of the MoH for the provision of chemotherapy from the public stocks. Thus, it relied exclusively on the transfer of drugs from cancer centers in other provinces. Through the advocacy efforts of local staff, chemotherapy approval was obtained in 2019, and a stand-alone center is currently under construction. At the moment, the oncology unit is staffed by two oncologists. It is primarily dedicated to the administration of chemotherapy and hormonal therapy, and it lacks diagnostic scanning, genetic tests, immunohistochemistry, immunological therapy, biological therapy, and radiotherapy. The new center is anticipated to include a broader range of diagnostic and therapeutic capacities.

4 Discussion

The aim of this article has been to highlight the impact of war on oncology infrastructure in five Iraqi provinces, specifically those that were impacted directly by the recent ISIL conflict. Examining each of the five provinces across the three periods (Before ISIL, During ISIL, After ISIL) has revealed important commonalities and differences in the experience of conflict at the level of cancer care services. These commonalities and differences are explored in greater detail in the following sections.

4.1 Common Challenges Across the Five Provinces

4.1.1 Gaps in cancer data/registry

An extensive analysis of the epidemiological data from each of the five provinces is not included in this study due to a lack of reliability in the data. The cancer registry in Iraq, including the overall data management system, has suffered under protracted conflict (20). Particularly in the five provinces affected by the ISIL conflict, war-induced displacements of cancer patients as well as the phenomenon of cross-border travel for care have exacerbated overall gaps in Iraq's cancer registry. Table 2 summarizes the MoH cancer data in the five provinces compared to country-wide averages for the year 2020 (21). Both the crude incidence rate (CIR) and distribution of the top ten cancers are of questionable reliability due to conflict-related displacement, migration, and cross-border care-seeking patterns. It is worth noting that the cancer of unknown primary (CUP) is among the top ten cancers in Nineveh in 2020, unlike the status ten years ago, in 2009 (22) nor even twenty years ago, in 1999 (23). Though CUP globally can range from 2.3% to 5% (24), the existence of a 3.94% CUP rate in Nineveh – compared to CUP in Erbil, Basra, Karbala, or in Iraq as a whole, where the rates were 2.53%, 2.44%, 1.01%, and 2.63%, in sequence – is a clear indication of the conflict-related difficulties and degradation of

TABLE 2 Cancer data from the five provinces compared to the whole country, extracted from the 2020 cancer registry (21).

	Nineveh	Anbar	Kirkuk	Salah al-Din	Diyala	IRAQ
Population	3926931	186416	168346	1678554	1722983	40150200
New cases	2511	1212	956	1083	1281	31692
CIR	63.94/100000	65/100000	56.8/100000	64.52/100000	74.35/1000000	78.93/100000
1st Top ten	Breast	Breast	Breast	Breast	Breast	Breast
2nd Top ten	Lung	Thyroid	CRC	Thyroid	CNS	Lung
3rd Top ten	CRC	CRC	Lung	Lung	Lung	CRC
4th Top ten	CNS	Lung	CNC	CRC	CRC	CNS
5th Top ten	Leukemia	NHL	NHL	Leukemia	Leukemia	Leukemia
6th Top ten	Stomach	HL	Prostate	CNC	Stomach	Urinary bladder
7th Top ten	Thyroid	Leukemia	Leukemia	Urinary bladder	Prostate	Thyroid
8th Top ten	NHL	CNC	Kidney	Stomach	Thyroid	NHL
9th Top ten	CUP	Stomach	Ovary	Skin	Skin	Prostate
10th Top ten	Skin	Urinary bladder	Uterus	Uterus	Urinary bladder	Stomach
Top ten no. (%)	1687 (67.18%)	877 (72.36%)	671 (70.19%)	747 (69.98%)	869 (67.84%)	20874 (65.87%)

CIR, Crude incidence rate; CNS, central nervous system; CRC, colorectal cancers; CUP, cancer of unknown primary; HL, Hodgkin's Lymphoma; NHL, Non-Hodgkin's Lymphoma.

cancer diagnostic capacity that led to the higher rate of CUP in Ninevah in the recent years.

4.1.2 Human resources

Across the five provinces examined in this study, maintaining the necessary human resources in medical and radiation oncology has been a persistent challenge (14). At the country-wide level, the origin of this problem dates to the 2003 US-led invasion and occupation, when many highly experienced doctors fled the country due to threats, intimidation, and violence (15). The 2014-2017 ISIL conflict displaced many oncologists and placed heavy burdens on those who remained in place. Over the past five years, progress has been made towards developing cohorts of local oncology specialists, but persistent gaps remain. The slow pace of reconstruction and lack of resources directed towards public oncology centers has increasingly incentivized both cancer specialists and nurses to allocate time to private clinics. Though private clinics may expand access for some patients in the short-term, the solidification of this trend may also reduce the quality and availability of public oncology to a vulnerable war-affected population.

4.1.3 Lack of radiotherapy

As noted in the results, the persistent lack of radiotherapy has become a glaring issue across the five provinces impacted by the ISIL conflict. While other provinces in the South and Kurdistan region have witnessed an increase in radiotherapy capacity in recent years (25), the five provinces included in this study have yet to see any progress in this domain. By the end of 2022, there were a total of 34 functional linacs for radiotherapy (25 linacs are public and 9 are private): 8 in the federal capital, Baghdad, 5 in Kurdistan's three provinces, and 21 in the nine provinces south of Baghdad. None were available in the five provinces highlighted in this study (25).

4.1.4 Pharmaceutical supply

In theory, the Iraqi MoH provides cancer drugs and chemotherapy free of charge to all Iraqi citizens. But in practice, pharmaceutical supply has proven to be unreliable, particularly during heightened episodes of conflict. During the ISIL period (2014-2017), shortages in pharmaceuticals forced patients to rely either upon private pharmacies and/or the black market to purchase chemotherapy and other medications. The slow pace of oncology reconstruction in some provinces has exacerbated gaps in the public system and buoyed the private pharmaceutical market. Recent policy research has shown that increasingly unchecked privatization and endemic corruption has led to a proliferation of fake and expired medications (26), deepening citizens' overall distrust of medicine.

4.1.5 Diagnostic capacity

As has been identified in other areas of the Middle East facing protracted conflict (27), diagnostic capacity in Iraq remains weak and is a major reason why so many cancer patients travel abroad for care. With limited cross sectional anatomical studies (CT and MRI scanners) and absent nuclear medicine studies, particularly during acute phases of conflict, oncologists in the five provinces examined have too often been forced to piece together a diagnosis by relying upon a patchwork of simple X-rays, ultrasounds, and blood tests, compared to other provinces that did not pass through such ISIL conflict and had showed remarkable progress in cancer diagnostics (14, 27, 28).

