

Universal health coverage and global health in oncology

Edited by

Joerg Haier, Marine Hovhannisyan and Siegfried Geyer

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Universal health coverage and global health in oncology

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Overview of Cancer Control in Armenia and Policy Implications

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Cancer is the second leading cause of death in Armenia. Over the past two decades, the country has seen a significant rise in cancer morbidity and mortality. This review aims to provide up-to-date info about the state of cancer control in Armenia and identify priority areas of research. The paper analyzes published literature and local and international statistical reports on Armenia and similar countries to put numbers into context. While cancer detection, diagnosis, and treatment are improving, the prevalence of risk factors is still quite high and smoking is widespread. Early detection rates are low and several important screening programs are absent. Diagnosis and treatment methods are not standardized; there is a lack of treatment accessibility due to insufficient government coverage and limited availability of essential medicines. Overall, there is room for improvement in this sector, as research is limited and multidisciplinary approaches to the topic are rare.

Keywords: cancer policy, cancer epidemiology, cancer risk factors, cancer prevention, early detection of cancer, cancer treatment, developing countries, Armenia

INTRODUCTION

With an overall rise in the incidence of noncommunicable diseases in the world, cancer has become one of the leading causes of morbidity and mortality (1). A significant part of the burden of this disease is shared by low and middle-income countries (LMICs). Some projections estimate that by 2030, nearly 70% of all cancer cases will be diagnosed in these countries (1).

In recent years, there has been a sharp increase in cancer-related epidemiologic indicators in Armenia. Cancer is now the second leading cause of death in Armenia, accounting for 21% of all deaths (2, 3). The incidence and prevalence of cancer have increased significantly over the past decade, with an even greater increase expected by 2040 (2, 4).

Armenia also compares poorly with the countries of the region and globally (2). It has been among the top five countries with the highest incidence and mortality of cancer in the region of Western Asia (2). Taking into account the country's limited resources in the treatment and management of cancer, it is essential that Armenia strengthens its prevention and early detection strategies which would prove more efficient in resource management (5). This is especially important when considering the lifestyle and habits of the people in Armenia and the region, which are, in general, far from healthy (6).

This review is meant to provide a comprehensive description of the situation in Armenia regarding different aspects of cancer, such as incidence, prevalence, morbidity, mortality, prevention, early detection, and treatment. We aim to help identify priority areas of research and improvement in this field.

MATERIALS AND METHODS

The review is based on published literature and national and international reports. In addition, experts were consulted to confirm the information provided in older reports and to identify areas where research is lacking. Epidemiology data were graphed and their trends analyzed using the Joinpoint Regression Program version 4.9.0.0 which utilizes the permutation test to choose the best Jointpoint model that fits the data (7). It is worth mentioning that data from the National Institute of Health (NIH) are not based on a population-based cancer registry, as Armenia does not have one. GLOBOCAN data are estimated based on the cancer registries of neighboring countries (2).

RESULTS AND DISCUSSION

Overview of the Health System

Armenia is a middle-income country located between Europe and Asia, with a population of 2.9 million people (8). It has a GDP per capita of \$4,600, which is slightly above the lower threshold of upper-middle-income countries (9). Armenia acquired independence following the dissolution of the Soviet

Union in 1991 (10). It suffered a devastating earthquake in 1988, followed by a years-long war, during which health care reforms were not considered a priority (10, 11). After gaining independence, Armenia's health care system underwent a steep transformation from a centralized Soviet system, in which all levels of health care were publicly financed, to a highly fragmented one, financed mainly out-of-pocket (10). Government expenditure on health constitutes about 1.24% of the GDP, compared to an average of 4% for upper-middle-income countries (12, 13). As a result of this and the lack of significant voluntary health insurance coverage, out-of-pocket health expenditure accounts for about 84% of the current health expenditure (12). This is well above the World Health Organization's (WHO) recommended maximum of 20% (14), and it surpasses the out-of-pocket health expenditure rates of all other countries worldwide (2017 estimates) (12).

Organization of Cancer Care Financing

Total expenditure on cancer constitutes around 1.9% of Armenia's current health expenditure (5). European countries spend considerably more on cancer, with a corresponding average of 6% (15). Several state laws and initiatives in Armenia do, however, aim to cover the cost of cancer care (16).

Surgical treatment and radiation therapy are provided free of charge for all cancer patients through a program launched by the Government in 2019 (17). However, the allocated budget for this program did not correspond to the demands of the public sector which has led to a rise in treatment wait times (18). Furthermore, the inadequate budget may have additional downstream consequences such as the inability to assure high-quality care, along with the potential outmigration of clinicians from the public sector (19).

While outpatient and inpatient cancer care are fully covered by the government for all cancer patients, only vulnerable groups receive full coverage for chemotherapeutic treatment (16). However, 'full coverage' is not actually achieved because there is a spending limit on chemotherapy even for vulnerable groups (16). The government covers around \$750-worth of chemotherapy per year for vulnerable individuals and only half of that for non-vulnerable persons.

Infrastructure

Overall, 14 centers provide chemotherapy and three centers provide radiation therapy in Armenia. Many medical centers provide surgical interventions for cancer patients, but only eight of them provide specialized oncological surgery. Pediatric oncology services are provided in only one center in the country. Six of the fourteen available centers that provide cancer care are publicly owned (20, 21). Armenia does not have the issue of overloaded facilities; difficulties arise primarily due to the ill distribution of these facilities. The majority of cancer care facilities are situated in the capital city, Yerevan, where one-third of the population resides. Outside of Yerevan, there are only two centers that provide chemotherapy and oncological surgery (Gyumri and Vanadzor). There are no centers that provide radiotherapy outside of Yerevan. Thus,

regions that are sparsely populated do not have equal access to cancer care facilities, contributing to the delay or complete neglect of necessary treatment. On the other hand, having cancer centers in these sparsely populated regions is not sustainable. Therefore, difficulties in access to care should be countered by facilitating the transport and stay of patients in Yerevan, creating outreach clinics for Yerevan-based clinicians to visit regularly, and expanding the scope of telemedicine.

Workforce

In Armenia, there are 89 medical oncologists, 18 hematologists, 11 radiation oncologists, 51 surgical oncologists, and 11 pediatric oncologist-hematologists (3). Thus, one adult specialist provides care for about 73–88 new malignant cases per year, and one pediatric oncologist-hematologist provides care for about 8 new cases per year (3). These numbers are similar to many Eastern European countries, such as Ukraine and Hungary, and they indicate a surplus of oncologists (22). However, the geographic distribution of this workforce is not ideal (3). While several provinces have a shortage of oncologists, two of Armenia's eleven provinces have a complete lack of medical oncologists (3). Similarly, all pediatric oncologists and hematologists are located in the capital city Yerevan (3).

The education of specialists consists of a 6-year basic medical training followed by a 3-year residency training program in either hematology, oncology, or pediatric hematology-oncology. Graduates of the oncology residency program can officially work as medical, radiation, or surgical oncologists. However, they usually receive further training in the case of the latter two. Every year, around 8–10 students enroll in the oncology residency program. It is worth mentioning that the department of pediatric oncology and hematology of Yerevan State Medical University (YSMU) has recently been created in 2019. Armenia is among the first in former Soviet countries that created a unified “pediatric hematologist-oncologist” specialty, and currently, 10 fellows are enrolled in this program.

Several professional medical associations have been established in the past decade, these associations actively organize scientific events to ensure the professional development of specialists.

Cancer Statistics and Epidemiologic Measures

According to the Ministry of Health of Armenia, the crude cancer incidence rate in 2019 was 266.9 per 100,000 people (3). The cancers with the highest incidence rates were breast, colorectal, and cervical, among females and lung, bladder, and colorectal among males (**Figure 1A, Table 1A of the supplement**). The crude rate of prevalent cancer cases was 1699.5 per 100,000 people, with a female predominance. Breast, colorectal, cervical, uterine, bladder, and lung cancers were the most prevalent (**Figure 1B, Table 1B of the supplement**). The crude mortality rate in 2019 was 183.4 per 100,000 people — slightly higher among men than women (3).

Analysis of Trends

The incidence, prevalence, and mortality rates of cancer increased from 1991 until 2014, after which incidence became

relatively constant, while prevalence showed an upward trend and mortality showed a slightly downward trend. A 2-joinpoint model best describes the increase in incidence rate in the past three decades. The annual percent change in incidence rate was significantly different from zero from 1997 to 2019 at a 0.05 significance level. As shown in **Figure 2**, the incidence rate has increased by 6.65% annually from 1997 to 2006, and by 2.29% annually from 2006 to 2019 (3). The drop in incidence in 2019 seen in **Figure 2** is partly due to a change in methodology as post-mortem diagnoses were excluded that year. As for the increase in prevalence rate, a 3-joinpoint model was selected to best describe the data. The annual percent change in the prevalence rate was significantly different from zero from 2000 to 2019 at a 0.05 significance level. As shown in **Figure 3**, the prevalence rate has increased by 12.04% annually from 2000 to 2003, and by 2.26% annually from 2003 to 2009 and by 6.41% from 2009 to 2019 (3). The increase in mortality rate is described by a 3-joinpoint model as shown in **Figure 2**. The annual percent change in mortality rate was significantly different from zero from 1994 to 2015 at a 0.05 significance level. Mortality has increased by 5.41% annually from 1994 to 2006 and by 2.38% annually from 2006 to 2015 (3, 23–27). The incidence rates of breast, cervical, lung, colorectal, prostate, and stomach cancers have fluctuated in the past 8 years and did not show any significant trends. **Figure 4** presents the trends in the incidence rate of these frequently encountered cancers from 2012 to 2019 (3, 28, 29).

Stage at Diagnosis

As of 2019, nearly half (49.6%) of all cancers are diagnosed at stages III or IV (3). Furthermore, as much as 80% of lung cancers and 70% of stomach cancers are diagnosed at these stages (3). For perspective, this can be compared to neighboring countries, such as Georgia, where around 59% of all cancers are diagnosed at a late stage (30). **Table 1** shows the percentage of cases at each stage at the time of diagnosis for common cancer types in Armenia in 2019 (3).

According to GLOBOCAN 2020, Armenia was ranked third for the highest incidence of cancer in Western Asia (2). Armenia also had the highest mortality rate in the region and ranked 17th highest worldwide (2). The prevalence rate was also higher in Armenia compared to other LMICs, ranking third in Western Asia (2). This is possibly due to the high prevalence of risk factors, incomplete screening strategies, as well as issues with diagnostic and treatment modalities. On the other hand, the incidence rate of cancer in Armenia is considerably lower than that of most high-income countries. This may be due to the underdiagnosis of cancer in the country and it does not necessarily suggest that the cancer burden in Armenia is lower (2).

Risk Factors and Prevention

The cancer with the highest mortality rate in Armenia is lung cancer – a prominent risk factor of which is smoking (2, 3). About 28% of the population of Armenia smokes (51% of all males and 2% of all females) (6). Armenia's smoking rate is higher than the world average (20%) (31). Around half of the

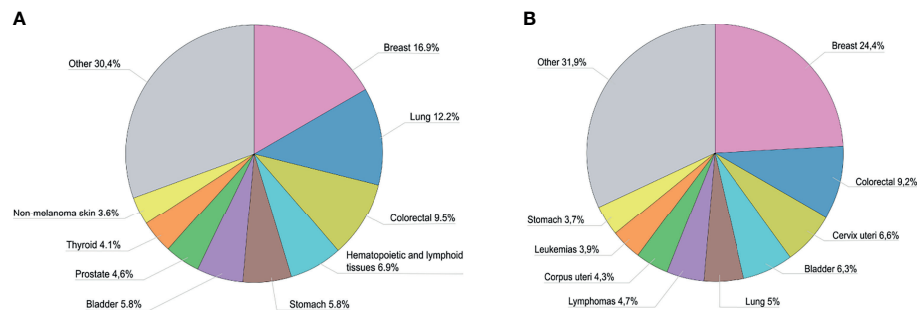


FIGURE 1 | (A) Proportion of new cases by cancer type in Armenia in 2019^a. **(B)** Proportion of prevalent cases by cancer type in Armenia in 2019^a. ^aData are adapted from the Statistical Yearbook of Armenia: Health and Healthcare 2020 (3).

people who smoke are predicted to die prematurely (32). While the proportion of smokers in neighboring Georgia is higher (31%), their lung cancer incidence rate is lower than that of Armenia (2, 33). Further research in the area is needed to determine whether the difference is significant. It is possible that the smoking rate among certain groups of the Armenian population, such as women or adolescents, is underestimated due to inaccurate self-reporting. Also, a large proportion of smokers in Armenia consume a higher than average amount of cigarettes per day.

Over the years, Armenia has failed to adopt proper strategies to combat tobacco use. Most notably, it failed to ensure smoke-free environments – except for schools and hospitals – and the implementation of many laws and regulations that aimed to restrict tobacco use was unsuccessful (34). That being said, Armenia was able to enforce the labeling of most tobacco products as harmful and the banning of sales to underage individuals (34).

In February 2020, the Armenian parliament approved a law that introduced further restrictions on tobacco use, including a ban on smoking in a wide range of locations (35). The law will gradually enter into force in the upcoming years, with the most notable ban to be introduced in 2022 (35). The law promises to introduce heavier sanctions upon violation compared to previous tobacco-related regulations (35).

Another common risk factor for cancer is alcohol consumption (36). High alcohol consumption increases the risk of developing cancers of the mouth, throat, larynx, esophagus, colorectum, liver, and breast (36). The last 3 cancer types have a high incidence rate in Armenia, which may be attributed to the high level of alcohol consumption in the country (3). Around 5.0% of all cancers in males and 1.8% of all cancers in females in Armenia are attributed to alcohol consumption (37). Armenia has an average rate of alcohol consumption compared to countries of the Commonwealth of Independent States (CIS), ranking behind Belarus, Russia,

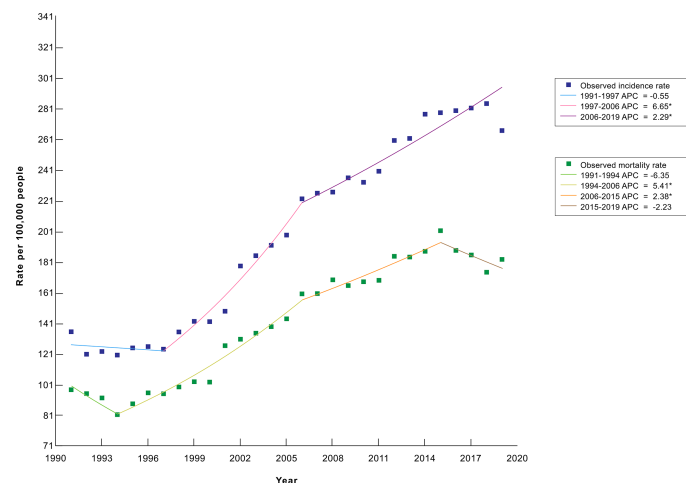


FIGURE 2 | Trends in the crude cancer incidence rate and the crude cancer mortality rate from 1991 to 2019 in Armenia, per 100,000 people^a. ^aData are adapted from the Statistical Yearbook of Armenia: Health and Healthcare 2020 (3) and the Statistical Yearbook of Armenia 1993-1994, 1995-1996, 2001, 2004, and 2009 (23-27). *Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.

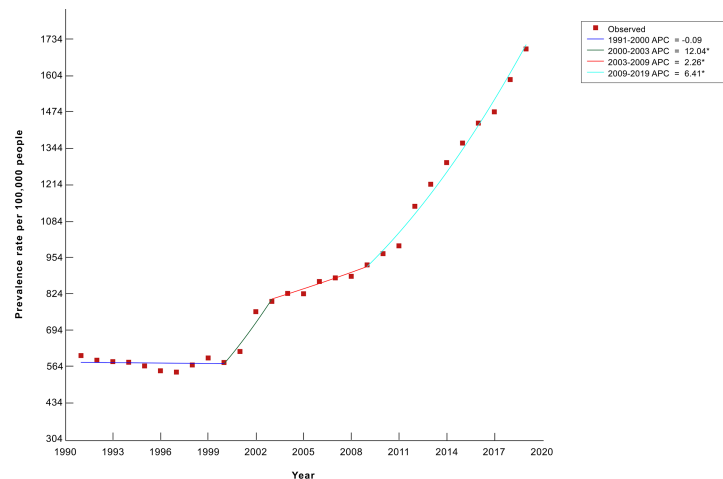


FIGURE 3 | Trends in the crude cancer prevalence rate from 1991 to 2019 in Armenia, per 100,000 people^a. ^aData are adapted from the Statistical Yearbook of Armenia: Health and Healthcare 2020 (3). *Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.

Moldova, Ukraine, Georgia, and Kyrgyzstan (38). Most of these countries have a higher incidence rate of alcohol-related cancers than Armenia (2), including colorectal, lip, oral cavity, throat, and esophageal cancers (2).

An unhealthy diet and physical inactivity are among the main risk factors for cancer (39). According to the 2016 national STEPS survey, about 20% of adults in Armenia are obese (14% of males and 25% of females) and 48% are overweight (6). Thus, the proportion of people with unhealthy weight is considerably higher than the world average (13% obese, 39% overweight), but closer to the European average (22% obese and 50% overweight) (40, 41). About 21% of Armenians are considered physically inactive, as they perform less than 150 minutes of moderate-intensity work per week (6). This is close to the average proportion of inactive people in LMICs, yet lower than

the global average (6, 38, 42, 43). Salt intake in Armenia is twice the daily recommendation by WHO, which is 5 g daily (6, 44). The majority of Armenians (76%) eat less than the WHO recommended average of 5 servings of fruit and/or vegetables per day (6). Armenia ranks fifth among countries that consume the least amount of vegetables – followed by neighboring Georgia (45). On the other hand, Armenians consume processed meat at remarkably higher amounts than other countries in Central Asia and the South Caucasus (45). This potentially contributes to Armenia's incidence rate of colorectal cancer, which is higher than that of any other country in said region (2).