4.1.6 Cross-border & high-cost cancer journeys

Cancer patients have managed the lack of radiotherapy and other gaps in cancer services through cross-provincial treatment journeys in addition to international travel across borders. Between 2014 and 2017, cross-provincial referrals posed a significant risk for cancer patients from the ISIL-occupied provinces, who were repeatedly denied passage or interrogated by state security forces at checkpoints (11). Over the past five years, arbitrary denials at checkpoints have become less common, but nonetheless, the reliance upon travel for radiotherapy and other cancer services places profound practical and financial burdens upon Iraqi families. Cancer patients from a wide range of regions and socio-economic circumstances continue travelling to Iraq's oncology hubs (e.g., Baghdad, Sulaymaniyah and Karbala) and to international private centers (e.g., Beirut, Istanbul, Amman) for cancer diagnostics and treatments, often selling homes and properties to fund lengthy periods of treatment away from home. For a cancer patient population that is already struggling to rebuild their homes and lives after war, the extra cost of cross-provincial and cross-border travel represents a catastrophic financial burden (12).

4.1.7 Uneven distribution of care (urban/rural)

As a rule, cancer services are concentrated in the provincial capitals and remain totally absent in towns and mid-sized cities. For cancer patients residing in the rural areas of geographically vast provinces such as Anbar and Nineveh, the journey to the provincial capital for oncology is itself a major hardship and an expression of a glaring urban/rural divide. The urban/rural divide in medical infrastructure prolongs displacement, with displaced families often remaining in urban areas to retain access to oncology and other specialized medical services.

4.2 Variations in the Impact of War on Oncology Across Five Provinces

Though the shared challenges facing cancer services discussed above are vast, researchers must caution against an overly general narrative. Indeed, the impacts of war on oncology have locally distinct dimensions. These distinctions are highlighted in the following political economy analysis.

4.2.1 Before ISIL

Before the rise of ISIL, the level of advancement in oncology was widely divergent across the five provinces studied. By 2013 (the year before the takeover of ISIL), Nineveh was home to well-established advanced oncology services; in Anbar, Salah al-Din, and Kirkuk, new oncology structures were emerging to varying degrees; in Diyala, no progress had been made. The uneven distribution of oncology resources across the five provinces reflected Iraq's gradual transition from a highly centralized care delivery model to a partially federalized one. As early as the 1980s, Mosul (alongside Baghdad and Basra) witnessed the emergence of comprehensive high-level services because the MoH designed the national healthcare apparatus to channel tertiary referrals to the country's three largest cities. This coordinated system of referrals continued but became less sustainable after the US-led invasion of 2003. Not only did Iraq's hospitals in major cities suffer under the weight of violence and the proliferation of corruption, but the enshrinement of federalism in the 2005 constitution also encouraged the development of more localized medical infrastructures. Therefore, an increasing number of provinces (e.g., Kirkuk, Anbar, Salah al-Din, Erbil, Sulaymaniyah, etc.) witnessed the gradual emergence of oncology from 2007 onward. The progress towards localized care would not be seamless, however. The introduction of the federal model coincided with the emergence of political parties that exerted control over specific provinces (29, 30), which obscured the coherence of health governance at the local level.

4.2.2 During the ISIL period

Oncology witnessed different impacts of the ISIL conflict depending on the locality. In Mosul, ISIL allowed the city's well-established oncology services to continue basic operations partly because the group saw the city as its capital and wanted to maintain hospitals to treat the core of its fighting force. But cutting off supply lines to the city led to the gradual deterioration of public oncology and the emergence of a chaotic *ad hoc* system reliant upon private purchases and smuggling of drugs – at great cost for local cancer patients. In Anbar, nascent oncology services were curtailed entirely once ISIL took over the portion of the city where the oncology department was located due to the forced displacement of medical personnel. The relative proximity of Baghdad's sizeable medical infrastructure meant that many of Anbar's cancer patients could resume care in the capital city. Still, those who remained in the province suffered from a total lack of access to care. The irony of the evolution of oncology in Kirkuk is that the ISIL period arguably represented the pinnacle of its advancement and the height of its challenges. Oncology services were under extreme duress (due to the influx of displaced patients from surrounding provinces), and yet oncology services arguably reached their highest levels of progression (due to the shift of budgetary support towards pharmaceuticals from other provinces).

4.2.3 After the ISIL period

Understanding the highly variable pace of oncology reconstruction requires close attention to political economic dynamics. Recent research in policy and political science has shown that the military offensive against ISIL reshaped the political composition of different provinces in significant ways, directly impacting the pace of reconstruction (30). In Nineveh and Kirkuk, the military campaign against ISIL led to a fragmentation of the local political order and the proliferation of factions competing for influence (30, 31). The resulting lack of coherence at the level of governance has slowed the pace of reconstruction in both provinces (30), with important implications for the rebuilding of oncology infrastructure and the delivery of cancer services. In Nineveh, the rebuilding of oncology facilities has witnessed repeated delays and oncologists continue to work in makeshift structures. In Kirkuk, the level of cancer care delivery has stagnated amid a lack of consensus among competing local political factions as well as reductions of government-provided pharmaceuticals.

In contrast, the reconstruction of oncology has proceeded relatively quickly in Anbar, in part due to the relative coherence of the political environment. Though political dynamics in Anbar are by no means simple (32), it was the sole province where a single political coalition emerged in the wake of the ISIL defeat that gained control over the local government as well as influential positions at the federal government level. Consequently, the various governmental authorities overseeing healthcare (e.g., the MoH, the Anbar Directorate of Health, and the Anbar provincial government) have been able to work relatively effectively together to restore and expand oncology. Encouraged by political stability, economic activity in Anbar spiked in the post-liberation era due to heavy foreign investment (33, 34). Though these foreign funds were not directly allocated towards public oncology institutions, they contributed to the overall rebuilding of the province's housing units and economy, which enabled the speedy return of both the general population and oncology specialists.

This is not to say that post-conflict political economy is the only lens through which one can explain the variable pace of reconstruction. Differences in the level of war-related infrastructural damage have also played a role. While the aerial bombing was a feature of the liberation campaign in all major anti-ISIL battles, including Ramadi, there was arguably no destruction as total as what was witnessed in western Mosul, the site of Nineveh's oncology infrastructure. The strategy of the Iraqi Security Forces and the US-led Coalition was to encircle and isolate ISIL into the western segment. The targeting practices that followed showed little signs of meaningful discrimination between military structures and civilian spaces, resulting in scores of civilian deaths (35). With most of the roads on the western side destroyed or badly damaged, supplying reconstruction projects was a challenge in and of itself. Healthcare reconstruction has languished, generating enormous challenges in access to care (36).

4.3 Implications for cancer research in regions of war

4.3.1 Strengthening research on local cancer care delivery

A growing body of research is exploring the impact of war on oncology in the Middle East and across regions under conflict (37, 38). The bulk of this literature has viewed the understanding of cancer under conflict through a humanitarian lens (39), with particular attention paid to cancer care for refugees and displaced persons (40–42). These studies have highlighted the enormously complicated and fragmentary nature of treatment pathways for cancer care under conflict, such as "being unfamiliar with the health system, delays in health-seeking behavior because of competing priorities, financial limitations, or fear of persecution because of political or security issues related to their situation" (41). The humanitarian research lens is important and deserves resources and attention; however, in Iraq and many conflict-affected contexts, the medical infrastructures that absorb the bulk of cancer care needs during and especially after the formal cessation of conflict are local public oncology hospitals, which are too often ignored by humanitarian medicine and research.

By analyzing the impact of war on public cancer hospitals in five Iraqi provinces, this article connects the dots between the 'conflict' period (in which the humanitarian sector plays an important role) and the 'post-conflict' period (in which local hospitals are the centerpiece of care). Building upon prior work that has stressed the need for cancer research capacity development in the conflict-affected regions of the MENA (43), this study emphasizes the need for more research that focuses on locally specific care delivery dynamics in conflict-affected regions. In the Iraqi context, partnerships between the country's public oncology centers and international research bodies can facilitate this effort.

4.3.2 Strengthening epidemiological and environmental research

Though the focus of this article has been on the impact of war on cancer care and oncology infrastructure, it should also be noted that in each of these five provinces there are ongoing concerns and debates over the impact of war on the environment and the implications for cancer incidence. The US usage of depleted uranium munitions both in the 1990s and during the 2003-2011 period led to several important but methodologically limited studies examining potential linkages to the prevalence of certain cancers and other health conditions (5–7); however, such research has lacked the necessary resources and sustained support to establish clarity on this issue both at the national level and in distinct localities. Enduring questions over the impact of environmental exposure on cancer incidence will linger so long as local cancer research institutions lack the necessary funding to conduct interdisciplinary epidemiological and environmental studies, ideally in collaboration with partners across the Middle East region facing similar legacies of war.

4.4 Implications for Cancer Policy

4.4.1 Navigating oncology reconstruction amid complex local realities

Regarding the challenge of oncology reconstruction in the wake of conflict, the article indicates that the best-laid national cancer care plans must face political and economic realities at the national and sub-national levels. War disrupts and fragments local political orders in ways that endure long after formal hostilities have ceased. In the Iraqi context, provinces with more political fragmentation in the aftermath of the ISIL conflict have also witnessed a slower road to recovery in oncology and the broader medical infrastructure. In such fraught environments, the reconstruction of oncology requires building support and agreement among competing political groups and other local stakeholders. To that end, developing a granular understanding of the post-conflict political economy must be an integral part of the cancer policy formulation and implementation process.

4.4.2 Supporting public oncology institutions

Though addressing the gaps in cancer care described in this article will require the efforts of a broad set of stakeholders and diverse policy approaches, the growing calls for the greater privatization of medicine in Iraq should be received with caution. War has generated gaps in public medicine that are increasingly filled by a fragmented array of private services in Iraq and neighboring countries. As a direct consequence of this trend, catastrophic medical expenditure has become a major problem for families struggling to piece back their lives in the wake of conflict. Though the further expansion of private care is probably inevitable and may improve access to oncology for some patients, the hope of most Iraqi oncologists is for the government and international organizations to support them in strengthening public oncology hospitals across the country's 19 provinces, equipping these institutions with the capacity to provide comprehensive care during the current period of post-conflict recovery and relative stability, and in the face of whatever future wars may come.

5 Conclusion

Previous studies have called attention to the devastating impact of war on Iraq's once robust public oncology infrastructure. While this research has shown important trends in the war-induced deterioration of specific cancer services, it has yet to explain the uneven impacts of conflict across different regions and localities. The aim of this study has been to contextualize and understand local variations in the impact of war on oncology and the pace of reconstruction. The operational capacity of public cancer services in the five provinces directly impacted by the ISIL conflict (Nineveh, Anbar, Kirkuk, Salah al-Din and Diyala) was analyzed across three periods — before, during, and after the ISIL conflict. The major claim of the study is that conflict generates both immediate and long-term political and economic dynamics that contribute to locally specific divergences in the delivery of care and pace of reconstruction. Departing from the humanitarian focus of prior research on cancer under conflict, the article calls for increased scholarly attention to the variable capacities of public hospitals impacted by war — as they are the oncology infrastructures serving conflict-affected patients both during and long after hostilities formally cease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

The first author and the corresponding author are the owners of this project. Both the first author and corresponding author drafted the manuscript and arranged the interviews. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Central nervous system tumors in patients coming from areas of conflict in the Middle East/North Africa region: an experience from King Hussein Cancer Center

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Introduction: The global cancer burden has been disproportionately shifting towards low- and middle-income countries (LMICs). Limited availability and accessibility to screening, treatment and surveillance, increase in the prevalence and lack of control of risk factors, and underdeveloped healthcare infrastructures have greatly contributed to the disparity in the global cancer burden.

Methods: A retrospective cohort study was conducted that included adult and pediatric patients with an established diagnosis of Central Nervous System (CNS) tumors including brain or spinal tumors of which different demographic, clinical characteristics, and financial burden were presented.

Results: 749 patients were included stemming from various countries in the Middle East/North Africa (MENA) region including Libya (34.2%), Palestine (19.8%), Iraq (15.4%), Syria (14.6%) Yemen (14.5%), and Sudan (1.5%). Most patients were adults (66%) with a median age of 34-year-old. 104 patients had died (13.9%), 80 patients were still alive (10.7%) and most of the patients (n= 565, 75.5%) were lost to follow-up. The added cost of managing these patients is 10,172,935 Jordanian Dinars (JOD), with King Hussein Cancer Foundation (KHCF) covering around 34.3% of the total cost.

Conclusion: Our study aimed at taking a closer look at patients coming from areas of conflict in the MENA region diagnosed and treated for CNS tumors at

King Hussein Cancer Center (KHCC) over a 12-year period. It was found that even with the contributions of the Jordanian sources almost half of the patients were faced with the entire financial burden of treatment alone.