Yet another risk factor for cancer is air pollution, which accounts for up to 30% of lung cancer cases worldwide (46, 47). Armenia ranks 23rd in the world regarding air pollution and has two of the ten most air-polluted cities in Western Asia (46).



FIGURE 4 | Trends in the incidence of frequently encountered cancers (2012-2019) in Armenia, rate per 100,000 people^a. ^aData are adapted from the Statistical Yearbook of Armenia: Health and Healthcare, for the years 2014-2020 (3, 28, 29).

TABLE 1 | The percentage of cases in each stage at the time of diagnosis for common cancers in Armenia, 2019.

Type of cancer	Stage I-II (%)	Stage III (%)	Stage IV (%)
Breast	76.8	6.9	16.3
Cervical	37.1	44.0	19.0
Lung	17.2	19.3	63.5
Colorectal	34.4	36.0	29.6
Stomach	30.6	26.9	42.5
Bladder	77.2	10.7	12.2
Prostate	35	28.8	36.1
All	50.4	19.5	30.1

(Data are adapted from the Statistical Yearbook of Armenia: Health and Healthcare 2020) (3).

The mining industry is a significant contributor to this problem (48). It is estimated that the emission of hazardous substances into the atmosphere due to mining, and other related operations, accounts for 13% of total emissions (48). The soil in towns proximal to mining sites is contaminated with several carcinogenic elements, including arsenic, lead, and cadmium (49). Moreover, about 57% of the capital city's residents are affected by ground contamination through the use of contaminated irrigation water (50). Overall, mining operations throughout the country are poorly regulated (50).

Screening and Early Detection

The majority of Armenia's population is vaccinated against hepatitis B in the first year after birth (34). HPV vaccination became a part of the national immunization program in late 2017 and has since been provided to females ages 13-14 free of charge. Vaccine coverage is increasing at a slow rate and remains low at an estimated 10% (51, 52). The low uptake of this vaccine may be due to the lack of knowledge about its necessity and the spread of false information about its harm (51, 52). According to a study among parents of teenage girls, some family physicians have advised against taking the vaccine (51). Although a great challenge, this misinformation must be addressed, especially when considering that the incidence rate of cervical cancer in Armenia is the second-highest in the region (2).

Armenia first launched a systematic screening program for cervical cancer in January 2015 (53). Within one year, around 110,000 women, ages 30-60, were screened by Pap smear (around 30% coverage) (53, 54). This marked a three-fold increase compared to the number of women who underwent cervical cancer screening in 2012 (53). The 3-year coverage rate now stands at 41% among this population (55), and fails to reach a 70% coverage rate achieved by many LMICs worldwide (56, 57).

Armenia does not have a systematic breast cancer screening program. The proportion of women aged 30-60 who underwent mammography screening during the past 3 years was lower in 2012 than in 2016 (about 12%) (54). This low rate can be partially explained by the lack of free of charge mammography examination services for the general population and high-risk groups alike (54). However, in 2020, a mobile mammography screening unit was introduced to screen for breast cancer among women aged 50-70 throughout the country (58). As for the less

effective ultrasound breast examination, it is offered in polyclinics free of charge but its 3-year coverage among women aged 30-60 is only 23% (54). Furthermore, the Armenia Demographics and Health Survey (DHS) of 2010 showed that 78% of women did not know how to perform a breast self-examination, despite health care providers being required to teach it to their patients during annual check-ups (59). In addition, only around 10% of women aged 30-50 reported ever receiving a manual breast examination by a health care provider (59).

Opportunistic colorectal cancer screening is also available in polyclinics (60). But because screening for colorectal cancer is recommended to be done systematically (61), a screening program will be launched for people aged 55-75 in the near future.

As for prostate cancer, only around 6% of males have had a prostate ultrasound examination at least once in the past year, which is done on an opportunistic basis, as recommended (54, 61).

With the implementation of the aforementioned screening and secondary prevention strategies, cervical tumors were detected in 15% of women who underwent screening in the last 1-3 years (54). Breast tumors were detected in 25% of women who underwent mammography examination in the last 1-3 years (54). In addition, numerous actions were taken to educate the general public about the importance of early detection of different cancer types (62). Likewise, screening guidelines were published for primary healthcare providers on providing screening for cervical cancer (63). It is worth noting that, as shown in **Figure 4**, the incidence of cervical cancer has not seen any major changes after the implementation of systematic screening in 2015. Incidence is expected to decrease through the detection and treatment of precancerous lesions, but it may be too early to see a trend yet. Nevertheless, there was a reported increase in the proportion of cases detected in early stages among females aged 30-60 during the first two years of the program (64); but such an increase did not occur in the general female population (3, 29, 54, 64-66).

A recent initiative towards the modernization of early detection strategies is the Armenian Research Infrastructure on Cancer Research (ARICE) project. ARICE is a HORIZON 2020 Twinning project between YSMU, the Medical University of Graz, Charles University Prague (CUP), and the International Agency for Research on Cancer (IARC) of WHO, which is aiming to build up a cancer biobank and a cancer management training network for establishing biomarker analysis standards for early detection of cancer specifically in the Armenian population (67).

Diagnosis

Diagnostic methods in Armenia have undergone a major improvement during the past decade, however, challenges remain (68). Diagnostic imaging modalities are present and available to patients in Armenia at lower rates than in most Eastern European countries (69). Armenia has about 2.4 MRI scanners and at least 7 CT scanners per 1,000,000 population (69). A PET/CT scanner was recently acquired and there is a

novel center for nuclear medicine within one of the medical centers in Yerevan (70, 71). Still, experts in the field argue that some of the essential cancer imaging techniques are either outdated or completely absent (i.e. the SPECT/CT scanners, most of which are old) (61). In addition, the lack of protocols substantially hinders the diagnostic process. Even though many clinicians/radiologists utilize guidelines from prominent foreign associations, no government-set protocols exist and there are discrepancies among different institutions in terms of diagnostic approaches.

As for laboratory examinations, all essential tools for laboratory diagnosis are available. Nonetheless, a major problem in this field lies in the lack of good documentation practice, as most institutions have no laboratory information management system. This leads to a greater risk of making errors and the loss of important data.

As for genetic testing for cancer, there is a specialized genetic center in Armenia, which performs analyses of the full list of somatic mutations of genes (e.g. EGFR, KRAS, NRAS, BRAF, ALK) for targeted therapies required by the international guidelines, as well as Next Generation Sequencing analyses (NGS) of the hereditary cancer gene panel (84 genes) associated with all known types of hereditary cancers, all according to the European Molecular Quality Network requirements. Nevertheless, genetic testing is conducted infrequently due to the high cost of most testing options and/or the unaffordability of possible targeted therapy.

Lastly, pathologists have highlighted many major problems in the field of histopathologic diagnostics. The main issue is the insufficient personnel and laboratory facilities required to manage large volumes of examination specimens (61). The methods many pathologists use in their practice are not consistent with internationally approved histopathologic

protocols, such as proper tissue staining and slicing technique. This creates further confusion and redundancy among oncologists, as they often receive inconclusive examination results, requiring repeat biopsies (61).

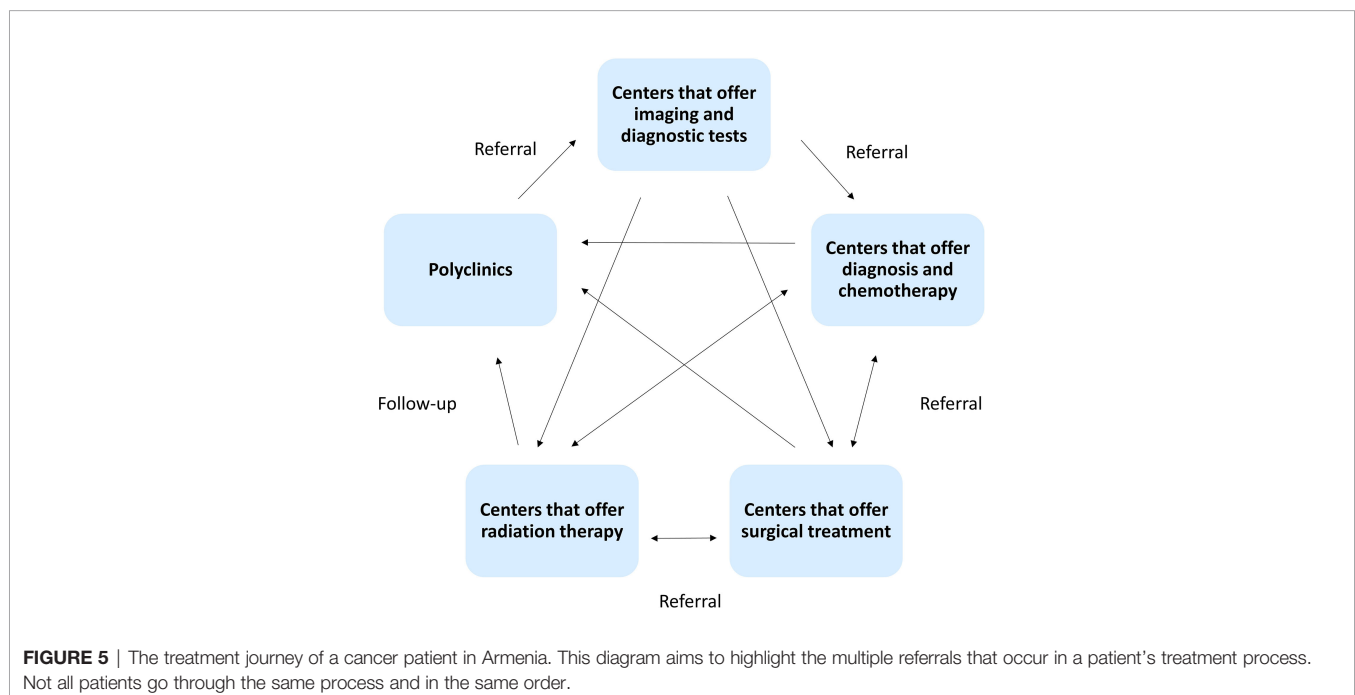
Treatment

All main cancer treatment modalities are available in Armenia, including surgery, radiotherapy, and medication therapy. **Figure 5** presents a simplified diagram of the process of cancer treatment in Armenia.

Surgical oncology is not a registered specialty in Armenia and many surgeons who practice the specialty are also involved in other non-oncological surgical procedures. Despite that, the National Center of Oncology has nine departments specialized in the surgical treatment of cancer (61). Most of the necessary treatment options are available and accessible, but several novel treatments, such as arterial embolization of tumors, are absent. In addition, surgeons generally do not follow a uniform national protocol, which leaves plenty of room for discrepancies.

The provision of radiation therapy is mostly centralized (61). Armenia has two linear accelerators and one Telecobalt unit, all located in the capital city, Yerevan. There used to be a Telecobalt unit in the second most populated city of Gyumri, but it was decommissioned recently in 2020. There is also one center that offers brachytherapy (61). Despite this, there are problems with the immobilization devices, which are limited and therefore often reused or used inconsistently. This increases the adverse effects of radiotherapy and directly impacts its efficiency (61).

Medical oncology in Armenia is fairly up-to-date. However, a major limitation in this field is the accessibility and registration status of medication. The national essential medicines list (EML) in Armenia includes 37 out of 62 of the antineoplastic and supportive cancer medicines listed in WHO's EML (72, 73).



However, the registration of many of the medications in the EML is not regularly renewed. Among the cancer drugs that are considered nationally essential, 30% are not registered and research shows that drugs which are not registered are mostly inaccessible to patients (74, 75). A study conducted in 2018 reported that 8 out of the 30 essential pediatric cancer medicines were not available in Armenia at the time (76). The study reported a decrease in the percentage of registered essential medicines since 2016, which highlights the lack of effort directed at solving this issue (76, 77).

The lack of proper state coverage of cancer medicines makes access to them impossible for a large majority of the population. Even when a certain part of treatment is covered by the state, clinicians report that many patients cannot pay for the non-covered part which renders their treatment incomplete. In addition to that, clinicians strongly emphasize patients' inability to cover the cost of novel therapies. According to one clinician, only 1 out of 10 patients who need immunotherapy can cover its cost. In 2020, the state launched a program to provide the targeted therapy drug Trastuzumab free of charge for women with non-metastatic HER2/neu positive breast cancer (78). Also, pediatric cancer treatment is provided almost completely free of charge thanks to charitable organizations.

Recently, access to medicines has become even more limited due to the novel coronavirus (COVID-19) pandemic as Armenia's drug supply routes have been suspended. This impacted the availability of some of the essential cancer medications. As a result, many treatment plans were changed by substituting the unavailable medication with available ones.

Concerning the transplantation of hematopoietic stem cells, the Hematology Center after Prof. R. Yeolyan offers autologous hematopoietic cell transplantation (79). However, allotransplantation was not available until very recently, and patients used to be redirected to foreign institutions. With the launch of allogeneic transplantation in 2021, allotransplantation for cancer patients will soon be performed locally.

As discussed earlier, a lack of national guidelines poses issues on many fronts, including treatment modalities. Even those who are provided with national guidelines by the Ministry of Health rarely implement them. The ones that are used are mostly taken from the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and others. Hence, they do not correspond to the contemporaneous treatment conditions in the country. That being said, detailed guidelines for

the management of 17 types of pediatric cancers were adapted and developed between 2019 and 2020, following the centralization of pediatric cancer care in the Pediatric Cancer and Blood Disorders Center of Armenia in early 2019. In addition, few centers in Armenia utilize multidisciplinary tumor boards.

Finally, several institutions in the country are involved with providing palliative care. Most of the palliative care medications included in the WHO EML are registered and available in Armenia (73). Nevertheless, disparities exist between the need and the actual availability of palliative care services (80). Palliative care in Armenia suffers from a lack of state-approved treatment guidelines, a shortage of trained personnel, a lack of awareness in patients about drug use, as well as policy and legislation-related issues (80, 81). A study conducted in 2015 revealed that while 80% of cancer patients suffered from moderate to severe pain, only 8% received a strong opioid analgesic (80). As a result of this and several other studies, the National Strategy on Palliative Care Action Plan was adopted (81). Following the approval of the action plan, oral morphine became officially registered in Armenia in mid-2018 and is now more easily accessible to patients with cancer, albeit with occasional shortages (74, 81).

A timeline of major events that contributed to the development of cancer care in Armenia is shown in **Figure 6**. It is worth noting that charitable organizations have significantly contributed to the development of cancer care. In the nineties, pediatric cancer care was largely covered by the "Hilfe fur Armenia Foundation" (Germany); later on, in different periods, charities such as "Bridge of Health", "Nvirir Kyanq", "Ognem", "Fund 100", "Menq enq", and "City of Smile" have continued to fund the treatment of patients as well as the professional development of physicians and other capacity-building projects. The City of Smile foundation is currently the largest cancer charity organization in Armenia and it has been undertaking most of the coverage for pediatric oncology in the last few years. Recently, the foundation has extended its support to also cover the diagnosis and treatment of young adults aged 19 to 25. Adult cancer patients also receive charitable support in certain cases, e.g. the Max Foundation provides Glivec® free of charge for patients with chronic myeloid leukemia (CML). There are also several patient advocacy organizations and support groups, such as the Henaran Foundation, that provide legal, psychological, and social support to cancer patients in addition to financial support.

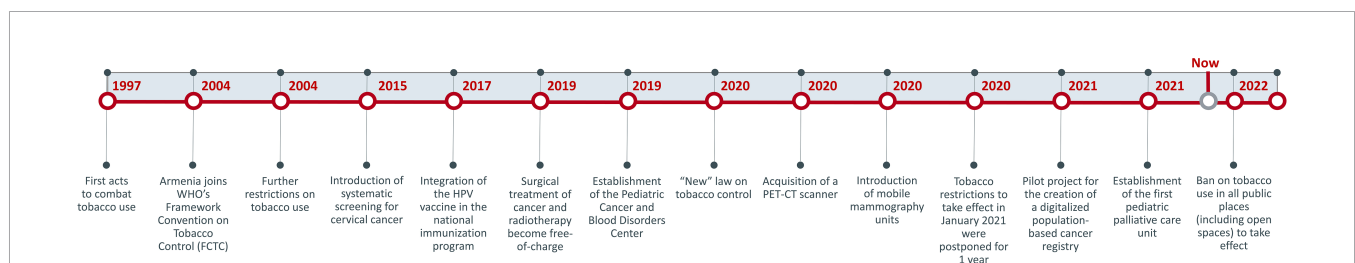


FIGURE 6 | Timeline of major events in the development of cancer care in Armenia.