KEYWORDS

cancer care facilities, oncology service, areas of conflict, MENA region, Arab countries, central nervous tumors, financial burden

1 Introduction

The global cancer burden has been disproportionately shifting towards low- and middle-income countries (LMICs) with more than 50% of the 14.1 million cancer cases and with a projected 60% increase in the cancer burden by 2030 (1). Limited availability and accessibility to screening, treatment and surveillance, increase in the prevalence and lack of control of risk factors, and underdeveloped healthcare infrastructures have greatly contributed to the disparity in the global cancer burden (2). These problems have been further augmented by the disintegration of the healthcare systems due to the protracted conflicts prevalent in multiple countries in the Middle East and North Africa (MENA) region (3). A 2016 survey in Syria revealed a severe scarcity in cancer diagnosis and treatment resources including a shortage of specialized physicians, limited or lack of imaging modalities such as Magnetic Resonance Imaging (MRI), genetic testing, radiation therapy, bone marrow transplantation, and clinical trials (4). Similar conditions can be expected in multiple regions where long-lasting conflicts have been raging for decades. King Hussein Cancer Center (KHCC) is the largest comprehensive specialized cancer care institute in Jordan and one of the largest in the MENA region, and thus it has become a hub for many patients from neighboring countries seeking specialized cancer care, as well as many refugees currently housed in Jordan. Central nervous system (CNS) tumors are relatively rare tumors. However, they are still a significant cause of cancer related mortality and morbidity, specifically in children and young adults where they approximately cause 30% and 20% of cancer related mortalities, respectively (5). One of the most important prognostic factors in these tumors is the diagnostic interval which is defined as the time between symptom onset and the establishment of a diagnosis. Coven SL et al. found the median diagnostic interval of 42 days in a population of 146 American children (6), while Lu P et al. reported 97 days in a population of 433 Chinese children (7). Several publications addressed the overall burden of cancer among refugees. Mansour A et al. reviewed the burden of Syrian Refugees at KHCC including the cost burden. It was estimated that the cost of treating 869 Syrian patients with cancer was 15.6 million Jordanian Dinars (JOD) (22.1 million USD) annually; an important limiting factor to the access of proper and timely treatment (8). This has been reiterated in several other publications in countries from outside Jordan hosting Syrian refugees (9, 10). Mansour R et al. reviewed the burden of cancer among Palestinians living in the Palestinian Territories under the Israeli occupation that received treatment at KHCC in 2018 and 2019. Interestingly, CNS tumors were among the most common in which the initial diagnosis was changed among pathology reviewed at KHCC. However, detailed description of the discordant diagnosis was not mentioned in the paper (accepted for publication in Frontiers in Oncology). Most of the aforementioned literature discusses cancer in general, including description of the most common cancers (11). Literature on individual cancer types is scarce, but when available, would also focus on the most common types of cancer including breast in female patients (12). Focusing on pediatric cancer in children, a paper in 2020 comparing Syrian refugees to Turkish children with cancer reported significant differences in median age and median follow-up, metastatic or advanced-stage disease, relapse or progression and poor compliance to treatment and lower rates of overall and progression free survival in Syrian compared to Turkish patients (13). Interestingly, Syrian refugees were the focus of many studies, and other cancer patients from other areas of conflict were rarely reported, including patients from Yemen, Palestine, Libya, Iraq, and Sudan. Also, CNS tumors form only a small number of cases, thus when lumped with other tumors, the detailed description of the features unique to CNS tumors is barely presented.

We aim to describe CNS tumors among patients coming from countries in conflict in the MENA region, including the demographics, the diagnostic challenges and the financial burden and sources of funding in this group of patients managed at KHCC over a 12-year period.

2 Methods

2.1 Study design and participants

A retrospective cohort study was conducted that included adult and pediatric patients with an established diagnosis of CNS tumors including brain or spinal tumors (ICD-O Codes between C70.0-C72.9) that were referred to KHCC from countries/areas with ongoing conflicts, or patients residing in Jordan from any of the following countries; Iraq, Libya, Palestine, Sudan, Syria, and Yemen between 2010 and 2021.

The hospital electronic medical records, radiology reports and pathology reports were used to extract the following data including demographics, tumor primary site based on the International

Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), tumor type and grade as originally classified and then reclassified based on the 2021 WHO CNS classification, type of treatment including surgery, chemotherapy, and radiotherapy at both KHCC and other centers outside KHCC, and when available, survival status. The financial records were obtained from the Financial Department at KHCC, which included the cost of the management of the case, as well as the source of funding. This study was approved under number 22KHCC153.

2.2 Statistical analysis

Descriptive statistics were used for patient characteristics and clinical features of the study sample including describing demographics, histopathology, and sources of funding. Frequency with percentage was used to describe categorical variables.

Patients with non-applicable data in different variables, and patients who were lost to follow-up or who had a single visit to KHCC were excluded before conducting analyses. Pearson's Chi-square test was used to compare differences between categorical variables in different nationalities.

All data analyses were conducted using Stata version 17 software (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC.). The statistical significance was set at a 2-sided P<0.05.

3 Results

3.1 Demographics

As demonstrated in Table 1, this cohort included patients from areas of conflicts in the MENA region of which 256 patients were from Libya (34.2%), 148 from Palestine (19.8%), 115 from Iraq (15.4%), 110 from Syria (14.6%), 109 from Yemen (14.5%), and 11 from Sudan (1.5%). Of the total 749 patients, 429 were males (57.3%). The difference in gender among the included patients of the countries of conflict was statistically significant (p = 0.018). The median age at diagnosis was 34-years-old, 494 (66%) patients were adults and 255 (44%) were children or adolescents (< 18 years old).

3.2 Clinical characteristics

The most common sites of CNS tumors in order were cerebrum including thalamus (n=363, 48.5%), meninges (n=130, 17.4%), cerebellum (n=126, 16.8%), brainstem (n=71, 9.5%), spinal cord (n=34, 4.5%), and cranial nerves (n=22, 2.9%) followed by other nervous systems sites (n=3, 0.4%). Based on the 2021 WHO Classification of Tumors of the Central Nervous System, the most common type of tumors encountered in this study were gliomas, glioneuronal tumors, and neuronal tumors (n=446, 59.5%) followed by meningiomas (n=131, 17.5%). However, the least encountered tumors were those of the sellar region, germ cell tumors, and choroid plexus tumors (0.3%, 0.5%, and 0.7% respectively). The majority of tumors were categorized as grade 4 WHO CNS tumors (n=341, 45.5%) followed by grade 1, 2, and 3 (n=233, 31.1%, n=89, 11.9%, and n=73, 9.7% respectively). Table 2 shows further details of the various diagnostic categories.

Out of the 749 patients at KHCC, 187 patients underwent surgery (25%), 169 received chemotherapy (22.6%), and 306 received radiotherapy (40.9%). This is compared to 197 patients who had surgery (26.3%), 48 received chemotherapy (6.4%), and 56 received radiotherapy (7.4%) outside KHCC before receiving treatment at KHCC. There was a statistically significant difference in the number of patients between countries who did and did not receive chemotherapy at KHCC ($p = 0.03$) and radiotherapy outside of KHCC ($p = 0.043$).

Importantly, 26 (3.5%) patients had a major discrepancy in diagnosis when admitted to KHCC, 4 (0.5%) patients had minor changes in diagnosis and the rest of patients did not have any change in diagnosis (96%).

A hundred and four patients of the study population had died (13.9%) and 80 patients were still alive (10.7%) at time of collection of the data. Unfortunately, most of the patients (n= 565, 75.5%) were lost to follow-up, including 8 (1.1%) patients who had only a single visit to our center. Statistically, after excluding patients who were lost to follow-up and of single visits, there was a significant difference in the outcome between the countries in relation to survival (p = 0.027).

3.3 Sources of funding

The total cost of managing 749 patients was 10,172,935 JOD (equivalent to 14,348,467 USD). Patients receiving treatment at KHCC were funded either by Jordanian sources (n=171, 22.8%), by the corresponding government of the patient (n=242, 32.3%), by private insurance (n=14, 1.9%) or were self-funded (n=321, 42.9%). The amount of funds by each source in the included countries is demonstrated in Table 3. It is worth mentioning that Jordanian sources contributed 4,604,632 JOD (6,494,626.2 USD), accounting for 45.3% of the total cost of treatment for the patients, out of which King Hussein Cancer Foundation (KHCF) covered the costs of 3,492,383 JOD (4,925,849 USD), accounting for 34.3% of the total cost.

The countries of which individuals received the most of Jordanian sources of funding were Palestine (n=68, 2,240,698 JOD/3,158,579 USD) and Syria (n=59, 1,466,644 JOD/2,067,441 USD). In addition to that, the number of individuals receiving funding from their corresponding government was the highest in patients of Libyan nationality (n=199, 2,873,772 JOD/4,051,038 USD). Moreover, Yemenis patients receiving funding from private insurance were the highest among other countries (n=7, 82,592 JOD/116,426 USD) followed by Libyan patients (n=6, 32,396 JOD/45,667 USD). Furthermore, the countries of which individuals self-funded their medical expenses the most were Iraq (n=91, 440,772 JOD/621,338 USD) and Yemen (n=89, 478,709 JOD/674,816 USD). It is worth mentioning that the difference between the number of patients of each country in regard to different funding sources was statistically significant ($p < 0.05$).

TABLE 1 Demographics, clinical characteristics and outcome of included patients from areas of conflict.

	Total (n = 749)	Iraq (n = 115)	Libya (n = 256)	Palestine (n = 148)	Sudan (n = 11)	Syria (n = 110)	Yemen (n = 109)	*p-value*
Age (pediatrics/adults)								0.382
Adults (18 years and older)	494/749 (66%)	76/115 (66.1%)	181/256 (70.7%)	92/148 (62.2%)	7/11 (63.64%)	66/110 (60%)	72/109 (66.1%)	
Pediatrics (Younger than 18 years)	255/749 (34%)	39/115 (34.9%)	75/256 (29.3%)	56/148 (38.8%)	4/11 (37.36%)	44/110 (40%)	37/109 (33.9%)	
Gender								**0.018**
Female	320/749 (42.7%)	49/115 (42.6%)	123/256 (48%)	55/148 (37.2%)	8/11 (72.8%)	36/110 (32.7%)	49/109 (45%)	
Male	429/749 (57.3%)	66/115 (57.4%)	133/256 (52%)	93/148 (62.8%)	3/11 (27.2%)	74/110 (67.3%)	60/109 (55%)	
Surgery								
At KHCC								0.696
Yes	187/749 (25%)	23/40 (57.5%)	81/136 (59.6%)	34/67 (50.7%)	1/3 (33.3%)	28/46 (60.9%)	20/31 (64.5%)	
No	136/749 (18.1%)	17/40 (42.5%)	55/136 (40.4%)	33/67 (49.3%)	2/3 (66.7%)	18/46 (39.1%)	11/31 (35.5%)	
Not Applicable	426/749 (56.9%)	75/749 (10%)	120/749 (16%)	81/749 (10.8%)	8/749 (10.1%)	64/749 (8.5%)	78/749 (10.4%)	
Outside of KHCC								0.589
Yes	197/749 (26.3%)	28/28 (100%)	84/85 (98.8%)	34/34 (100%)	2/2 (100%)	21/22 (95.5%)	28/28 (100%)	
No	2/749 (0.3%)	0/28 (0%)	1/85 (0.2%)	0/34 (0%)	0/2 (0%)	1/22 (4.5%)	0/28 (0%)	
Not Applicable	550/749 (73.4%)	87/749 (11.6%)	171/749 (22.8%)	114/749 (15.2%)	9/749 (1.2%)	88/749 (11.7%)	81/749 (10.8%)	
Chemotherapy								
At KHCC								**0.03**
Yes	169/749 (22.6%)	20/115 (17.4%)	61/256 (23.8%)	45/147 (30.6%)	3/11 (27.3%)	25/110 (22.7%)	15/109 (13.8%)	
No	579/749 (77.3%)	95/115 (82.6%)	195/256 (76.2%)	102/147 (69.4%)	8/11 (72.7%)	85/110 (77.3%)	94/109 (86.2%)	
Not Applicable	1/749 (0.1%)	0/749 (0%)	0/749 (0%)	1/749 (0.1%)	0/749 (0%)	0/749 (0%)	0/749 (0%)	
Outside of KHCC								0.369
Yes	48/749 (6.4%)	4/43 (9.3%)	26/133 (19.5%)	9/59 (15.3%)	0/2 (0%)	5/40 (12.5%)	4/47 (8.5%)	
No	276/749 (36.9%)	39/43 (90.7)	107/133 (80.5%)	50/59 (84.7%)	2/2 (100%)	35/40 (87.5%)	43/47 (91.5%)	
Not Applicable	425/749 (56.7%)	72/749 (9.6%)	123/749 (16.4%)	89/749 (11.9%)	9/749 (1.2%)	70/749 (9.3%)	62	
Radiotherapy								
At KHCC								0.084
Yes	306/749 (40.9%)	51/115 (44.34%)	103/256 (40.2%)	72/148 (48.6%)	6/11 (54.5%)	37/110 (33.6%)	37/109 (33.9%)	

(Continued)