Recommendations

Based on this review, we have designed a list of recommendations that address the major problems associated with the burden of the disease;

1. Ensure the implementation of anti-tobacco laws and regulations and encourage a healthy lifestyle. Expand the National Cancer Control Plan (NCCP) with regard to primary prevention by adding a timeline for each objective, defining every objective in measurable terms, and monitoring implementation.
2. Create a population-based national cancer registry to obtain a good understanding of the epidemiology of cancer in the country, especially with regards to culturally specific risk factors.
3. Boost early detection by increasing cancer awareness among the general population and primary healthcare providers, as well as ensuring equitable access to all screening services especially for the early detection of breast cancer.
4. Improve access to medicines by ensuring the timely registration of all those deemed essential by WHO and ensuring full cost coverage for at least those that are considered essential nationally. Regarding painkillers, improve access by raising awareness among prescribing physicians on the necessity of effective pain management among cancer patients.
5. Improve diagnosis quality by upgrading diagnostic documentation and management systems in accordance with current guidelines, as well as by ensuring the development of an appropriate workforce and facilities for histopathology services.
6. Improve treatment outcomes by creating multidisciplinary tumor boards and participating in partnership programs with developed countries, creating national cancer management guidelines, importing novel approaches and techniques, and most importantly, monitoring the quality and adherence to guidelines.
7. Within the NCCP, define the specific role of different sectors of the government and society, such as the education sector, environmental sector, ministry of labor, NGOs, medical associations, patient advocacy groups, etc.

CONCLUSION

Cancer control in Armenia has improved greatly over the past decade. Developments are observed in almost all aspects of cancer care and prevention. Still, there is plenty of room for improvement, and shortcomings are often identified by health authorities. However, rapid improvement seems somewhat impossible due to economic, cultural, and political factors.

Note: This article reviews the cancer situation in Armenia before the war which occurred from September 27, 2020, to November 10, 2020. The implications of the war are not taken into account in this review.

AUTHOR CONTRIBUTIONS

KB: conceptualization, data curation and literature search, interpretation of data, project administration, writing of the original draft, visualization (figures), validation of all data provided in the paper. TA: conceptualization, data curation and literature search, interpretation of data, project administration, writing of the original draft, visualization (figures), validation of all data provided in the paper. AMe: data curation and literature search, reviewing and editing. SS: validation of data on health care organization, interpretation of problems and suggesting of solutions, critical revision and editing of the paper. DZ: validation of data on adult medical oncology, critical revision and editing of the paper. LSaf: validation of data on adult medical oncology, critical revision and editing of the paper. LSar: validation of data on pediatric hematology and oncology, critical revision and editing of the paper. AA: validation of data on adult medical oncology, critical revision and editing of the paper. LH: validation of data on adult medical oncology, critical revision and editing of the paper. AV: validation of data on adult hematology and oncology, critical revision and editing of the paper. ATad: validation of data on risk factors and prevention, critical revision and editing of the paper. DM-N: validation of data on policy and epidemiology, critical revision and editing of the paper. PK: validation of data on cancer pathology, critical revision and editing of the paper. TSag: validation of data on radiation oncology, critical revision and editing of the paper. MK: validation of data on surgical oncology, critical revision and editing of the paper. HV: validation of data on radiology, critical revision and editing of the paper. MH: validation of data on policy and epidemiology, critical revision and editing of the paper. TSar: validation and provision of data on genetics, critical revision and editing of the paper. KS: validation and provision of data on research and genetics, critical revision and editing of the paper. DB: validation of data on genetics, critical revision and editing of the paper. ATan: validation of data on cancer care organization and management, critical revision and editing of the paper. SD: validation of data on cancer care organization and management, critical revision and editing of the paper. AMu: validation of data on health policy and regulations, critical revision and editing of the paper. GT: conceptualization, validation of data on pediatric oncology, philanthropy, and global comparisons, critical revision and editing of the paper, supervision and mentorship. SB: conceptualization, data curation, validation of all data provided in the paper, critical revision and editing of the paper, project administration, supervision and mentorship. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.782581/full#supplementary-material>

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Inequality in Accessibility of Proton Therapy for Cancers and Its Economic Determinants: A Cross-Sectional Study

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Background: Cancer is a leading cause of death in the world, and the estimated new cancer cases were 19 million and the estimated cancer deaths were around 10 million worldwide in 2020. Proton therapy (PT) is a promising treatment for cancers; however, only few patients with cancer received PT due to limited number of PT centers worldwide, especially in low- and middle-income countries.

Methods and Results: Cross-sectional country level data were collected from publicly available information. Lorenz curves and Gini coefficient were used to assess the inequality in accessing to PT, and zero-inflated Poisson models were used to investigate the determinants of number of PT facilities in each country. The Gini coefficients were 0.96 for PT centers and 0.96 for PT chambers, which indicated high level of inequality. Total GDP had a significant impact on whether a country had a practical PT center, whereas total GDP and GDP per capita had significant impacts on the number of PT centers.

Conclusion: Extremely high inequality exists in accessibility of PT centers among all countries in the world. Economic development was the most important factor determining the adoption of PT; thus, with the growth in global economics, more PT centers can be expected in near future.

Keywords: proton therapy, inequality, accessibility, cancer treatment, economic determinants

INTRODUCTION

Cancer is a leading cause of death which ranks as top 2 cause of death before the age of 70 years in 112 and top 4 in 135 of 183 countries in the world (1). In 2020, the worldwide new cancer cases were estimated 19,292,789, and the estimated cancer deaths were 9,958,133 (1). In the United States, 26% of all patients with cancer received radiation therapy as part of the initial treatment (2). In the United Kingdom, 27% of those receiving at least one of the main treatment types were treated with radiotherapy, and cancers of the head and neck had the highest proportion of radiotherapy (83%) (3). In Europe, approximately

45%–55% of newly diagnosed cancer cases required radiotherapy (4). Although the actual radiotherapy utilization rates in middle-income countries were relatively lower, the optimal radiotherapy utilization rates were also around 50% (5).

Proton therapy (PT) has many advantages comparing to conventional techniques such as photon therapy. PT can reduce low and intermediate radiation dose to normal tissues, which improves the outcomes of patients with cancer by reducing treatment-related toxicities and/or allowing a higher safe radiation doses to enhance tumor control rates (6). The effectiveness of PT was shown in many systematic reviews in different types of cancers [e.g., head and neck cancer (7), breast cancer (8), prostate cancer (9), rectal cancer (10), nasopharyngeal cancer (11), gastrointestinal malignancies (12), chordoma (13), and gliomas (14) and different age groups (15, 16).

The number of PT centers was rapidly increasing in the last decades: in 2000, there were only 10 operational facilities worldwide and this number increased to 25 in 2010, and by the end of 2020, there were 95 PT facilities in clinical operation (17). However, PT is more expensive than conventional radiation treatment technologies. The construction cost of a PT center is up to over US\$200 million (6, 18, 19), which is four times of the construction cost of a photon facility (19), and the operational cost is at least US\$ 25 million per year, which is 1.5 times higher than a photon facility (19).

Compared with the huge number of patients with cancer worldwide, the number of patients who can get access to PT was limited, especially for those patients from low- and middle-income countries (LMICs). Considering distributions of age, stage and types of cancers, and evidence and trends in PT usage, at least 1% (conservative) up to 7.5% (generous) of the total patients treated with RT will be treated with PT in LMICs (20).

In this study, we aim to assess the inequality in accessibility of PT among all countries in the world and explore what are the determinants of number of PT centers in each country.

MATERIALS AND METHODS

Data

The cross-sectional country level data were collected from publicly available information. Data for the number of PT facilities in clinical operation by the end of 2021 were collected from website of Particle Therapy Co-Operative Group (PTCOG) (17). Data for country level statistics and indices in 2020, including gross domestic product (GDP), GDP per capita, total population, total investment, and general government total expenditure, were collected from International Monetary Fund (IMF) World Economic Outlook (WEO) database (21). In addition, the age-standardized incidence rate in 2020 for all cancers for each country was collected from the International Agency for Research on Cancer, Global Cancer Observatory (GCO) platform (22).

Statistical Analysis

Data analyses were performed on individual country level. Categorical variables were presented as counts and proportions, and continuous variables were presented with histograms and

density curves instead of summary descriptive statistics. Because the economic indices usually had right-skewed distributions, log-transformation was applied. Correlations between independent variables were assessed with Spearman rank correlation.

The inequality of accessibility to PT facilities among countries was measured by Gini coefficient and presented with Lorenz curves (23). Gini coefficient was originally developed to measure the income or wealth inequality, with a value of 0 indicating perfect equality and value of 1 indicating maximal inequality.

The dependent variable was number of PT centers in operation in each country by the end of 2021. Since most countries included in the analysis did not have PT centers, zeros were the majority in the dependent variable. Thus, equidispersion assumption was first assessed by dispersion test, and $\alpha > 0$ (dispersion > 1) indicated overdispersion and $\alpha < 0$ (dispersion < 1) indicated underdispersion. In case of overdispersion, zero-inflated Poisson regression was used to identify the factors significantly associated with number of PT centers in each country. The zero-inflated Poisson model is a mixture model combining a count model (a Poisson regression with log link) and a zero-inflated model (a logistic regression model) (24). To ensure the robustness of the conclusion, we also performed a sensitivity analysis using different models including zero-inflated negative binomial regression, negative binomial logit hurdle model, and Poisson logit hurdle model in the multivariable analysis and compared these models with zero-inflated Poisson regression.

All economic variables and cancer incidence were first explored with univariable analysis. Missing values in these variables were imputed with the median values. Variables for multivariable analysis were determined based on significance and (multi-)collinearity. Likelihood ratio test will be performed when model comparison is necessary.

All the statistical analyses were performed with R version 3.6.1, RStudio version 1.2.5001, and packages PerformanceAnalytics (distribution and correlation), ineq (Lorenz curves), acid (Gini coefficients), AER (testing for overdispersion), and pscl (zero-inflated Poisson regression and Vuong test for model comparison). P-values smaller than 0.05 were considered as statistically significant.

RESULTS

Countries Included in This Study

The IMF WEO database contained data from 196 countries or regions, which were included as the study sample. The GCO platform provided cancer incidences of 185 countries or regions. According to PTCOG data, until the end of 2021, there were 20 countries or regions had PT centers (number of centers ranged from 1 to 41) in clinical operation, whereas 176 countries or regions had no PT centers.

Data from different sources were merged by ISO code or country name, into the analysis dataset. Data from the 20 countries or regions with PT centers were presented in **Table 1**, whereas the full dataset of all 196 countries or regions was provided in the **Supplementary Material**.

The distributions of (\log_{10} -transformed) economic indices and cancer incidences were presented in **Supplementary Figure 1**.

TABLE 1 | Characteristic of countries or regions with PT centers in operation.

Country	Number of PT Centers	Number of PT Chambers	GDP (in Billions U.S. dollars)	GDP Per Capita (in U.S. dollars)	Population (in Millions)	Total Investment rate (% of GDP)	General Government Total Expenditure (% of GDP)	Age-Standardized Incidence Rates in All Cancers (per 100,000)
United States	41	110	20,893.75	63,358.55	329.77	21.15	45.45	362.20
Japan	18	32	5,045.10	40,088.52	125.85	25.57	45.04	285.10
Germany	5	14	3,843.34	46,215.65	83.16	21.15	50.84	313.20
Russia	5	9	1,478.57	10,115.34	146.17	23.99	39.41	234.30
China	3	9	14,866.74	10,511.36	1,414.35	43.12	36.53	204.80
Italy	3	8	1,884.94	31,604.77	59.64	17.50	57.29	292.60
United Kingdom	3	7	2,709.68	40,394.15	67.08	17.22	49.11	319.90
France	3	6	2,624.42	40,298.81	65.12	23.68	61.78	341.90
Netherlands	3	6	913.13	52,454.85	17.41	21.74	45.36	349.60
Taiwan	2	8	668.16	28,358.56	23.56	23.72	18.28	
Korea	2	5	1,638.26	31,638.25	51.78	31.86	25.19	242.70
Spain	2	2	1,280.46	27,179.64	47.11	20.69	52.27	277.20
Austria	1	4	432.52	48,592.74	8.90	25.75	57.37	255.70
Czech Republic	1	4	245.35	22,942.68	10.69	25.95	47.14	292.60
Denmark	1	4	356.09	61,151.47	5.82	22.93	53.76	351.10
Switzerland	1	4	751.88	87,366.60	8.61	28.51	36.48	317.60
India	1	3	2,660.24	1,929.67	1,378.60	29.28	31.07	97.10
Poland	1	3	595.92	15,699.35	37.96	17.17	48.66	267.30
Belgium	1	2	514.92	44,690.16	11.52	24.76	59.97	349.20
Sweden	1	2	541.06	52,130.65	10.38	24.78	51.81	288.60

Inequality in Accessibility of Proton Therapy

By December 2021, among all 196 countries or regions in IMF WEO database, only 20 (10.2%) of them had PT centers in operation, which covered a total population of 3.90 billion (50.9%) out of 7.67 billion in all countries.

The Lorenz curves, which represented the distributions of PT centers and chambers among all countries and weighted by their populations, were shown in **Figure 1**. The curves were all far away from the diagonal line and the Gini coefficients were 0.96 for PT centers (0.82 when weighted by population) and 0.96 for PT chambers (0.81 when weighted by population), which indicated high level of inequality.

Determinants of Accessibility of Proton Therapy

Overdispersion was observed in univariable Poisson regression models of all variables (dispersion ranged from 1.217 to 4.928, P-value ranged from 0.023 to 0.058) (**Supplementary Table 1**); thus, zero-inflated model was employed. In the univariable analysis, all variables except for general government total expenditure had significant effects on whether a country had no PT center (zero-inflated model) and the number of centers (count model) (**Table 2**). The higher these variables were the lower probability of having no PT center and the higher number of PT centers in a country.

Considering the high correlation between GDP and total population ($\rho = 0.76$), total investment ($\rho = 0.98$), general government total expenditure ($\rho = 0.98$) (**Supplementary Figure 1**), and the importance of GDP, the latter three economic variables were excluded from the multivariable analysis. Cancer

incidence also had a high correlation with GDP per capita ($\rho = 0.71$); thus, likelihood ratio test was performed to compare the model with cancer incidence and without cancer incidence, and no significant difference was found ($p = 0.096$), so cancer incidence was excluded from the multivariable analysis as well.

The final multivariable model included GDP and GDP per capita. GDP had a significant effect on whether a country had no PT center (zero-inflated model) and both GDP and GDP per capita had significant effects on the number of centers (count model) (**Table 2**). The direction of the effects was in line with univariable analysis. The sensitivity analysis showed similar results and no significant difference in model fitting was found between zero-inflated Poisson regression and other model options.

DISCUSSION

PT is a promising treatment for cancers, because it has a higher tumor control probability due to dose escalation and less side effects due to less radiation to normal tissue (19). Ten years ago, it was questioned whether PT is “too expensive to become true” given that the investment costs were considerably higher than photon therapy (19). If we look at the number of PT centers today, treating patients with cancer with PT did come true, at least in many developed countries. However, in most LMICs, patients with cancer had less or even no access to PT, and these countries have more population and patients with cancer.

(25, 26) In this study, we found the extremely high inequality in accessibility of PT centers among all countries in the world (Gini = 0.96), which is even more severe than the inequality

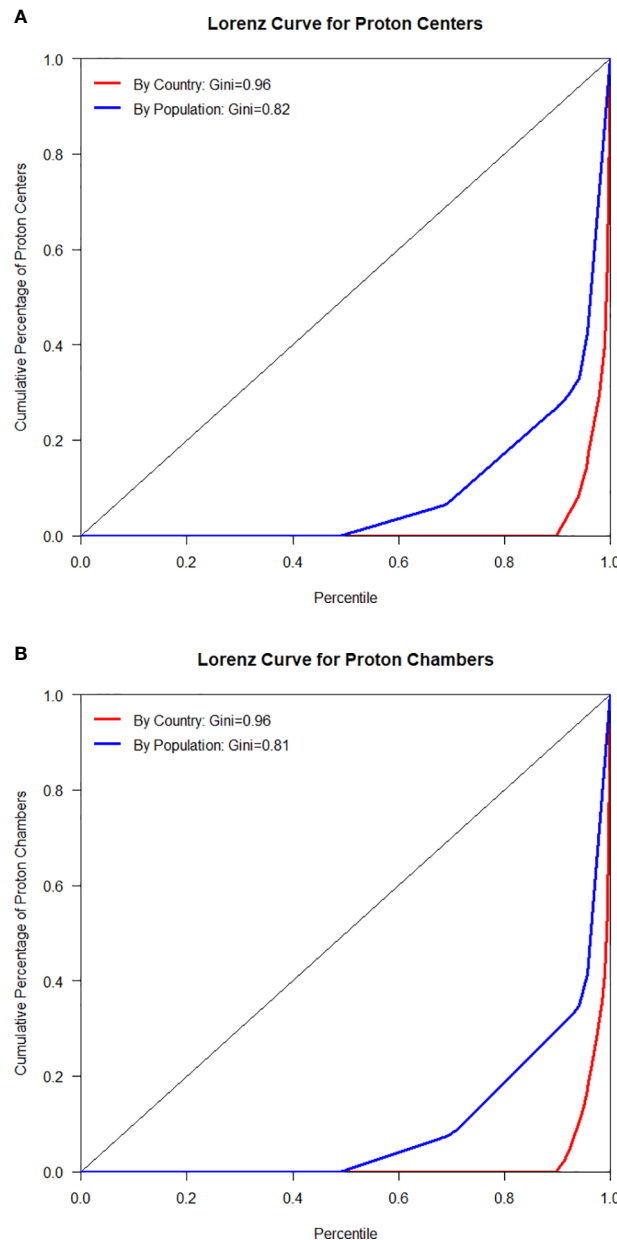


FIGURE 1 | Lorenz curves for PT centers **(A)** and chambers **(B)** by country and population.

observed in economic development (Gini = 0.87 for GDP). Our empirical data analyses showed that the total GDP had a significant impact on whether a country had a practical PT center, whereas the total GDP and GDP per capita had significant impacts on the number of PT centers.

The inequality was also observed before in other cancer treatments such as radiotherapy, and the inadequacy of radiotherapy facilities in LMICs has been an issue of worldwide concern (27). On the basis of DIRAC and the World Bank data, the number of megavoltage units per 1,000 cancer cases who need radiotherapy was 0.2, 0.7, 1.7, and 2.3 in

the low-income countries (LICs), the LMICs, the upper middle-income countries, and the high-income countries (HICs), separately (28). In addition, more than 90% of patients with the most to gain from radiotherapy cannot access to the treatment in LICs (5). Thus, there were some debates on why LMICs should invest in PBT facilities given that radiotherapy or even basic health care necessities are not met yet (20).

We also noticed that, even within HICs, only a small proportion (21%, 17 of 80) had PT centers in operation, whereas several developing countries had their PT centers either in operation (e.g., China and India) or being constructed (e.g.,

TABLE 2 | Univariable and multivariable analyses of determinants of number of PT centers.

Independent variable*	Univariable Analysis				Multivariable Analysis			
	Count Model		Zero-Inflated Model		Count Model		Zero-Inflated Model	
	(Poisson With Log Link)		(Binomial With Logit Link)		(Poisson With Log Link)		(Binomial With Logit Link)	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
GDP	2.323	<0.001	−3.522	0.019	2.138	<0.001	−3.768	0.056
GDP per capita	2.178	<0.001	−2.466	0.002	1.660	<0.001	−1.259	0.482
Population	0.933	<0.001	−1.560	<0.001				
Investment	1.830	<0.001	−3.405	0.002				
Expenditure	2.534	<0.001	−72.93	0.522				
Cancer incidence rate	8.833	<0.001	−5.784	0.033				

*All independent variables were log-transformed with \log_{10} .

Argentina). LMICs may have lower overall construction cost, much lower personnel cost, and operational expenses, and the total cost of PT can be much lower than HICs (20). LMICs have good opportunity in having fast growth in the number of PT centers and number of patients treated with PT. This “advantage of backwardness” was observed in construction of infrastructural facilities, such as high-speed railway.

Although the number of PT centers increased rapidly, their average volume was relatively stable. According to surveys of European PT centers, in 2020, the average number of patients treated by a PT center is 223 (range of 29–950) (25, 26), which is similar to that in 2015 (221, range of 40–557) (26). Thus, increasing the number of PT centers played an important role in getting more patients treated by PT.

It is worth noting that, despite of a significant initial investment is required for PT, construction of a PT center is only the first step of getting patients access to PT. According to a recent survey among 19 PT centers in Europe, the top reasons why patients with cancer not receiving PT were lack of evidence for the effectiveness of protons over photons, reimbursement issues, technical issues, and patient referral (25). Although PT is not new, the high costs of setting up and operating PT facilities limited the research and development, which is needed to maximize its clinical efficacy (29). Because of lack of funding and reimbursement and methodological issues in conducting randomized controlled trials (RCTs), evidence from phase II or phase III clinical trials was limited (25). More RCTs or real-world studies are needed to generate high-quality level 1 evidence (30). PT is more costly than conventional photon therapy; thus, payers played an important role in determining whether, when and which patients will be treated by PT. However, according to investigations on insurance approval for PT in the United States, the initial denial rate was around 70% and around 30% patients remained denied after appeal (30, 31). The availability of qualified professionals is another issue. A PT team may consist radiation oncologists, medical physicists, dosimetrists or treatment planners, and radiation therapists (32), and they all require years of training and the expense can be high. All these challenges need to be solved to promote patients' access to PT.

There were several limitations in this study. First, when assessing the accessibility, PT centers were counted by countries, and it was possible that some countries without PT centers can refer their patients with cancer to another country,

which may reduce the inequality. Second, the explanatory variables considered in the analysis were highly correlated and thus cannot be included in the multivariable analysis, which is common in empirical studies in economics. Third, cancer incidence for all cancers was used in the analysis, instead of cancer incidence per cancer. This is because there was no clear rule accepted in all countries on which cancers can be treated with PT. Last, the study used cross-sectional data; thus, no conclusion on causal relation can be drawn from the results.

CONCLUSION

Extremely high inequality in accessibility of PT centers was observed among all countries in the world. Most of PT centers in operation are located in HICs. Total GDP and GDP per capita had significant impacts on the number of PT centers, which indicated that economic development was the most important factor determining the adoption of PT in cancer treatment in different counties. With the growth in global economics, more PT centers can be expected in near future.

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

ZX and MW contributed to conception and design of the study. ZX and JW organized the database and performed the statistical analysis. ZX, JW, and JX wrote the first draft of the manuscript. ZC supervised the study and critically appraised and revised the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.876368/full#supplementary-material>

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Pre-Procedural Anxiety and Associated Factors Among Women Seeking for Cervical Cancer Screening Services in Shenzhen, China: Does Past Screening Experience Matter?

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Background: Research gaps exist in addressing the psychological harm related to the cervical cancer screening. Anxiety is the most common distress driven by the screening procedures, which may be affected by past screening experience (PSE) but with uncertainty. This study aimed to evaluate the pre-procedural anxiety in cervical cancer screening and to identify the influence attributed to PSE.

Methods: A cross-sectional survey targeted women seeking for cervical cancer screening services was conducted from June 5th to December 31st, 2020 in Shenzhen. The 20-item state anxiety scale of the State-Trait Anxiety Inventory (STAI-S) was applied to measure pre-procedural anxiety, in which a score of 40 or higher was regarded with anxiety symptom. Logistic regression models were established to explore potential associated factors of pre-procedural anxiety both for women with and without PSE.

Results: Overall, 3,651 women were enrolled, in which 36.1% had never been screened and the remaining 63.9% had been screened at least once before. Women without PSE demonstrated more prevalent pre-procedural anxiety (74.5% vs. 67.8%, $P < 0.001$) than their experienced counterparts. Among women without PSE, having heard of cervical cancer screening was associated with a lower likelihood of pre-procedural anxiety (OR: 0.37, 95%CI: 0.25~0.56). Among experienced women, participating three or more times screening was negatively associated with anxiety symptom (OR: 0.67, 95%CI: 0.53~0.84), however, both receiving screening within three years (OR: 1.58, 95%CI:

1.27~1.97) and unknowing previous screening results (OR: 1.42, 95%CI: 1.11~1.82) increased the susceptibility of pre-procedural anxiety.

Conclusions: Women participating in cervical cancer screening commonly present pre-procedural anxiety. The association between PSE and pre-procedural anxiety may be influenced by past screening times, interval, and results. Psychological counseling according to women's PSE before cervical cancer screening is warranted of necessity.

Keywords: cervical cancer, past screening experience, pre-procedural anxiety, psychological harm, associated factor

INTRODUCTION

Cervical cancer is the fourth frequent malignancy in females worldwide (1). Almost all cancers in the cervix were caused by the high-risk human papillomavirus (HPV) (2). Routine cervical screening is one of the most essential prevention strategies, leading to great success in reducing the disease burden. However, women are required to receive gynecological procedures for cervical examination and sampling, which can be regarded as an invasive operation performed by a healthcare provider. Screening related procedures may act as stressors and bring adverse psychological outcomes. Notably, evidence about the psychological harm of cervical screening is restricted to distress induced by switching screening methods, receiving abnormal results, and following colposcopy related procedures (3–5). Research gaps exist in addressing the psychological harm before and during the screening process.

Recent systematic reviews identified the psychological harm of cancer screening procedures, in which anxiety was the most commonly assessed construct (6, 7). Anxiety is thought to be a future-oriented affective status that reflects one's preparation to cope with uncertainty but possibly negative situations without a triggering stimulus (8). Anxious feelings may be prevalent when women treat pain as the most important determinant of cervical screening participation (9). However, scant studies examined cervical screening related anxiety and only followed non-mainstream screening methods, like optical spectroscopy and visual inspection (10, 11). Anxiety driven by HPV or cytology based methods remain to be investigated.

Past screening experience (PSE) may impact on cervical cancer screening related anxiety. Anxious feelings could appear among those without PSE due to uncertainty of screening procedures. For women who have ever been screened, on one hand, they may prefer less frequent screening in order to avoid frequent anxiety, worry, or nervousness (12). On the other hand, anxiety may also be alleviated by repeated participation and fully understanding of screening procedures, as exposure to the feared situation helps to deal with specific anxiety (13). As more and more females are encouraged to receive cervical screening, there is a urgent need to understand screening related anxiety among women with and without PSE. Hence, based on a cross-sectional survey in Shenzhen, we evaluated the pre-procedural anxiety and associated factors among women seeking for cervical cancer screening services, in order to address the dearth of

information about the psychological harm associated to cervical cancer screening and to identify the influence attributed to PSE.

MATERIALS AND METHODS

Study Setting and Participants

A cross-sectional survey has been conducted from June 5th to December 31st, 2020 in Pinghu Maternity-child Healthcare and Family Planning Service Center of Longgang District, Shenzhen. It has been one of the most influential and public screening centers funded by the local government, offering free screening services of common diseases for nearly 8,000 women per year. Women could have access to cervical cancer screening services if they were engaged in sexual behavior, not pregnant, and at an age range from 20 to 65 years old. During the survey period, women who came to this screening site seeking for cervical cancer screening services and met above criteria were invited to participate in our survey. Here, we excluded women without a smartphone or incapacitated women due to intellectual or other disability. They would be provided with a full explanation and invitation of the present survey by trained research assistants. With informed consent, women were asked to finish an online questionnaire before they received gynecological assessment and subsequent screening procedures. The questionnaire was available to access *via* scanning a unique quick response code with their smartphones, which was hosted by WenJuanXing (Changsha Haoxing Information Technology Co., Ltd., China). Totally, we collected 3717 questionnaires and excluded 66 questionnaires with unknown age information or out-of age range. Ethical approval was obtained from the medical ethics committee of Shenzhen Maternity and Child Healthcare Hospital.

Measurement

Demographic Characteristics and Reproductive Health Condition

A structured questionnaire containing different aspects was employed in this study. Demographic characteristics were firstly collected based on self-report, containing age, ethnicity, local household registration, marital status, education level, occupation types, and monthly income level. Information on women's reproductive health was also required, such as age at

menarche and first sexual intercourse (coitarche), the number of sexual partners in recent one year, condom and oral contraceptive use, parity, age at first delivery, malignancy diagnosis of first-degree relatives, and previous diagnosis of vaginitis. Detailed division of above-mentioned variables were listed in **Table 1**.

Past Cervical Screening Experience

All women were asked to recall previous experience of cervical cancer screening. The past participation of screening was evaluated by asking “Before the survey time, approximately how many times have you ever participated in cervical cancer screening? (none/once/twice/three or more times)”. Women without PSE were assessed with the awareness of cervical cancer screening service via asking “Before the survey time, have you ever heard of cervical cancer screening? (yes/no)”. Specific questions was developed to query past screening experience, containing “When did you receive previous screening? (within/over 3 years)” and “What was the result of previous screening? (normal/abnormal/unknown)”.

Health Habit

We further gathered variables of health habits in their daily routines. Women needed to recall specific life events, including active and passive exposure to smoking, the duration of sitting per day, the number of walking steps per day, and the frequency of physical exercise per week. Here, active smoking was defined as ever or currently smoking at least one cigarette per day on average. In addition, women exposed to tobacco smoke more than 15 minutes, at least one day per week were regarded with passive smoking. Walking steps were calculated according to the pedometer function of their smart-phones. Physical exercise referred to common exercise forms, including sports, running, swimming, dancing, mountain climbing, rope skipping, etc.

Psychological Health Status

Recent psychological health of the participants was measured through an ultra-brief screening scale named the Patient Health Questionnaire-4 (PHQ-4). It consists of a 2-item anxiety scale and a 2-item depression scale, assessing the frequency of psychological distress in recent two weeks. Each item was rated in four response options (not at all=0, several days=1, more than half of the days=2, and almost every day=3). Therefore, a total score of the four items was ranged from 0 to 12. Suggested by previous validation (14), those who scored ≥ 3 on PHQ-4 were considered to have psychological distress. In the present study, the internal consistency reliability of the PHQ-4 was found to be acceptable (Cronbach's α : 0.86).

Pre-Procedural Anxiety

Pre-procedural anxiety was assessed by the state anxiety scale of the State-Trait Anxiety Inventory (STAI-S). The STAI-S is composed of 20 items that reflect the transient emotional response to a stressful situation. It measures the anxious symptom at the moment of scoring, which has been widely adopted to identify anxiety in the Chinese population (15). Hence, the participants in our survey were all required to

finish the STAI-S prior to gynecological procedures, in order to figure out their present feelings. All items of the STAI-S were responded on a 4-point Likert-type scale, contributing to a total score of 20 to 80. The score of the STAI-S positively correlates with the severity of anxiety. A total score of 40 or higher was applied to reflect anxious symptom in the present study, in line with past investigations (15–17). The Cronbach's α of STAI-S in this study was 0.88.

Statistical Analyses

All data were analyzed descriptively by means of the SPSS 21.0 software (IBM Corp., Armonk, NY). Categorical variables were presented with numbers and frequencies, and continuous data were presented with means and standard deviations. For women with different characteristics (demographics, reproductive health condition, health habits, etc), the chi-square test was applied to detect the difference of anxiety level across subgroups, while the t-test and one way ANOVA were used to compare the distributed difference of STAI-S score. Logistic regression models were established to explore potential associated factors of pre-procedural anxiety both for women with and without PSE. Variables with $P \leq 0.10$ in the uni-variate analysis were included in the multi-variate logistic regression models. Associated factors were identified with the stepwise procedure. Odds ratios (OR) and 95% confident intervals (CI) were calculated to estimate the strength of associations. Statistical significance was set to be less than 0.05 with a two-tailed test.

RESULTS

Characteristics of All Participants

In total, 3,651 women were included in analysis (**Figure 1**), with an average age of 40.65 years (standard deviation: 7.56). Of all participants, 36.1% had never been screened before, while the remaining women had been screened at least once (once: 27.8%, twice: 17.5%, and three times or more: 18.6%) (**Figure 2**). Moreover, 302 women never heard of cervical cancer screening, accounted for 22.9% of non-experienced women. Among women with PSE, approximately three quarters received screening services within recent three years and reported normal screening results.

Characteristics of the participants varied by PSE (**Table 1**). Compared to those without PSE, experienced women were likely to be older, Han ethnic, local household registered, married, and well-educated (all $P < 0.05$). These two groups also varied in occupation types, age at coitarche, the number of sexual partners, parity, malignancy diagnosis of first-degree relatives, and previous diagnosis of vaginitis (all $P < 0.05$). Furthermore, experienced women tended to have healthier habits, such as no smoking, walking more steps, and more frequent physical exercise (all $P < 0.05$).

Prevalence of Pre-Procedural Anxiety in Cervical Cancer Screening

The average score of STAI-S was 42.72 (standard deviation: 8.64) in this survey. Women without PSE demonstrated significantly

TABLE 1 | Characteristics of the participants varied by PSE (N=3651).

Variables	PSE		P value	Overall, n (%)
	Without, n (%)	With, n (%)		
Demographic characteristic				
Age (year)			<0.001	
<41	765 (58.0)	1147 (49.2)		1912 (52.4)
≥41	554 (42.0)	1185 (50.8)		1739 (47.6)
Ethnicity				
Han	1211 (91.8)	2197 (94.2)	0.005	3408 (93.3)
Others	108 (8.2)	135 (5.8)		243 (6.7)
Local household registration				
Yes	184 (13.9)	503 (21.6)	<0.001	687 (18.8)
No	1135 (86.1)	1829 (78.4)		2964 (81.2)
Marital status				
Single/divorced/widow	87 (6.6)	105 (4.5)	0.006	192 (5.3)
Married	1232 (93.4)	2227 (95.5)		3459 (94.7)
Education level				
Junior middle school or below	859 (65.1)	1321 (56.6)	<0.001	2180 (59.7)
Senior middle school	254 (19.3)	575 (24.7)		829 (22.7)
College or above	206 (15.5)	436 (18.7)		642 (17.6)
Occupation types				
Administrator/professional	139 (10.5)	266 (11.4)	0.017	405 (11.1)
Worker	520 (39.4)	787 (33.7)		1307 (35.8)
Business services personnel	178 (13.5)	343 (14.7)		521 (14.3)
Housewife/unemployed woman	332 (25.2)	632 (27.1)		964 (26.4)
Others	150 (11.4)	304 (13.0)		454 (12.4)
Monthly income (RMB)				
<5,000	1030 (78.1)	1758 (75.4)	0.065	2788 (76.4)
≥5,000	289 (21.9)	574 (24.6)		863 (23.6)
Reproductive health condition				
Age at menarche (year)				
<12	32 (2.4)	71 (3.0)	0.052	103 (2.8)
12 to 15	1053 (79.8)	1781 (76.4)		2834 (77.6)
≥16	234 (17.7)	480 (20.6)		714 (19.6)
Age at coitarche (year)				
<18	119 (9.0)	130 (5.6)	<0.001	249 (6.8)
18 to 24	954 (72.3)	1698 (72.8)		2652 (72.6)
≥25	246 (18.7)	504 (21.6)		750 (20.5)
The number of sexual partners in recent one year				
0	116 (8.8)	157 (6.7)	0.020	273 (7.5)
1	1113 (84.4)	2044 (87.7)		3157 (86.5)
≥2	90 (6.8)	131 (5.6)		221 (6.1)
Consistent condom use during sexual intercourse				
No	1117 (84.7)	1954 (83.8)	0.48	3071 (84.1)
Yes	202 (15.3)	378 (16.2)		580 (15.9)
Oral contraceptive use				
Never	1094 (82.9)	1947 (83.5)	0.67	3041 (83.3)
Ever	225 (17.1)	385 (16.5)		610 (16.7)
Parity				
0	52 (3.9)	43 (1.8)	<0.001	95 (2.6)
1	334 (25.3)	587 (25.2)		921 (25.2)
2	660 (50.0)	1258 (53.9)		1918 (52.5)
≥3	273 (20.7)	444 (19.0)		717 (19.6)
Age at first delivery (year) ^a				
<18	160 (12.6)	287 (12.5)	0.099	447 (12.2)
18 to 24	647 (51.1)	1095 (47.8)		1742 (47.7)
25 to 29	371 (29.3)	761 (33.2)		1132 (31.0)
≥30	89 (7.0)	146 (6.4)		235 (6.4)
Malignancy diagnosis of first-degree relatives				
No/unknown	1251 (94.8)	2143 (91.9)	0.001	3394 (93.0)
Yes	68 (5.2)	189 (8.1)		257 (7.0)
Previous diagnosis of vaginitis				
No	928 (70.4)	1334 (57.2)	<0.001	2262 (62.0)
Yes	391 (29.6)	998 (42.8)		1389 (38.0)

(Continued)

TABLE 1 | Continued

Variables	PSE		P value	Overall, n (%)
	Without, n (%)	With, n (%)		
Health habit				
Active smoking				
Never	1282 (97.2)	2300 (98.6)	0.002	3582 (98.1)
Ever	37 (2.8)	32 (1.4)		69 (1.9)
Passive smoking				
Never	1131 (85.7)	1967 (84.3)	0.26	3098 (84.9)
Ever	188 (14.3)	365 (15.7)		553 (15.1)
Sitting hours per day				
<5	732 (55.5)	1337 (57.3)	0.28	2069 (56.7)
≥5	587 (44.5)	995 (42.7)		1582 (43.3)
Walking steps per day				
<5000	855 (64.8)	1353 (58.0)	<0.001	2208 (60.5)
≥5000	464 (35.2)	979 (42.0)		1443 (39.5)
Frequency of physical exercise per week				
0	610 (46.2)	735 (31.5)	<0.001	1345 (36.8)
1	367 (27.8)	684 (29.3)		1051 (28.8)
2	206 (15.6)	495 (21.2)		701 (19.2)
≥3	136 (10.3)	418 (17.9)		554 (15.2)
Psychological health status				
Psychological distress in recent two weeks				
No	1074 (81.4)	1849 (79.3)	0.12	2923 (80.1)
Yes	245 (18.6)	483 (20.7)		728 (19.9)

^aNonparous women were not included.