TABLE 1 Continued

	Total (n = 749)	Iraq (n = 115)	Libya (n = 256)	Palestine (n = 148)	Sudan (n = 11)	Syria (n = 110)	Yemen (n = 109)	*p-value*
No	443/749 (59.1%)	64/115 (55.65%)	153/256 (59.8%)	76/148 (51.4%)	5/11 (45.4%)	73/110 (66.4)	72/109 (66.1%)	
Not Applicable	0	0	0	0	0	0	0	
Outside of KHCC								**0.043**
Yes	56/749 (7.4%)	3/40 (7.5)	33/123 (26.8%)	6/53 (11.3%)	0/2 (0%)	5/35 (14.3%)	9/47 (19.1%)	
No	244/749 (32.6%)	37/40 (92.5%)	90/123 (73.2%)	47/53 (88.7%)	2/2 (100%)	30/35 (85.7%)	38/47 (80.9%)	
Not Applicable	449/749 (60%)	75/749 (10%)	133/749 (17.8%)	95/749 (12.7%)	9/749 (1.2%)	75/749 (10%)	62/749 (8.3%)	
Discrepancy in Diagnosis								0.445
Major	26/749 (3.5%)	4/115 (3.5%)	13/256 (5.1%)	4/148 (2.7%)	0/11 (0%)	4/110 (3.6%)	1/109 (0.9%)	
Minor	4/749 (0.5%)	1/115 (0.8%)	1/256 (0.4%)	0/148 (0%)	0/11 (0%)	0/110 (0%)	2/109 (1.8%)	
No change in diagnosis	719/749 (96%)	110/115 (95.7%)	242/256 (94.5%)	144/148 (97.3%)	11/11 (100%)	106/110 (96.4%)	106/109 (97.3%)	
Outcome								0.027
Alive	80/749 (10.7%)	11/115 (9.6%)	14/256 (5.5%)	29/148 (19.6%)	0/11 (0%)	23/110 (20.9%)	3/109 (2.8%)	
Dead	104/749 (13.9%)	16/115 (13.9%)	38/256 (14.8%)	26/148 (17.6%)	2/11 (18.2%)	17/110 (15.5%)	5/109 (4.6%)	
Lost to follow-up	557/749 (74.4%)	85/115 (73.9%)	203/256 (79.3%)	93/148 (62.8%)	9/11 (81.8%)	68/110 (61.8%)	99/109 (90.8%)	
Single visit	8/749 (1.1%)	3/115 (2.6%)	1/256 (0.4%)	0/148 (0%)	0/11 (0%)	2/110 (1.8%)	2/109 (1.8%)	

Bolded values refer to statistically significant p-value ($p < 0.05$).

4 Discussion

This study aimed to describe patients with an established diagnosis of a CNS tumor who came from areas of ongoing conflicts in the MENA region to receive treatment at KHCC in Jordan. To our knowledge, our study is the first to take a closer look at this patient population as the literature is scarce. We aimed to describe the challenges they faced in attaining proper healthcare including both diagnostic workup and appropriate treatment as well as the financial burden that they as well as the Jordanian sources and the KHCF faced in order to achieve it.

Our study included a total of 749 patients stemming from various countries in the MENA region including 256 patients were from Libya (34.2%), 148 from Palestine (19.8%), 115 from Iraq (15.4%), 110 from Syria (14.6%), 109 from Yemen (14.5%), and 11 from Sudan (1.5%). Sixty-six percent of the patients were adults and the median age of diagnosis was 34 years old with a statistically significant male predominance (57.3%). The majority of patients had grade 4 tumors at presentation (45.5%) according to the WHO CNS tumor classification, with gliomas, glioneuronal, and neuronal tumors (59.5%) being the most common, followed by meningiomas (17%). The majority of the tumors were found in the cerebrum (48.5%) followed by the meninges (17.4%) and the cerebellum (16.8%). The treatment regimens at KHCC mostly consisted of radiotherapy (40.9%), surgery (25%), and chemotherapy (22.6%). Interestingly, 26 (3.5%) patients had a major discrepancy in diagnosis when admitted to KHCC while the majority had their diagnosis confirmed (96%) and received treatment. As of the writing of this study, 10.7% of the patients were confirmed to be alive and 13.9% were deceased, while the rest of the patients (75.5%) were lost to follow-up. Among the accounted-for patients the overall survival was significantly different between different nations (p = 0.027).

The countries of which individuals were recorded to receive the majority of the total fund were Palestine (3,366,743 JOD/4,745,959 USD) and Libya (3,179,845 JOD/4,482,497 USD). This might be explained by the fact that Libyan (n=61) and Palestinian (n=45) patients were the highest individuals to receive chemotherapy regiments at KHCC compared to patients of other countries. Moreover, the discrepancy of the number of patients receiving chemotherapy may be attributed to the prolonged duration needed to complete regimens of chemotherapy leading them to prefer receiving their treatment in their home countries. Additionally,

TABLE 2 Primary CNS tumors sites, type, and grade based on the WHO CNS tumors classification.

	Total (n = 749)	Iraq (n = 115)	Libya (n = 256)	Palestine (n = 148)	Sudan (n = 11)	Syria (n = 110)	Yemen (n = 109)
Primary Sites							
Cerebrum including thalamus	363/749 (48.5%)	60/115 (52.2%)	120/255 (47.1%)	78/147 (53.1%)	7/11 (63.6%)	54/110 (49.1%)	44/108 (40.7%)
Meninges	130/749 (17.4%)	19/115 (16.5%)	56/255 (22%)	15/147 (10.2%)	1/11 (9.1%)	14/110 (12.7%)	25/108 (23.1%)
Cerebellum	126/749 (16.8%)	21/115 (18.3%)	32/255 (12.5%)	29/147 (19.7%)	2/11 (18.2%)	19/110 (17.3%)	23/108 (21.3%)
Brainstem	71/749 (9.5%)	10/115 (8.7%)	25/255 (9.8%)	10/147 (6.8%)	1/11 (9.1%)	13/110 (11.8%)	12/108 (11.1%)
Spinal Cord	34/749 (4.5%)	4/115 (3.5%)	11/255 (4.3%)	11/147 (7.5%)	0/11 (0%)	6/110 (5.5%)	2/108 (1.9%)
Cranial and paraspinal nerves	22/749 (2.9%)	1/115 (0.9%)	11/255 (4.3%)	4/147 (2.7%)	0/11 (0%)	4/110 (3.6%)	2/108 (1.9%)
Other nervous system sites	3/749 (0.4%)	0/115 (0%)	1/256 (0.4%)	1/148 (0.7%)	0/11 (0%)	0/110 (0%)	1/109 (0.9%)
Tumor Type/2021 CNS Tumors Classification							
Gliomas, glioneuronal and neuronal tumors	446/749 (59.5%)	77/115 (66.9%)	143/255 (56.1%)	89/146 (60.9%)	9/11 (81.8%)	69/109 (63.3%)	59/109 (54.1%)
Meningioma	131/749 (17.5%)	20/115 (17.4%)	56/255 (22%)	15/146 (10.2%)	1/11 (9.1%)	14/109 (12.8%)	25/109 (23%)
Embryonal tumors	97/749 (13%)	11/115 (9.6%)	24/255 (9.4%)	26/146 (17.8%)	1/11 (9.1%)	18/109 (16.5%)	17/109 (15.6%)
Cranial and paraspinal nerve tumors	31/749 (4.1%)	2/115 (1.7%)	16/255 (6.3%)	8/146 (5.5%)	0/11 (0%)	2/109 (1.8%)	3/109 (2.75%)
Hematolymphoid tumors	17/749 (2.3%)	4/115 (3.5%)	5/255 (2%)	3/146 (2.1%)	0/11 (0%)	3/109 (2.8%)	2/109 (1.8%)
Mesenchymal, non-meningothelial tumors	11/749 (1.5%)	0/115 (0%)	7/255 (2.7%)	2/146 (1.4%)	0/11 (0%)	0/109 (0%)	2/109 (1.8%)
Choroid plexus tumors	5/749 (0.7%)	1/115 (0.9%)	1/255 (0.4%)	1/146 (0.7%)	0/11 (0%)	1/109 (0.9%)	1/109 (0.9%)
Germ cell tumors	4/749 (0.5%)	0/115 (0%)	1/255 (0.4%)	1/146 (0.7%)	0/11 (0%)	2/109 (1.8%)	0/109 (0%)
Tumors of the sellar region	2/749 (0.3%)	0/115 (0%)	2/255 (0.7%)	0/146 (0%)	0/11 (0%)	0/109 (0%)	0/109 (0%)
Melanocytic tumors	1/749 (0.1%)	0/115 (0%)	0/255 (0%)	1/146 (0.7%)	0/11 (0%)	0/109 (0%)	0/109 (0%)
Not applicable	4/749 (0.5%)	0/115 (0%)	1/256 (0.4%)	2/148 (1.4%)	0/11 (0%)	1/110 (0.9%)	0/109 (0%)
WHO grade							
1	233/749 (31.1%)	34/114 (29.8%)	99/254 (39%)	33/145 (22.7%)	3/10 (0.3%)	27/105 (25.7%)	37/108 (34.3%)
2	89/749 (11.9%)	15/114 (13.2%)	25/254 (9.8%)	19/145 (13.1%)	0/10 (0%)	12/105 (11.5%)	18/108 (16.7%)
3	73/749 (9.7%)	13/114 (11.4%)	23/254 (9.1%)	21/145 (14.5%)	1/10 (0.1%)	6/105 (5.7%)	9/108 (8.3%)
4	341/749 (45.5%)	52/114 (45.6%)	107/254 (42.1%)	72/145 (49.7%)	6/10 (0.6%)	60/105 (57.1%)	44/108 (40.7%)
Not applicable	13/749 (1.8%)	1/115 (0.9%)	2/256 (0.8%)	3/148 (2%)	1/11 (9.1%)	5/110 (4.5%)	1/109 (0.9%)