Bold values indicate statistical significance ($P < 0.05$).

higher score of STAI-S than those with PSE (43.64 vs. 42.28, $P < 0.001$). When using a cut-off value of 40, the overall prevalence of pre-procedural anxiety was 70.3%. Compared to the experienced counterparts, a higher prevalence of anxious symptom was reported among women without PSE (74.5% vs. 67.8%, $P < 0.001$). The prevalence of anxious symptom decreased with the increased times of past screening participation (P for trend < 0.001) (Figure 3). Regardless of whether women had been screened before, distinct STAI-S scores and prevalence of anxiety

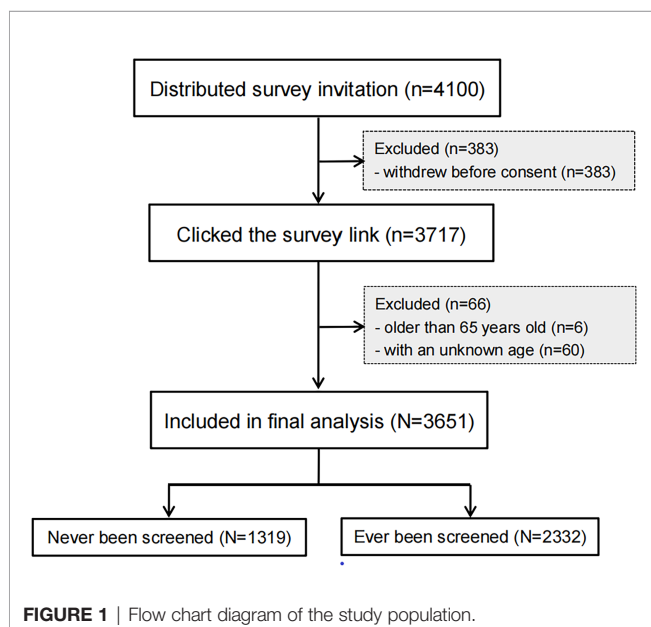
were detected across subgroups of varied characteristics (Tables 2, 3).

Factors Associated With Pre-Procedural Anxiety Among Women Without PSE

Factors associated with pre-procedural anxiety among women without PSE were found in the multi-variate logistic regression model (Table 2). Higher odds of being anxious were shown if women were older (OR: 1.57, 95%CI: 1.15~2.15), married (OR: 2.33, 95%CI: 1.37~3.97), nonparous (OR: 2.38, 95%CI: 1.01~5.61), and having psychological distress (OR: 2.85, 95%CI: 1.94~4.19). Potential protective factors of anxiety included receiving higher education (OR: 0.45, 95%CI: 0.31~0.65), having older age at first delivery (OR: 0.50, 95%CI: 0.28~0.91), walking more steps per day (OR: 0.63, 95%CI: 0.48~0.82), and having heard of cervical cancer screening (OR: 0.37, 95%CI: 0.25~0.56).

Factors Associated With Pre-Procedural Anxiety Among Women With PSE

Distinct associated factors were detected among women with PSE (Table 3). Women who were susceptible to pre-procedural anxiety were identified as: having two or more sexual partners (OR: 2.11, 95%CI: 1.13~3.93), sitting longer per day (OR: 1.25, 95%CI: 1.03~1.51), having psychological distress (OR: 3.00, 95%CI: 2.30~3.91), receiving screening within three years (OR: 1.58, 95%CI: 1.27~1.97), and unknowing previous screening results (OR: 1.42, 95%CI: 1.11~1.82). Women that were less likely to be anxious tended to receive higher education (senior middle school: OR: 0.61, 95%CI: 0.49~0.77; college or above: OR: 0.59, 95%CI: 0.45~0.77), earn higher monthly income (OR: 0.79, 95%



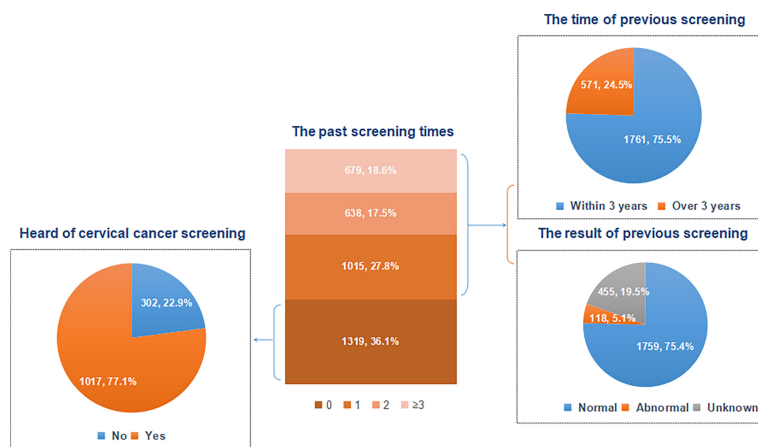


FIGURE 2 | Past cervical cancer screening experience of all participants.

CI: 0.64~0.92), be diagnosed with vaginitis (OR: 0.77, 95%CI: 0.64~0.92), do physical exercise per week (two times: OR: 0.66, 95%CI: 0.51~0.86; three or more times: OR: 0.63, 95%CI: 0.48~0.83), and participating three or more times screening (OR: 0.67, 95%CI: 0.53~0.84).

DISCUSSION

Negative psychological response to cervical cancer screening procedures has been considered to be a barrier to screening uptake. The present study explicitly investigated the prevalence of pre-procedural anxiety during cervical cancer screening

among Chinese females using a cross-sectional design. Overall, nearly three quarters of the participants suffered pre-procedural anxiety, suggesting the substantial psychological harm derived by cervical cancer screening. To our knowledge, this study is a forerunner to explore the influence of PSE on the anxious symptom prior to the cervical cancer screening procedures. Notably, PSE may bring varied effects on the pre-procedural anxiety due to the difference of past screening times, interval and results. These novel findings help to develop proper guidance in reducing the psychological harm and promoting more uptake of cervical cancer screening.

Scant studies investigate the pre-procedural anxiety symptom in cervical cancer screening. This study reported a high level of the pre-procedural anxiety, with over 70% women rating a score

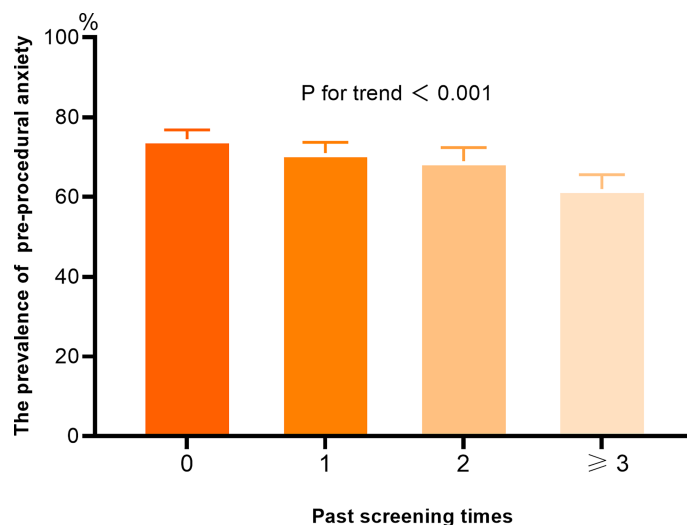


FIGURE 3 | The prevalence of pre-procedural anxiety according to the past screening times.

TABLE 2 | Pre-procedural anxiety and associated factors among women without PSE (N=1319).

Variable	STAI-S score (mean, SD)	P value ^a	The prevalence of anxiety (n, %)	P value ^b	Uni-variate OR (95%CI) ^c	Multi-variate OR (95%CI)
Demographic characteristic						
Age (year)						
<41	42.47 (9.00)	<0.001	526 (68.8)	<0.001	1.00 (reference)	1.00 (reference)
≥41	45.25 (7.33)		457 (82.5)		2.14 (1.64, 2.80)	1.57 (1.15, 2.15)
Ethnicity						
Han	43.56 (8.42)	0.26	898 (74.2)	0.30	1.00 (reference)	
Others	44.55 (8.76)		85 (78.7)		1.29 (0.80, 2.08)	
Local household registration						
Yes	41.86 (9.94)	0.008	118 (64.1)	<0.001	1.00 (reference)	
No	43.93 (8.15)		865 (76.2)		1.79 (1.29, 2.49)	
Marital status						
Single/divorced/widow	42.51 (8.58)	0.20	55 (63.2)	0.012	1.00 (reference)	1.00 (reference)
Married	43.72 (8.44)		928 (75.3)		1.78 (1.13, 2.80)	2.33 (1.37, 3.97)
Education level						
Junior middle school or below	44.69 (7.70)	<0.001	686 (79.9)	<0.001	1.00 (reference)	1.00 (reference)
Senior middle school	42.86 (9.03)		178 (70.1)		0.59 (0.43, 0.81)	0.73 (0.52, 1.02)
College or above	40.20 (9.67)		119 (57.8)		0.35 (0.25, 0.48)	0.45 (0.31, 0.65)
Occupation types						
Administrator/professional	41.33 (9.85)	0.002	88 (63.3)	0.011	1.00 (reference)	
Worker	44.23 (7.40)		401 (77.1)		1.95 (1.31, 2.92)	
Business services personnel	43.47 (9.07)		131 (73.6)		1.62 (1.00, 2.61)	
Housewife/unemployed	44.24 (8.69)		256 (77.1)		1.95 (1.27, 3.00)	
woman						
Others	42.58 (8.79)		107 (71.3)		1.44 (0.88, 2.36)	
Monthly income (RMB)						
<5,000	44.08 (8.11)	0.001	793 (77.0)	<0.001	1.00 (reference)	
≥5,000	42.07 (9.42)		190 (65.7)		0.57 (0.43, 0.76)	
Reproductive health condition						
Age at menarche (year)						
<12	42.75 (8.56)	0.83	23 (71.9)	0.80	0.89 (0.41, 1.94)	
12 to 15	43.67 (8.54)		782 (74.3)		1.00 (reference)	
≥16	43.61 (8.05)		178 (76.1)		1.10 (0.79, 1.53)	
Age at coitarche (year)						
<18	45.57 (8.24)	0.004	97 (81.5)	0.041	1.00 (reference)	
18 to 24	43.69 (8.33)		715 (74.9)		0.68 (0.42, 1.10)	
≥25	42.49 (8.84)		171 (69.5)		0.52 (0.30, 0.88)	
The number of sexual partners in recent one year						
0	43.97 (8.18)	0.021	86 (74.1)	0.22	1.00 (reference)	
1	43.42 (8.59)		823 (73.9)		0.99 (0.64, 1.53)	
≥2	45.96 (6.63)		74 (82.2)		1.61 (0.82, 3.19)	
Consistent condom use during sexual intercourse						
No	43.80 (8.22)	0.14	844 (75.6)	0.043	1.00 (reference)	
Yes	42.74 (9.62)		139 (68.8)		0.71 (0.51, 0.99)	
Oral contraceptive use						
Never	43.91 (8.28)	0.017	832 (76.1)	0.005	1.00 (reference)	
Ever	42.33 (9.16)		151 (67.1)		0.64 (0.47, 0.88)	
Parity						
0	44.87 (8.46)	0.028	41 (78.8)	0.004	1.78 (0.88, 3.60)	
1	42.48 (8.60)		226 (67.7)		1.00 (reference)	
2	43.90 (8.54)		498 (75.5)		1.47 (1.10, 1.96)	
≥3	44.18 (7.95)		218 (79.9)		1.89 (1.30, 2.75)	
Age at first delivery (year)						
Nonparous	44.87 (8.46)	0.010	41 (78.8)	0.006	1.37 (0.65, 2.91)	2.38 (1.01, 5.61)
<18	44.04 (8.02)		501 (77.4)		1.26 (0.85, 1.87)	0.93 (0.61, 1.41)
18 to 24	43.37 (8.56)		117 (73.1)		1.00 (reference)	1.00 (reference)
25 to 29	43.58 (8.70)		271 (73.0)		1.00 (0.66, 1.51)	0.83 (0.53, 1.30)
≥30	40.74 (9.75)		53 (59.6)		0.54 (0.31, 0.94)	0.50 (0.28, 0.91)
Caner history of first-degree relatives						
No/unknown	43.77 (8.39)	0.013	938 (75.0)	0.11	1.00 (reference)	
Yes	41.16 (9.18)		45 (66.2)		0.65 (0.39, 1.10)	
Previous diagnosis of vaginitis						

(Continued)

TABLE 2 | Continued

Variable	STAI-S score (mean, SD)	P value ^a	The prevalence of anxiety (n, %)	P value ^b	Uni-variate OR (95%CI) ^c	Multi-variate OR (95%CI)
No	44.04 (8.42)	0.008	706 (76.1)	0.046	1.00 (reference)	
Yes	42.69 (8.46)		277 (70.8)		0.76 (0.59, 1.00)	
Health habit						
Active smoking						
Never	43.63 (8.47)	0.88	956 (74.6)	0.83	1.00 (reference)	
Ever	43.84 (8.07)		27 (73.0)		0.92 (0.44, 1.92)	
Passive smoking						
Never	43.78 (8.38)	0.15	853 (75.4)	0.068	1.00 (reference)	
Ever	42.81 (8.88)		130 (69.1)		0.73 (0.52, 1.02)	
Sitting hours per day						
<5	43.93 (8.60)	0.16	561 (76.6)	0.049	1.00 (reference)	
≥5	42.27 (8.25)		422 (71.9)		0.78 (0.61, 1.00)	
Walking steps per day						
<5000	44.38 (8.21)	<0.001	672 (78.6)	<0.001	1.00 (reference)	1.00 (reference)
≥5000	42.27 (8.73)		311 (67.0)		0.55 (0.43, 0.71)	0.63 (0.48, 0.82)
Frequency of physical exercise per week						
0	45.06 (7.69)	<0.001	491 (80.5)	<0.001	1.00 (reference)	
1	42.58 (9.25)		262 (71.4)		0.61 (0.45, 0.82)	
2	42.11 (8.64)		137 (66.5)		0.48 (0.34, 0.68)	
≥3	42.41 (8.24)		93 (68.4)		0.52 (0.35, 0.79)	
Psychological health status						
Psychological distress in recent two weeks						
No	43.08 (8.50)	<0.001	779 (72.5)	0.001	1.00 (reference)	1.00 (reference)
Yes	46.08 (7.78)		204 (83.3)		1.88 (1.31, 2.70)	2.85 (1.94, 4.19)
Past cervical cancer screening experience						
Heard of cervical cancer screening						
No	46.93 (6.36)	<0.001	268 (88.7)	<0.001	1.00 (reference)	1.00 (reference)
Yes	42.66 (8.75)		715 (70.3)		0.30 (0.21, 0.44)	0.37 (0.25, 0.56)

^aP for t test or one-way ANOVA.^bP for chi-square test.^cVariables with P ≤ 0.10 in the uni-variate analysis were included in the multi-variate logistic regression model.

Bold values indicate statistical significance (P < 0.05).

above 40 in the STAI-S scale. The mean score (42.72) was much higher than that (30.2) in the USA (10). A relatively lower mean score (33.0) has also been detected before women underwent a Pap smear in the Netherlands (18). Despite of the ethnic, culture, and socio-economic differences, this disparity may also result from the distinct knowledge of HPV and cervical cancer. It has been revealed that better HPV knowledge was associated with lower anxiety and concerns during screening (19). Therefore, the prevalent pre-procedural anxiety in our survey may be partly explained by the knowledge gaps about HPV between China and other developed countries that we have previously found (20). Interestingly, the anxious level before screening was likely to be weaker than that in the diagnosis stage. Irish researchers observed a higher mean score of the STAI-S scale (45.31) prior to colposcopy (21). Colposcopy is usually applied for further diagnostic evaluation after receiving abnormal cervical cancer screening results. The fear of being diagnosed with malignancy along with complicated operations may bring more worries during colposcopy than screening procedures. Pre-procedural anxiety may associate with colposcopy-related pain and discomfort (22, 23). Nevertheless, our findings support the urgent need for the delivery of psychological assessment and support to the female population before screening procedures start.

Past participation of cervical cancer screening may help to reduce the anxiety or other negative psychological reactions in the current screening round. In our study, women without PSE had higher level of pre-procedural anxiety than their experienced counterparts. Similar findings have also been observed in other types of cancer screening. For colorectal cancer screening, patients without previous experience demonstrated greater anxiety when undergoing colonoscopy (24). For breast cancer screening, women who received mammogram at the first time tended to be more distressed than those having prior mammograms (25). However, the impact of PSE on screening-related anxiety may be obscured by a family history of cancer diagnosis. There was a inconsistent finding among women with a family history of breast cancer that women who had undergone mammography screening previously were vulnerable to longer-term distress (26). The possible explanation lies that a woman is more stressful to receive screening services regardless of having PSE if her relative has been diagnosed with or died from cancer. In addition, we noticed that the prevalence of pre-procedural anxiety decreased when the times of past screening participation increased in our study. This contrasted with another study in breast cancer screening, in which the anxiety level increased with the number of previous mammograms done (27). The difference in screening methods, medical apparatus and instruments, and

TABLE 3 | Pre-procedural anxiety and associated factors among women with PSE (N=2332).

Variable	STAI-S score (mean, SD)	P value ^a	The prevalence of anxiety (n, %)	P value ^b	Uni-variate OR (95%CI) ^c	Multi-variate OR (95%CI)
Demographic characteristic						
Age (year)						
<41	41.84 (8.94)	0.018	754 (65.7)	0.033	1.00 (reference)	
≥41	42.70 (8.46)		828 (69.9)		1.21 (1.02, 1.44)	
Ethnicity						
Han	42.25 (8.73)	0.49	1489 (67.8)	0.79	1.00 (reference)	
Others	42.78 (8.37)		93 (68.9)		1.05 (0.72, 1.53)	
Local household registration						
Yes	40.72 (9.54)	<0.001	297 (59.0)	<0.001	1.00 (reference)	
No	42.71 (8.42)		1285 (70.3)		1.64 (1.34, 2.01)	
Marital status						
Single/divorced/widow	41.83 (8.79)	0.59	70 (66.7)	0.79	1.00 (reference)	
Married	42.30 (8.71)		1512 (67.9)		1.06 (0.70, 1.60)	
Education level						
Junior middle school or below	43.38 (8.06)	<0.001	975 (73.8)	<0.001	1.00 (reference)	1.00 (reference)
Senior middle school	41.35 (9.20)		353 (61.4)		0.56 (0.46, 0.70)	0.61 (0.49, 0.77)
College or above	40.16 (9.40)		254 (58.3)		0.50 (0.40, 0.62)	0.59 (0.45, 0.77)
Occupation types						
Administrator/professional	40.17 (9.81)	<0.001	152 (57.1)	<0.001	1.00 (reference)	
Worker	43.19 (7.97)		578 (73.4)		2.07 (1.55, 2.77)	
Business services personnel	41.38 (8.86)		221 (64.4)		1.36 (0.98, 1.89)	
Housewife/unemployed woman	42.40 (8.84)		425 (67.2)		1.54 (1.15, 2.07)	
Others	42.53 (8.74)		206 (67.8)		1.58 (1.12, 2.22)	
Monthly income (RMB)						
<5,000	42.81 (8.47)	<0.001	1242 (70.6)	<0.001	1.00 (reference)	1.00 (reference)
≥5,000	40.66 (9.24)		340 (59.2)		0.60 (0.50, 0.73)	0.79 (0.64, 0.92)
Reproductive health condition						
Age at menarche (year)						
<12	41.63 (8.81)	0.28	49 (69.0)	0.19	1.10 (0.66, 1.84)	
12 to 15	42.16 (8.76)		1191 (66.9)		1.00 (reference)	
≥16	42.81 (8.51)		342 (71.2)		1.23 (0.98, 1.53)	
Age at coitarche (year)						
<18	43.87 (8.49)	0.092	97 (74.6)	0.23	1.00 (reference)	
18 to 24	42.23 (8.73)		1147 (67.6)		0.71 (0.47, 1.07)	
≥25	42.04 (8.69)		338 (67.1)		0.69 (0.45, 1.07)	
The number of sexual partners in recent one year						
0	43.57 (8.43)	<0.001	116 (73.9)	<0.001	1.00 (reference)	1.00 (reference)
1	41.95 (8.78)		1354 (66.2)		0.69 (0.48, 1.00)	0.80 (0.54, 1.18)
≥2	45.89 (6.85)		112 (85.5)		2.08 (1.14, 3.81)	2.11 (1.13, 3.93)
Consistent condom use during sexual intercourse						
No	42.44 (8.53)	0.058	1341 (68.6)	0.063	1.00 (reference)	
Yes	41.44 (9.54)		241 (63.8)		0.80 (0.64, 1.01)	
Oral contraceptive use						
Never	42.25 (8.68)	0.71	1329 (68.3)	0.33	1.00 (reference)	
Ever	42.43 (8.87)		253 (65.7)		0.89 (0.71, 1.12)	
Parity						
0	41.37 (9.08)	<0.001	26 (60.5)	0.001	0.87 (0.46, 1.64)	
1	41.40 (8.84)		374 (63.7)		1.00 (reference)	
2	42.19 (8.73)		849 (67.5)		1.18 (0.96, 1.45)	
≥3	43.79 (8.27)		333 (75.0)		1.71 (1.30, 2.25)	
Age at first delivery (year)						
Nonparous	41.37 (9.08)	0.65	26 (60.5)	0.62	0.75 (0.39, 1.44)	
<18	42.55 (8.73)		757 (69.1)		1.09 (0.83, 1.44)	
18 to 24	42.30 (8.27)		193 (67.2)		1.00 (reference)	
25 to 29	41.99 (8.87)		506 (66.5)		0.97 (0.72, 1.29)	
≥30	42.00 (8.50)		100 (68.5)		1.06 (0.69, 1.62)	
Caner history of first-degree relatives						
No/unknown	42.36 (8.66)	0.15	1463 (68.3)	0.13	1.00 (reference)	
Yes	41.41 (9.28)		119 (63.0)		0.79 (0.58, 1.08)	
Previous diagnosis of vaginitis						

(Continued)

TABLE 3 | Continued

Variable	STAI-S score (mean, SD)	P value ^a	The prevalence of anxiety (n, %)	P value ^b	Uni-variate OR (95%CI) ^c	Multi-variate OR (95%CI)
No	42.76 (8.60)	0.004	933 (69.9)	0.012	1.00 (reference)	1.00 (reference)
Yes	41.67 (8.82)		649 (65.0)		0.80 (0.67, 0.95)	0.77 (0.64, 0.92)
Health habit						
Active smoking						
Never	42.27 (8.71)	0.73	1558 (67.7)	0.38	1.00 (reference)	
Ever	42.81 (9.25)		24 (75.0)		1.43 (0.64, 3.20)	
Passive smoking						
Never	42.30 (8.68)	0.80	1337 (68.0)	0.75	1.00 (reference)	
Ever	42.18 (8.87)		245 (67.1)		0.96 (0.76, 1.22)	
Sitting hours per day						
<5	41.92 (8.90)	0.019	879 (65.7)	0.012	1.00 (reference)	1.00 (reference)
≥5	42.77 (8.43)		703 (70.7)		1.25 (1.05, 1.50)	1.25 (1.03, 1.51)
Walking steps per day						
<5000	43.14 (8.61)	<0.001	970 (71.7)	<0.001	1.00 (reference)	
≥5000	41.10 (8.72)		612 (62.5)		0.66 (0.55, 0.79)	
Frequency of physical exercise per week						
0	44.01 (8.27)	<0.001	552 (75.1)	<0.001	1.00 (reference)	1.00 (reference)
1	42.84 (8.31)		483 (70.6)		0.80 (0.63, 1.01)	0.92 (0.72, 1.17)
2	40.86 (8.77)		301 (60.8)		0.51 (0.40, 0.66)	0.66 (0.51, 0.86)
≥3	40.01 (9.28)		246 (58.9)		0.47 (0.37, 0.61)	0.63 (0.48, 0.83)
Psychological health status						
Psychological distress in recent two weeks						
No	41.30 (8.67)	<0.001	1186 (64.1)	<0.001	1.00 (reference)	1.00 (reference)
Yes	46.05 (7.80)		396 (82.0)		2.55 (1.98, 3.27)	3.00 (2.30, 3.91)
Past cervical cancer screening experience						
The total times of screening participation						
1	43.08 (8.48)	<0.001	721 (71.0)	<0.001	1.00 (reference)	1.00 (reference)
2	42.12 (8.60)		440 (69.0)		0.91 (0.73, 1.12)	0.85 (0.68, 1.08)
≥3	41.23 (9.04)		421 (62.0)		0.67 (0.54, 0.82)	0.67 (0.53, 0.84)
The time of previous screening						
Over 3 years	41.22 (9.05)	0.001	351 (61.5)	<0.001	1.00 (reference)	1.00 (reference)
Within 3 years	42.62 (8.57)		1231 (69.9)		1.46 (1.20, 1.77)	1.58 (1.27, 1.97)
The result of previous screening						
Normal	41.91 (8.78)	<0.001	1154 (65.6)	<0.001	1.00 (reference)	1.00 (reference)
Abnormal	42.08 (9.03)		85 (72.0)		1.35 (0.89, 2.04)	1.24 (0.80, 1.92)
Unknown	43.75 (8.21)		343 (75.4)		1.61 (1.27, 2.03)	1.42 (1.11, 1.82)

^aP for t test or one-way ANOVA.^bP for chi-square test.^cVariables with P ≤ 0.10 in the uni-variate analysis were included in the multi-variate logistic regression model.

Bold values indicate statistical significance (P < 0.05).

body parts lead to these inconclusive findings to some extent, however, other screening-related factors may play a potential role in the link between PSE and anxiety, such as screening frequency, and past screening results.

In our study, distinct associated factors of pre-procedural anxiety between women with and without PSE were found, especially variables specific to PSE. Among women with PSE, we confirmed the impact of past screening times on pre-procedural anxiety that women participating three or more times screening had less likelihood of being anxious. A similar result were detected among women without PSE that having heard of cervical cancer screening was associated with less anxiety. Both more screening participation and heard of screening indicate a better understanding of the screening procedures, which may help women to reduce the psychological discomfort in cervical cancer screening. Notably, this protective effect may be counteracted by a short screening

interval (within three years) and uncertainty of previous screening results as we observed in the present study. According to the screening guidelines, women can be screened every three or five years unless positive screening results for HPV testing or cytology appear (28). This means that screening repeatedly within three years is more likely to be owing to abnormal screening results, which may bring a heavier psychological burden (4, 29, 30). Furthermore, overscreening may present in these women, which can also result in significant anxiety (31). For women unknowing past screening results, less self-confidence and more worries in health status may become more salient when they engage in a new round of screening. Consedine et al. has proposed that there are different sources of anxiety in cancer screening, including fear of the screening process (e.g. pain, discomfort, embarrassment), fear of the screening outcomes, and undifferentiated fear of cancer (32). Hence, it can be inferred that PSE affects the sources of pre-

procedural anxiety in different manners. Fear of the screening process may be alleviated by past participation of screening, while fear of the screening outcome or getting cancer may be aggravated by a short screening interval and previous uncertain results. Further population-based investigations are needed to verify the contribution of PSE to pre-procedural anxiety with different sources in cervical cancer screening.

Study limitations were shown in the present study. As the study sample came from only one screening center as well as smartphone users, the prevalence of pre-procedural anxiety might be not able to generalize to the whole population in cervical cancer screening. Recall bias on PSE and other key information could not be avoided due to self-reported answers. Moreover, we conducted psychological assessment prior to the screening process rather than during the screening procedure, which might lead to underestimation of anxious feeling. The sources of anxiety could not be distinguished in our study as well. Thus, precise classification evaluation of screening related anxiety should be considered in further investigations. In addition, Women's psychological health status may be influenced by the COVID-19 pandemic to some extent. However, there was no difference of psychological distress in recent two weeks between women with and without PSE. Simultaneously, no local COVID-19 cases had been detected in Shenzhen during the survey time period. The impacts of the COVID-19 pandemic could be limited.

In conclusion, the current study lends to support that women participating in cervical cancer screening commonly present pre-procedural anxiety. Importantly, PSE may help to alleviate pre-procedural anxiety, which is influenced by past screening times, interval, and results. Even if women have not been screened before, having heard of cervical cancer screening is associated a lower likelihood of pre-procedural anxiety. Psychological counseling according to women's PSE before cervical cancer screening is warranted of necessity.

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DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the medical ethics committee of Shenzhen Maternity and Child Healthcare Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WL wrote and presented the original draft. WL, WH, CZ, and LZ were involved in data curation and visualization. WL, WH, CM, PL, ZL, and YW were involved in methodology, software, analysis, review and editing. WL, WH, and CM revised the manuscript and polished the language. SY and YW were involved in supervision. All authors contributed to the article and approved the submitted version.

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Preferred place of death and end-of-life care for adult cancer patients in Iran: A cross-sectional study

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Background: More than 50,000 deaths in terms of cancer occur annually in Iranian hospitals. Determining the preferred place of end-of-life care and death for cancer patients in Iran is a quality marker for good end-of-life care and good death. The purpose of this study was to determine the preferred place of end-of-life care and death in cancer patients.

Method: In 2021, the current descriptive cross-sectional investigation was carried out. Using the convenience sample approach, patients were chosen from three Tehran referral hospitals (the capital of Iran). A researcher-made questionnaire with three parts for demographic data, clinical features, and two questions on the choice of the desired location for end-of-life care and the death of cancer patients served as the data collecting instrument. Data were analyzed using SPSS software version 18. The relationship between the two variables preferred place for end-of-life care and death and other variables was investigated using chi-square, Fisher exact test, and multiple logistic regression.

Result: The mean age of patients participating in the study was 50.21 ± 13.91 . Three hundred ninety (69.6%) of the patients chose home, and 170 (30.4%) patients chose the hospital as the preferred place of end-of-life care. Choosing the home as a preferred place for end-of-life care had a significant relationship with type of care (OR = .613 [95% CI: 0.383–0.982], $P = .042$), level of education (OR = 2.61 [95% CI: 1.29–5.24], $P = 0.007$), type of cancer (OR = 1.70 [1.01–2.89], $P = .049$), and income level (*Mediate*: (OR: 3.27 (1.49, 7.14), $P = .003$) and *Low*: (OR: 3.38 (1.52–7.52), $P = .003$). Also, 415 (75.2%) patients chose home and 137 (24.8%) patients chose hospital as their preferred place of death. Choosing the home as a preferred place of death had a significant relationship

with marriage (OR = 1.62 [95% CI: 1.02–2.57], $P = .039$) and time to diagnostic disease less than 6 months (OR = 1.62 [95% CI: 0.265–0.765], $P = .002$).

Conclusion: The findings of the current research indicate that the majority of cancer patients selected their homes as the preferred location for end-of-life care and final disposition. Researchers advise paying more attention to patients' wishes near the end of life in light of the findings of the current study. This will be achieved by strengthening the home care system using creating appropriate infrastructure, insurance coverage, designing executive instructions, and integration of palliative care in home care services.

KEYWORDS

preferred place of death, preferred place of care, palliative care, end of life, cancer, hospice, Iran

Introduction

Cancer is the second leading cause of death in the world and the third leading cause of death in Iran (1–3). According to the World Health Organization, cancer caused the deaths of 10 million people in 2020 (1 in 6 deaths) with a mean age of 72 years worldwide (4). According to GLOBALCAN statistics, more than 110,000 new cases of cancer were detected in Iran in 2018, and by 2030, this figure is projected to rise to 156,000 (5). Iran has documented 55,785 cancer-related fatalities so far this year (1). In general, only 39% of countries report access to primary healthcare and 40% of countries report access to palliative care in community care and home care (6). Weakness in access to palliative care and end-of-life care is more serious in cancer patients. However, only 14% of cancer patients get the end-of-life care they need (out of the 34% that need it) (7). Despite these figures, the state of end-of-life care in Iran is only partially quantified. Recently, in terms of the increasing incidence of cancer and the decline in the quality of end-of-life care of these patients, this type of service has received more attention from health policymakers (8).