TABLE 3 Funding sources and amounts for patients with CNS tumors coming from areas of conflict receiving treatment at KHCC.

Number of patients	Total (n=749)	Iraq (n=115)	Libya (n=256)	Palestine (n=148)	Sudan (n=11)	Syria (n=110)	Yemen (n=109)	*p*-value
Source of Funding (no of patients,%) Cost (JOD) (% from the overall cost)								
Jordan	171 (22.8%) 4,604,632 JOD (45.3%)	23 (20%) 632,228 JOD (58%)	7 (2.7%) 102,535 JOD (3.2%)	68 (46%) 2,240,698 JOD (66.6%)	1 (9.1%) 3,673 JOD (5.6%)	59 (53.6%) 1,466,644 JOD (83.8%)	13 (11.9%) 158,854 JOD (22.1%)	**0.000**
Jordanian government	34 (4.5%) 1,050,638 JOD (10.3%)	0 (0%) 0 JOD (0%)	1 (0.4%) 6,300 JOD (0.2%)	27 (18.2%) 849,308 JOD (25.2%)	0 (0%) 0 JOD (0%)	4 (3.6%) 189,842 JOD (10.9%)	2 (1.8%) 5,188 JOD (0.7%)	
KHCF	124 (16.6%) 3,492,383 JOD (34.3%)	22 (19.1%) 627,795 JOD (57.6%)	1 (0.4%) 44,436 JOD (1.4%)	40 (27%) 1,391,305 JOD (41.3%)	1 (9.1%) 3,673 JOD (5.6%)	50 (45.5%) 1,273,778 JOD (72.8%)	10 (9.2%) 151,396 JOD (21.0%)	
Private sector	13 (1.7%) 61,611 JOD (0.6%)	1 (0.9%) 4,433 JOD (0.4%)	5 (2%) 51,799 JOD (1.6%)	1 (7%) 85 JOD (0.03%)	0 (0%) 0 JOD (0%)	5 (4.6%) 3,024 JOD (0.2%)	1 (0.9%) 2,270 JOD (0.3%)	
Corresponding government	242 (32.3%) 3868289 JOD (38%)	0 (0%) 0 JOD (0%)	199 (77.7%) 2,873,772 JOD (90.4%)	43 (29%) 994,517 JOD (29.5%)	0 (0%) 0 JOD (0%)	0 (0%) 0 JOD (0%)	0 (0%) 0 JOD (0%)	**0.000**
Private insurance	14 (1.9%) 132,848 JOD (1.3%)	1 (0.9%) 17,860 JOD (1.6%)	6 (2.3%) 32,396 JOD (1%)	0 (0%) 0 JOD (0%)	0 (0%) 0 JOD (0%)	0 (0%) 0 JOD (0%)	7 (6.4%) 82,592 JOD (11.5%)	**0.003**
Self-funded	321 (42.9%) 1,567,166 JOD (15.4%)	91 (79.1%) 440,772 JOD (40.4%)	43 (16.8%) 171,142 JOD (5.4%)	37 (25%) 131,528 JOD (3.9%)	10 (90.9%) 62,392 JOD (94.4%)	51 (46.4%) 282,623 JOD (16.2%)	89 (81.7%) 478,709 JOD (66.5%)	**0.000**
Total amount paid	10,172,935 JOD	1,090,860 JOD	3,179,845 JOD	3,366,743 JOD	66,065 JOD	1,749,267 JOD	720,155 JOD	

Bolded values refer to statistically significant p-value ($p < 0.05$).

these prolonged durations may require higher expenses on the patients, their funding sources, or on their companions who may not be covered by funding policies.

The country in which patients received the least amount of funding was Sudan (66,065 JOD/93,129 USD). Of note, Sudan recorded the highest percentage of deceased patients (18.2%). On the contrary, Yemen was the second least funded country (720,155 JOD/1,015,172 USD) with the least percentage of deceased patients (4.6%). It is important to note that the aforementioned countries recorded the highest number of individuals who were lost to follow up. Based on the previous observation we could not correlate the overall survival with the amount of received fund for each country.

In a study by Fan et al. investigating the burden and trends of brain and central nervous system cancers in 2019, the percentage of deaths in high-middle income countries was 70.33% and 82.82% in LMICs (14). After excluding patients who were lost to follow-up, we have found that 56.52% of patients coming from areas of conflict in the MENA region were dead.