Dying and caring for patients' preferred place in the last days of life are considered a quality marker to have good end-of-life care worldwide (9). Many of these patients in the final stages of life attach great importance to the preferred place for end-of-life care (PPOEOLC) and preferred place of death (PPOD), and this place will have a significant impact on their quality of life and death and care (10, 11). The terms "preferred place of death" (PPOD) and "preferred place for end-of-life care" (PPOEOLC) relate to people's preferences for where they would want to pass away or receive care in their last days, respectively (8). Awareness of patients' preferences about PPOEOLC and PPOD is essential for end-of-life palliative care planning (11). Besides, meeting these personal preferences is one of the ultimate criteria for success in palliative care (12). Therefore,

understanding the PPOEOLC and PPOD is the first step to ensuring adequate resources for patients. The significance of this topic is shown by the many preferred surveys conducted to calculate the PPOEOLC and PPOD in the United Kingdom (9), the United States (13), European nations (14), and other countries (15). Regardless of cultural or national distinctions, the majority of cancer patients have selected their home as their PPOEOLC and PPOD (11, 12, 16). A systematic review study by Fereidouni et al. (3) in 2021 and a study by Brogaard et al. in 2013 (12) also showed that more than half of cancer patients preferred home as the PPOD and end-of-life care.

However, the most common actual place of care and death for cancer patients in different countries is the hospital (15, 17, 18). In Iran, 60% of deaths occur in hospitals (18). The reported rate of achieving a PPOD in patients varies from 49% to 88% in western countries to 66% in south Africa (16). The effect of societal and cultural factors, sociodemographic factors, clinical characteristics, and patients' access to different palliative and psychiatric care is responsible for the variation in these data (19, 20). According to the conceptual framework created by Gomez and Higginson, the environment, the individual, and the illness all have an impact on where a person passes away. Sociodemographic details and the patient's choices for the location of death are examples of personal considerations. Environmental factors can be attributed to healthcare inputs (home care, hospital bed availability, and hospital admissions), social support (living arrangements, patient's social support network, and caregiver coping), and macro-social factors (historical trends, health care policy, and cultural factors) (21).

Other factors influencing the choice of PPOEOLC and PPOD include insufficient government support for palliative care as a dimension of universal health coverage, difficulty accessing drugs and inadequate training in drug use, lack of proper education, and limited financial resources in this context (22, 23). Studies have mainly examined the demographic and

patients' clinical characteristics affecting PPOEOLC and PPOD using multiple logistic models (24–26).

Iranians are mostly Shiite Muslims (5). Death is seen as a rebirth in Iranian-Islamic culture, and each person's death time is determined by divine destiny (27, 28). There is a distinction between a good death and a poor death in this society (28). Islam places a high value on death, as shown by the fact that the word "death" appears 84 times in the Muslim holy book, the Quran (27). Discussions about PPOC and PPOD are sensitive issues that are difficult to address without patient preparation, because they cause anxiety in the patient (11). For this reason, very few studies were conducted in Islamic countries on the PPOEOLC and PPOD. Finding a suitable and preferential place for end-of-life care and death to implement effective policies and planning based on the preferences of cancer patients is essential to providing more favorable palliative interventions. It also helps properly distribute resources to care units, such as hospitals, homes, or intermediate centers (hospices, long-term care centers) (3).

Despite all these advantages and how crucial it is to treat the PPOEOLC and PPOD issues, Iran's health system has so far paid little attention to them. As a result, the goal of the current research was to identify PPOEOLC and PPOD in Iranian cancer patients.

Materials and methods

Study design

This cross-sectional descriptive study was conducted from October to November 2021. The study population was hospitalized cancer patients and referred to the outpatient department of three referral hospitals in Tehran (the capital of Iran).

Study population

After learning the research's goals and completing a written informed permission form, patients who satisfied the inclusion criteria joined the trial *via* convenient ways. Inclusion requirements include having received a medically confirmed diagnosis of cancer, being above the age of 18, being able to read and write Persian, being in adequate physical condition to complete the questionnaire, and not having cognitive issues such as Alzheimer's or dementia. The required sample size was obtained based on the study of Alsirafy et al. (29) which was $P = 0.28$, and 345 people were obtained using the formula $n = Z^2 P (1-P) / d^2$ with 95% confidence level and $(d) = 0.05$; the sample size was calculated to be 370 people with design effect equal to 1.5.

$$n = \frac{Z_{1-\alpha/2}^2 P(1-P)}{d^2}$$

Data collection tool

The data collection tool included a researcher-made questionnaire consisting of three sections:

The first part includes the patient's demographic information including age, gender, level of education, marital status, number of children, employment status, monthly income, and race; the second part includes patients' clinical characteristics including type of care (inpatient/outpatient), type of cancer (gastrointestinal, breast, blood, other), insurance coverage (Social Security Insurance funded by the Social Security Organization, Armed Forces Insurance funded by the Ministry of Defense and Armed Forces Logistics, etc.) and time to diagnostic disease (less than 6 months, more than 6 months); and the third part includes two questions related to the PPOEOLC (home/hospital) and choosing PPOD (home/hospital).

The questionnaire's face validity was assessed using two quantitative and qualitative techniques. By concentrating on respondents' cognitive process while completing the scale, a cognitive interview is undertaken to determine the cause of inaccuracy in the scale (30). Ten cancer patients with diverse economic, social, and education levels were interviewed. They were requested to rate the legibility, clarity, and structure of the items, ease of comprehension, item difficulty, confusing words, item classification, ease of responding, language forms, and wording. Subsequently, the modifications were applied in the primary questionnaire. The impact score of each question was calculated to quantify face validity. For each item, the Likert scale was divided into five parts: I completely agree (score 5), I agree (score 4), I have no opinion (score 3), I disagree (score 2), and I completely disagree (score 1). Then a questionnaire was given to 10 specialists (three oncologists, five nursing professors, one palliative specialist, and one psychologist) to determine the validity. Then the impact score for each item of the questionnaire is calculated by the method (importance \times frequency = impact score). If the impact score is greater than 1.5, the item is suitable (31). The impact score for both questions was more than 1.5.

"At the end of life, some individuals choose to be cared for at home, while others prefer to be cared for in a hospital," was one of two questions connected to the PPOEOLC and the PPOD. Where would you rather get treatment as you near death? and "At the end of their lives, some individuals choose to pass away at home while others choose to pass away in a hospital. Where would you rather pass away?"

Data analysis

After data collection, the collected data were analyzed by SPSS software version 18. Descriptive analyses including frequency and percentage were used for qualitative data, and mean and standard deviation were used for normal quantitative data. The two primary variables, the PPOEOLC and the PPOD, together with demographic factors and clinical features of the subjects were examined using chi-square and Fisher exact tests. The threshold for statistical significance was set at $P = 0.05$. Finally, significant variables were included in the model through multiple logistic regression with the Wald backward method.

The effect of individual explanatory variables on the outcome variable was measured using the adjusted odds ratio (AOR) with a 95% confidence interval (CI).

Ethical consideration

Permission for this study was approved by the ethics committee of Baqiyatallah University of Medical Sciences with the code of ethics (IR.BMSU.REC.1399.42). Participants were assured of anonymity and confidentiality of the information obtained.

Result

Demographic and clinical characteristics of the patients

The mean age of 564 patients participating in the study was 50.21 ± 13.91 . Thus, 276 (48.9%) were aged 40–60 years. Furthermore, 189 (33.5%) patients were men and 375 (66.5%) were women. The number of 190 (33.8%) had elementary education, 274 (48.5%) had high school education, and 100 (17.8%) had academic education. Regarding the kind of cancer, there were 144 (28.5%) cases of gastrointestinal, 219 (43.4%) cases of breast, 55 (11.7%) cases of blood, and 83 (16.4%) cases of other cancers. In these individuals, the median time to diagnostic disease cancer was 24.83 26.18 months. Three hundred seventy-eight persons (70%) and 162 (30%) of the total population had cancer for more than 6 months, respectively (Table 1 shows the demographic and clinical characteristics of 564 cancer patients).

Preferred place for end-of-life care

Three hundred ninety (69.6%) patients chose home and 170 (30.4%) patients chose the hospital as their preferred place for end-of-life care (PPOC) (Figure 1). Univariate test showed that choosing home in outpatients (72.6%) was higher than in inpatients (59.7%), which shows a significant difference ($P = 0.005$). Moreover, the percentage of choosing home in women

(73.4%) was higher than in men (62.2%) ($P = 0.007$). People with academic education (77.6%) were more likely to receive care at home than other people with elementary education (59.6%) and high school (74.4%) ($P = 0.000$). Additionally, Persians (76%) picked their homes more often than other races ($P = 0.013$). The logistic model showed that inpatient patients had a lower likelihood of selecting home than outpatient patients (OR: 0.613 (.383, .982), $P = .042$). Patients with academic education had a higher likelihood of choosing home than patients with elementary education, although this difference was not statistically significant (OR: 2.61 (1.29, 5.24), $P = .007$). Patients with high school education had similar chances of choosing home as patients with elementary education. Chances of choosing home in two groups of patients with mediate income (OR: 3.27 (1.49, 7.14), $P = .003$) and low (OR: 3.38 (1.52, 7.52), $P = .003$) were significantly higher than in patients with high income. In other words, by decreasing income, the chance of choosing the home increased, and patients with breast cancer had a better chance of choosing a home than with gastrointestinal cancer (OR: 1.70 (1.01, 2.89), $P = .049$) (Table 2).

Preferred place of death

Four hundred fifteen (75.2%) patients chose home as their PPOD, while 137 (24.8%) people chose the hospital (Figure 1). Choosing a home as a PPOD in married patients (77.6%) compared to single patients (66.7%) was higher ($P = 0.014$). Also, patients with Armed Forces Insurance with 82.1% were the most patients who chose home as the PPOD ($P = 0.011$). Moreover, patients with a disease period of less than 6 months (84.9%) compared to patients with a period of more than 6 months (72%) had chosen home as the PPOD ($P = 0.002$). However, the logistic model showed that married people have a higher chance of choosing the home than single people (OR: 1.62 (1.02, 2.57), $P = .039$). Besides, people with a disease period longer than 6 months had a significantly lower chance of choosing the home than people with a disease period of less than 6 months (OR: 0.468 (.286, .765), $P = .002$). (Table 3).

Discussion

In Iran, there are no official statistics on the PPOEOLC and the PPOD in cancer patients. Therefore, the purpose of this study was to determine the PPOEOLC and PPOD in cancer patients. Given that there is a view in Iranian culture that discussing death and dying with patients is inappropriate because of stress and poor patient morale, the paucity of study in this field is likely a result of cultural and religious constraints. Thus, preference about the place of death and place of end-of-life care is not a stable concept and can change over time through discussion between healthcare professionals and patients

TABLE 1 Demographic and clinical characteristics of the 564 cancer patients.

Variable	Categories	n (%)
Type of care	Outpatient	435 (77.1%)
	Inpatient	129 (22.9%)
Sex	Male	189 (33.5%)
	Female	375 (66.5%)
Age (year)	Mean \pm SD*	50.21 \pm 13.91
	18–40	154 (27.3%)
	40–60	276 (48.9%)
	>60	134 (23.8%)
Marital status	Single	126 (22.4%)
	Married	437 (77.6%)
Number of children	Mean \pm SD	2.55 \pm 1.88
	0	67 (12.2%)
	1–3	366 (66.7%)
	≥ 4	116 (21.1%)
Education	Elementary	186 (33.8%)
	High school	267 (48.5%)
	Academic	98 (17.8%)
Job	Employed	126 (22.6%)
	Unemployed	431 (77.4%)
Ethnicity	Fars	264 (47.1%)
	Lor	52 (9.3%)
	Tork	151 (26.9%)
	Kord	78 (13.9%)
	Other	16 (2.9%)
Income	High	42 (7.6%)
	Mediate	306 (55.4%)
	Low	204 (37%)
Type of cancer	Gastrointestinal	144 (28.5%)
	Breast	219 (43.4%)
	Blood	59 (11.7%)
	Other	83 (16.4%)
Insurance	Tamin ejtemaee	214 (38.2%)
	Military	203 (36.3%)
	Other	143 (25.5%)
Time to diagnostic disease (month)	Mean \pm *SD	24.83 \pm 26.18
	≤ 6	162 (30%)
	>6	378 (70%)
Preferred place of care	Hospital	170 (30.4%)
	Home	390 (69.6%)
Preferred place of death	Hospital	137 (24.8%)
	Home	415 (75.2%)

*SD, standard deviation.

according to social, supportive, and individual conditions (32, 33).

By reviewing the literature, various studies have discussed the PPOEOLC and PPOD together (11, 12, 15, 34). However, in the present study, both concepts (PPOEOLC and PPOD) were surveyed using two separate questions. In the present study, most cancer patients chose home as their PPOEOLC and PPOD.

This result is consistent with a recent systematic review study by Fereidouni et al. (3), Choi et al. in South Korea (34), Yamagishi et al. in Japan (15), Skorstengaard et al. in Denmark (11), Alsirafy et al. in Egypt (35), Gu et al. in China (36), Lee et al. in Taiwan (37), and Nakamura et al. in Japan (38). A study by Brogaard et al. found that cancer patients chose 84% of their PPOEOLC, and 71% of their PPOD at home (12).

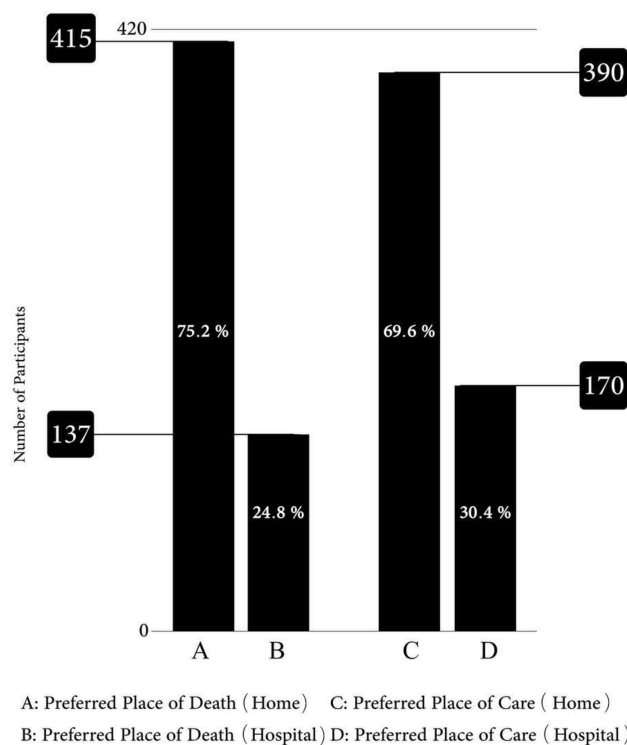


FIGURE 1

Preferred place of care and death of patients with cancer disease.

Another systematic review shows that the home is the PPOD for most cancer patients worldwide (3). The reason why individuals in various nations choose to pass away at home is probably impacted by a number of things. For instance, patients who preferred to pass away at home were more likely to do so if they were less educated, lived with their spouse or family, or were from rural regions (34, 36). Some patients may have a history of adversity in their lives, which influences their decision (39).

Dying and caring at home may have religious significance, because the home environment can facilitate cultural and religious ceremonies at the end of life as an integral part of peaceful death (16). The cultural family-centered principle of Iranian-Islamic society and patients' desire for family members to be present in bed when receiving end-of-life care is a feature of Iranian society that is effective to achieve the present result. According to other research, the capacity to address the patient's fundamental requirements, patient privacy, a more soothing environment for the patient and caregiver, and simple access to home care support systems are the most prevalent reasons patients opt to get their care at home (16, 40, 41). The hospital was the second priority as the PPOEOLC and PPOD of cancer patients. Consistent with the present study, the study by Choi et al. in South Korea (34), Skorstengaard et al. in

Denmark (11), and three other studies show that the hospital is the second priority as the PPOD and PPOEOLC (34, 36, 42, 43). The most common reasons of patients in choosing the hospital as the second PPOD and PPOEOLC in other studies include patients not wishing to be a burden on their family (40), having a reliable relationship between caregivers and patients (44), having a safer care environment, adequate facilities, and equipment to facilitate quality care, especially time to overcome pain and discomfort (45), poor functional status of the patient and the family's inability to provide effective and quality care, and lack of the participation of the palliative care team at home (16).

In accordance with Iranian society's culture, hospitals are seen as a secure and suitable setting for managing illness symptoms and suffering, particularly when doing so is challenging. The answer to the question about the PPOEOLC and PPOD was limited to two options of home and hospital. Other studies used places such as nursing home and hospice but in terms of the lack of development of hospice centers in Iran, as in many Middle-eastern countries (35). However, in countries where there are hospices, patients still choose home as their PPOD (9, 13, 46).

The findings of the current research are consistent with those of the studies by Jeurkar et al. (13) and Gu et al. (14),

TABLE 2 Correlations between variables and the preferred place of end-of-life care in cancer patients.