CNS tumors affect both children and adults and represent a substantial source of morbidity and mortality worldwide (15), especially in children and young adults where they approximately account for 30% and 20% of all cancer-related deaths respectively (5). The most common histological subtype of primary CNS cancer are gliomas; a large group of malignant brain tumors ranging from high-grade glioma (glioblastoma) to low-grade gliomas (astrocytoma, oligodendroglioma) (16). Glioblastomas, the most common primary brain cancer of glial origin, are almost always fatal within 2 years of diagnosis even with extensive surgical and medical therapy (17). In children, common histologies include medulloblastoma, germ-cell tumors, astrocytoma, brainstem gliomas, and ependymomas. Although these tumors are associated with high rates of morbidity and mortality, long-term survival can be achieved with comprehensive treatment strategies (18). The global burden of CNS cancer seems to be increasing significantly. A recent study found that in 2016 the global incidence of CNS tumors was approximately 330,000 cases with an estimated 227,000 deaths attributed to CNS tumors that same year. They also found that in the period between 1990 and 2016, the age-standardized incidence rates of CNS cancer increased globally by 17.3% (19). The effects that CNS tumors pose are underestimated by the incidence rates due to their high mortality rates and inherently disabling effects often rendering patients unfunctional for the rest of their lives (20). The burden of CNS tumors on healthcare systems is great and is often augmented by the fact that effective treatment is multimodal requiring access to an array of healthcare services including but not limited to chemotherapy, radiotherapy, and neurosurgical care (21). This highly specialized care is not widely available, especially in poor countries where war and conflict have been raging for decades forcing patients and their families to go through many difficulties just to gain access only to be faced with a lengthy and often pricy treatment plan putting further strain on their fragile livelihoods.

The total financial cost for the treatment of the 749 patients was about 10,172,935 JOD (equivalent to 14,348,467 USD). The main sources of funding included Jordanian sources, the corresponding government of the patients, private insurance, and self-funding by the patients or their families. Most of the patients' corresponding governments had no contribution to the treatment costs with the only exception being the Libyan and Palestinian governments contributing 90.4% and 29.5% of the total treatment costs respectively. About 42.9% (n=321) of the patients relied solely on out-of-pocket expenditure with only 1.9% (n=14) having any form of private insurance. The average out-of-pocket cost per patient was approximately 4882 JOD (6885 USD), which would constitute a massive financial burden given that the majority of patients come from low-income countries (Gross national income per capita of 1,085 USD or less, n=230), LMICs (Gross national income per capita of 1,086-4,255 USD, n=148) and upper-middle income countries (Gross national income per capita of 4,256-13,205 USD, n=371) (22), further emphasizing the financial hardships faced by these patients while dealing with the physical and psychological hardships of the disease itself. Even while limited by scarce resources, the Jordanian sources contributed about 45.3% (6,494,626.2 USD) of the total treatment costs, out of which the KHCF accounted for 34.3% of the total treatment cost.

The histopathological diagnosis was entirely changed for 3.5% (n=26) of the patients and showed minimal discrepancies in 0.5% (n=4) of the patients, highlighting the need for specialized neuropathologists not only during the treatment stage but also before coming to a conclusive diagnosis. Even though the majority of patients did not have any discrepancies in the diagnosis, a multitude of workups were done to either confirm or establish the diagnosis. Many of the patients included in the study did not have access to proper cancer diagnosis and treatment resources before presenting at KHCC, including specialized physicians, imaging modalities, and multiple blood tests that would be necessary for diagnosis and formulation of a treatment plan.

The biggest limitation of our study was the fact that the majority of the patients were lost to follow-up (75.5% n=565), a problem that commonly happens following the completion of treatment in many cancer patients. In a large cancer center in the United States, 22% (858 out of 3924) of breast cancer survivors were lost to follow-up after 10 years (23). In another study in the United Kingdom, 46% (256 out of 550) of cervical cancer patients were lost to follow-up after 3 years (24). However, this problem seems to be more prominent in developing countries as a study done in India found that almost 80% of their 690 cervical cancer patients were lost to follow-up within a 3-year period (25). The majority of our patient population was not indigenous to the country of Jordan and so most of them returned to their countries following treatment making follow-up extremely costly and difficult. Perhaps with the rise of telemedicine, these patients may be able to continue to receive expert care from the comfort of their homes, although this might also be limited by the inability to perform necessary tests and investigations in their home country that lacks such resources, thus limiting the ability to monitor for long-term effects of their treatment (chemotherapy, immunotherapy, or radiotherapy), and the potential risks of developing second, cancers.

5 Conclusion

In conclusion, our study aimed at taking a closer look at patients coming from areas of conflict in the MENA region diagnosed and treated for CNS tumors at King Hussain Cancer Center. We described the demographics, the diagnostic challenges, and the financial burden and sources of funding in this group of patients managed at KHCC over a 12-year period. A small percentage of patients had major discrepancies in their diagnosis and the majority of patients were lost to follow-up, we also found that even with the contributions of the Jordanian sources almost half of the patients were faced with the entire financial burden of treatment alone.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by King Hussein Cancer Center ethics committee. This study was waived from obtaining informed consent, as there was no direct interaction with participants or their legal guardian/ next of kin.

Author contributions

Conceptualization: MO and MA-H. Methodology: SAS. Formal analysis: SAS and MA-H. Data Collection: AA-A, AhM, HA-A, LI, MA, RH, and YA-S. Writing – original draft: JN and SAS. Writing – review and editing: AsM and MA-H. Supervision: MO, MA-H, and AsM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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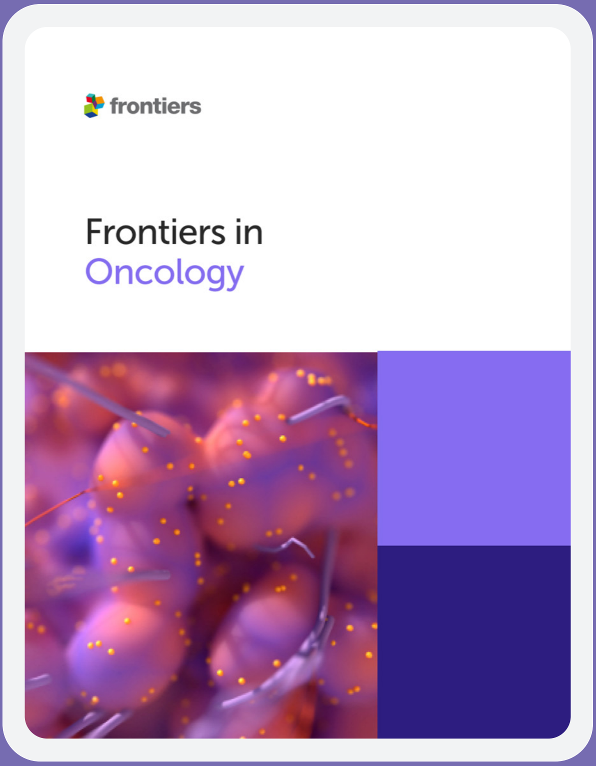

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