Variable	Categories	HospitalN (%)	HomeN (%)	P-value	Multiple logistic model	
					*OR (**CI 95%)	P-value
Type of care	Outpatient	118 (27.4%)	313 (72.6%)	0.005	Base Category	
	Inpatient	52 (40.3%)	77 (59.7%)		.613 (.383, 982)	.042
Sex	Male	71 (37.8%)	117 (62.2%)	0.007		
	Female	99 (26.6%)	273 (73.4%)			
Age	18-40	43 (28.1%)	110 (71.9%)	0.084		
	40-60	76 (27.8%)	197 (72.2%)			
	>60	51 (38.1%)	83 (61.9%)			
Marital status	single	39 (31.2%)	86 (68.8%)	0.78		
	married	130 (30.0%)	304 (70%)			
Number of children	0	18 (26.9%)	49 (73.1%)	0.19		
	1-3	102 (28.1%)	261 (71.9%)			
	≥4	42 (36.5%)	73 (63.5%)			
Education	Elementary	74 (40.4%)	109 (59.6%)	0.000	Base Category	
	High school	68 (25.6%)	198 (74.4%)		1.51 (.907, 2.51)	.113
	academic	22 (22.4%)	76 (77.6%)		2.61 (1.29, 5.24)	.007
Jobs	Employed	40 (31.7%)	86 (68.3%)	0.74		
	Unemployed	129 (30.2%)	298 (69.8%)			
Ethnicity	Fars	63 (24%)	199 (76%)	0.013		
	Lor	15 (28.8%)	37 (71.2%)			
	Tork	52 (34.9%)	97 (65.1%)			
	Kord	31 (39.7%)	47 (60.3%)			
	other	8 (50%)	8 (50%)			
Income	High	24 (57.1%)	18 (42.9%)	0.003	Base Category	
	Mediate	90 (29.6%)	214 (70.4%)		3.27 (1.49, 7.14)	.003
	low	54 (26.7%)	148 (73.3%)		3.38 (1.52, 7.52)	.003
Type of cancer	Gastrointestinal	52 (36.1%)	92 (63.9%)	0.006	Base Category	
	Breast	47 (21.6%)	171 (78.4%)		1.70 (1.01, 2.89)	.049
	Blood	23 (39.7%)	35 (60.3%)		.65 (.33, 1.29)	.225
	other	25 (30.1%)	58 (69.9%)		1.32 (.71, 2.46)	.381
Insurance	***Social security	50 (23.5%)	163 (76.5%)	0.006		
	***military	63 (31.3%)	138 (68.7%)			
	other	56 (39.2%)	87 (60.8%)			
Time to diagnostic disease (month)	≤6	55 (34%)	107 (66%)	0.14		
	>6	104 (27.7%)	271 (72.3%)			

*OR, odds ratio; **CI, confidence interval.

***Funder: Social Security Organization.

**Funder: Military Organization.

which found that married patients were more likely than single patients to choose home as their PPOD (36). This is most likely because the patient and spouse have a stronger emotional bond, which makes the home environment more calming for the patient. The results of the present study showed that outpatients had a significantly higher chance of choosing the home as a PPOEOLC than inpatients. Moreover, patients with a time to diagnostic disease the less than 6 months had a significantly higher chance of choosing the home as a PPOD than the patients' time to diagnostic disease of more than 6 months. The result of this study is contrary to the study of Gu et al. (36). The reason for this difference is most likely the

individual's incompatibility with the hospital environment at the beginning of the illness. Inpatients and people who have been ill for a long time are more likely to adapt to the hospital environment due to the longer hospital stay.

The patients with academic level of education are more likely to choose home as the PPOEOLC than patients with elementary and high school levels of education. This result is inconsistent with the study of Choi et al. (34) and the study of Chen et al. (47). The difference may be explained by the fact that patients with greater levels of education are more aware of and knowledgeable about conditions for self-care at home, which enhances the possibility that they will choose the home. In our

TABLE 3 Correlations between variables and the preferred place of death of cancer patients.

Variable	Categories	HospitalN (%)	HomeN (%)	P value	Multiple logistic model	
					OR (CI 95%)	P-value
Type of care	Outpatient	109 (25.7%)	315 (74.3%)	0.379		
	Inpatient	28 (21.9%)	100 (78.1%)			
Sex	Male	41 (22.7%)	140 (77.3%)	0.41		
	Female	96 (25.9%)	275 (74.1%)			
Age	18-40	45 (30.2%)	104 (69.8%)	0.13		
	40-60	58 (21.4%)	213 (78.6%)			
	>60	34 (25.8%)	98 (74.2%)			
Marital status	Single	41 (33.3%)	82 (66.7%)	0.014	Base category 1.62 (1.02, 2.57)	.039
	Married	96 (22.4%)	332 (77.6%)			
Number of children	0	16 (24.6%)	49 (75.4%)	0.67		
	1-3	93 (25.8%)	268 (74.2%)			
	≥4	24 (21.6%)	87 (78.4%)			
Education	Elementary	43 (23.8%)	138 (76.2%)	0.65		
	High school	65 (24.7%)	198 (75.3%)			
	academic	25 (26.3%)	70 (73.7%)			
Jobs	Employed	26 (21.1%)	97 (78.9%)	0.27		
	Unemployed	110 (25.9%)	314 (74.1%)			
Ethnicity	Fars	56 (21.8%)	201 (78.2%)	0.43		
	Lor	11 (21.6%)	40 (78.4%)			
	Tork	44 (29.9%)	103 (70.1%)			
	Kord	21 (26.9%)	57 (73.1%)			
	other	4 (25%)	12 (75%)			
Income	High	12 (28.6)	30 (71.4%)	0.92		
	Mediate	73 (24.3)	228 (75.7%)			
	low	51 (25.5)	149 (74.5%)			
Type of cancer	Gastrointestinal	29 (20.4)	113 (79.6%)	0.28		
	Breast	63 (28.9)	155 (71.1%)			
	Blood	14 (24.6)	43 (75.4%)			
	other	18 (22)	64 (78%)			
Insurance	Social security	57 (27)	154 (73%)	0.011		
	military	35 (17.9)	161 (82.1%)			
	other	45 (31.5)	98 (68.5%)			
Time to diagnostic disease (month)	≤6	24 (15.1)	135 (84.9%)	0.002	Base category .468 (.286,.765)	.002
	>6	104 (28)	268 (72%)			

OR, odds ratio; CI, confidence interval.

study, middle- and lower-income people chose home as their PPOEOLC more than high-income people; the reason for this choice is probably due to the financial inability of these people to pay for care and equipment in the hospital.

According to World Health Organization's World Cancer Statistics in 2020, the most common type of cancer in 2022 is breast cancer (2.26 million cases) (4). In our study, the type of disease was also a significant factor in choosing the home as a PPOEOLC, so that people with breast cancer chose home more than people with other cancers. The result of our study was in line with the study of Chen and the study of Blanchard et al. In the Blanchard study, breast cancer patients also chose the home as the PPOD (47, 48).

Conclusion

The results of the present study show that the majority of Iranian cancer patients chose home as the PPOEOLC and the PPOD. According to the findings of this study, experts advocate paying more attention to the preferences of terminally ill patients, strengthening the system of home healthcare. This will be accomplished through enhancing the home care system *via* the development of suitable infrastructure, insurance coverage, the drafting of executive directives, and the incorporation of palliative care into home care services. In addition, emphasizing death at home requires a fair distribution of health resources. For this purpose, more resources need to be allocated to home health care.

The strength of the study

The strength of the present study lies in the fact that we used patients' statements about their preferences rather than a proxy statement made by others, such as a family caregiver or other caregivers. Another strength of this study is that the question is asked from cancer patients about the PPOEOLC and PPOD, not from the general population without diagnosis; in fact, when people are well and live without diagnosis of life-limiting diseases or do not face death, they may use an abstract and unrealistic answer, while in our study this answer was concrete.

Limitations

Despite the inclusion of a wide range of potential predictors, observational studies may never be able to reduce the effect of confounding variables to zero. As patients approach their last days of life, cross-sectional evaluations may also alter the dynamic decision-making process of priorities, predictors of death, and home care. Another limitation of this study is that the "no preference" option was not considered as an answer that is suggested to be considered in future studies.

Implications for practice and future research

To achieve the patient's preferences at the end of life, it is important to have a preferred place to discuss death and document the decision. Therefore, it is important to ensure that all patients have the opportunity to speak about this issue in a supportive, practical, and compassionate manner. To increase their competency and confidence in end-of-life conversations, medical and nursing professionals' training may be strengthened. Death in hospitals is anticipated to predominate in the future, despite minor variations in the location of death throughout time. Therefore, it is necessary to take measures in this regard to improve the experiences of patients and their families at this time. Further research is needed on the impact of deprivation and other socioeconomic factors on preferences, the

reasons for lack of discussing the place of death, and the lack of expression of preference or change of preference.

Data availability statement

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

Author contributions

Study design: AF, MR, and SB; data collection: FH, MJ, MK, and ME; data analysis: MS and SB; study supervision: SB; manuscript writing: AF, MR, MS, FH, MK, MJ, ME, and SB; critical revisions for important intellectual content: AF, SB, and MR. 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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Global burden of major gastrointestinal cancers and its association with socioeconomics, 1990–2019

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Background: To understand the impact of common cancers of the gastrointestinal tract and help to formulate evidence-based policy, we evaluate the relationship between the burden of GI tract cancers and socioeconomics.

Methods: Data on GI tract cancer burden were obtained from the Global Burden of Disease (GBD) 2019 including mortality and incidence rates. According to the Socio-demographic Index (SDI) level, country and territory, and sex, etc., the data were further stratified. The association between the burden of GI tract cancer and socioeconomics, indicated by SDI, was described. Uncertainty analysis was estimated using bootstrap draw.

Results: In 2019, five major cancers of the gastrointestinal tract led to an age-standardized incidence rate (ASIR) of 61.9 (95% CI 56.1–67.6) per 100 000 person-years. From 1990 to 2019, five common tumors of the gastrointestinal tract related age-standardized death rates (ASDRs) decreased by –22.7% (–31.1 to –13.5). For the five common tumors, ASIRs and ASDRs were both higher in males than those in females. Globally, Mongolia, and several East Asia countries exhibited the highest ASIRs in 2019. The high SDI, and high-middle SDI locations recorded the highest incidence rate and death rate of colon and rectum cancer and pancreatic cancer. On the contrary, the low-middle SDI, and low SDI locations possessed the highest incidence rate and death rate of stomach cancer and esophageal cancer.

Conclusion: There is a profound association between socioeconomics and burden of common cancers of the gastrointestinal tract. It would be helpful for the high SDI, and high-middle SDI locations to pay special attention to the screening of colon and rectum cancer and pancreatic cancer while the low-middle SDI, and low SDI locations should pay more attention to the screening of stomach cancer and esophageal cancer.

KEYWORDS

epidemiology, public health, socioeconomics, gastrointestinal oncology, colorectal cancer

Introduction

According to the report from Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017, global estimates of all causes-related deaths are 55.9 million with an age-standardized death rate (ASDR) of 737.7 per 100 000 for 2017. Among these causes, neoplasms contribute to 9.6 million deaths and 121.2 per 100 000 of ASDRs (1). Besides, common gastrointestinal tract cancers are major contributors of the top seven causes of cancer-related death, including colon and rectum cancer (CRC), stomach cancer, liver cancer, pancreatic cancer, and esophageal cancer. Overall, common gastrointestinal tract cancers accounted for 36.2% of neoplasms-related deaths (1). The situation is similar in China. According to the Cancer Statistics in China 2015, the gastrointestinal tract cancers occupy five out of the six leading causes of cancer-related death except for lung cancer (2). Given the background exposed above, the proper handle of gastrointestinal tract tumors would significantly reduce the overall burden of tumor-related death.

Gastrointestinal tract cancers have some unique characteristics. First, it shows substantial geographical and temporal heterogeneity. For example, the ASIR of CRC in the Netherlands is 50.9 per 100 000 person-years, which is nine times more compared to that of Iraq in 2017 (3). Second, most common gastrointestinal tract cancers can be detected by routine examination in clinical practice. Third, risk or environmental factors play a crucial role in the tumorigenesis of gastrointestinal tract cancers such as *Helicobacter pylori* for stomach cancer, Hepatitis B virus for liver cancer.

Cumulating pieces of evidence have indicated that further intervention on related environmental factors should be incorporated into the prevention, diagnosis, and treatment of gastrointestinal tract cancers. Highlighting global and geographical trends can help to generate specialized local and global interventions to reduce disease burden of common

gastrointestinal tract cancers, and curtail the increasing of incident case numbers. Given the heavy burden of gastrointestinal tract cancers, several studies have focused on individual type of common cancer of the gastrointestinal tract (3–7). Recently, Arnold et al. (8) described the global burden due to common gastrointestinal tract cancers. Here, we further revealed the association between socioeconomics and the global burden of common cancers from the gastrointestinal tract.

Methods

Data sources

Age-standardized incidence rate (ASIR) and ASDR of common cancer of the gastrointestinal tract in this study were acquired from the Global Burden of Disease Study 2019, which covers 204 countries and territories (9). The International Classification of Diseases (the 10th revision) was adopted. Mortality and non-fatal estimates were described detailed in the previous studies (3, 7). Supplementary information was provided in [Supplementary Methods](#).

Uncertainty analysis

The 95% confidence interval (CI) of ASIR and ASDR of a specific tumor at a specific time point was extracted directly from GBD 2019. Uncertainty analysis on changing rate of ASIR or ASDR at a specific time point compared to another time point was calculated using the following method: 1) we assumed that the ASIR and ASDR in each year followed a log-normal distribution, and also the rates in different years were independent with each other. 2) Upon these assumptions, we performed uncertainty analysis. Based on the 25th and 975th

ranked values in all 1000 draws of a round of bootstrap draw, we measured the increase rate and the 95% CIs.

Sociodemographic Index

Sociodemographic Index (SDI) incorporates lag-distributed income per person, mean education for individuals aged ≥ 15 years, and the total fertility rate in women under the age of 25 years. SDI was generated according to the report by GBD 2016 Mortality Collaborators (10). The values of SDI ranges from 0 to 1, which reflects the development level of a country from worst to best. Low SDI, low-middle SDI, middle SDI, high-middle SDI, and high SDI, were set by $< 20^{\text{th}}$, $20^{\text{th}}-39^{\text{th}}$, $40^{\text{st}}-59^{\text{th}}$, $60^{\text{th}}-79^{\text{th}}$, $\geq 80^{\text{th}}$ percent of SDI values.

Statistical analysis

Both ASIR and ASDR of common cancer of the gastrointestinal tract were further stratified by sex or SDI, which were also obtained from GBD 2019 (<https://www.healthdata.org/>). The obtained data were shown in appendix. Python 3.7 (<https://www.python.org/>) was employed to generate the figures, which were drawn based on the obtained data shown in the appendix.

Results

The burden of common gastrointestinal tract cancers

According to the ASIR, colon and rectum cancer ranked the first out of the five major tumors, followed by stomach cancer, liver cancer, esophageal cancer, and pancreatic cancer. After age-standardization, there was an incidence rate of 61.9 (95% UI 56.1–67.6) and an death rate of 44.2 (40.9–47.6) per 100 000 person-years, in terms of 5 common gastrointestinal tract cancers in 2019 (S.Figure 1A, appendix p 14). From 1990 to 2019, ASIRs of stomach cancer, esophageal cancer, and liver cancer, depicted a decreasing trend per annum (S.Figure 1A). In the same period, there was a decline in ASDRs due to the five common tumors (-22.7% [-31.1 to -13.5]; S.Figure 1B; appendix p 8). Furthermore, in 2019, several East Asia countries or regions such as Mongolia, Taiwan (Province of China), Japan, Korea, and China, suffered the highest burden of the five common cancers evaluated by incidence rate (S.Figure 1C; appendix pp 19–34). Besides, the following countries or regions namely Mongolia, Greenland, North Korea, China, and Guinea carried the greatest burden in 2019, measured by the overall death rate associated with the five common cancers (S.Figure 1D; appendix pp 35–50).

The burden of colon and rectum cancer

Stratified using SDI, the ASIR of colon and rectum cancer was higher for high SDI locations compared to those that were lower in the high-middle, middle, low-middle, and low SDI locations (Figure 1A; appendix pp 53–61). In the past 30 years, a decreasing pattern was revealed in the ASDR of colon and rectum cancer in females compared with that remained stable in males (Figure 1B). The percentage change in ASIRs from 1990 to 2019 differed significantly between the SDI regions, with high-middle SDI locations (143.4% [129.6–158.8]), middle SDI locations (184.5% [162.3–209.6]) showing increases (Figure 1A; appendix p 10). On the other hand, death rates of high SDI locations (76.9% [71.0–83.3]) significantly declined during the same period (appendix p 9). Regarding the ASIR and ASDR, the males exhibited higher rates for colon and rectum cancers compared to the females (Figures 1A, B). In 2019, the ASIR of colon and rectum cancer also differed dramatically across the countries or regions. Specifically, the highest ASIR was recorded in Taiwan (Province of China) with 62.1 (48.9–80.1) per 100 000 person-years, then Monaco, Andorra, Slovakia, and Netherlands (Figure 1C; appendix pp 73–76). Greenland had the highest-burden of ASDR of colon and rectum cancer (Figure 1D).

The burden of liver cancer

Stratified using SDI, the ASIR and ASDR of liver cancer were highest in high, and middle SDI locations compared to those that were lower in high-middle, low-middle, and low SDI locations. There was a declining pattern in the ASIR of liver cancer in high-middle (53.8% [45.1–64.3]), and middle SDI locations (49.7% [41.0–60.3]) compared to the upward trend in high SDI locations (144.5% [130.3–159.8]; Figure 2A; appendix p 10). Between 1990 and 2019, the high-middle, middle, and low-middle SDI locations recorded a decreasing trend of the ASDR of liver cancer (Figure 2B). In comparison, the highest burden of liver cancer was over 150 times, that of the lowest burden (Figure 2C). The countries that demonstrated the highest-burden of ASIR of liver cancer also had the highest burden of ASDR of liver cancer (Figure 2D). Finally, for the ASDR of liver cancer, Mongolia possessed the highest-burden (115.2 [91.5–142.5] per 100 000 person-years), followed by Gambia, and Guinea (Figure 2D; appendix pp 77–80).

The burden of stomach cancer

In 2019, the ASIR of stomach cancer was 22.4 [19.8–25.3], and 9.7 [8.7–10.7] per 100 000 person-years in male and female, respectively (appendix p 112). Regarding the ASDR of

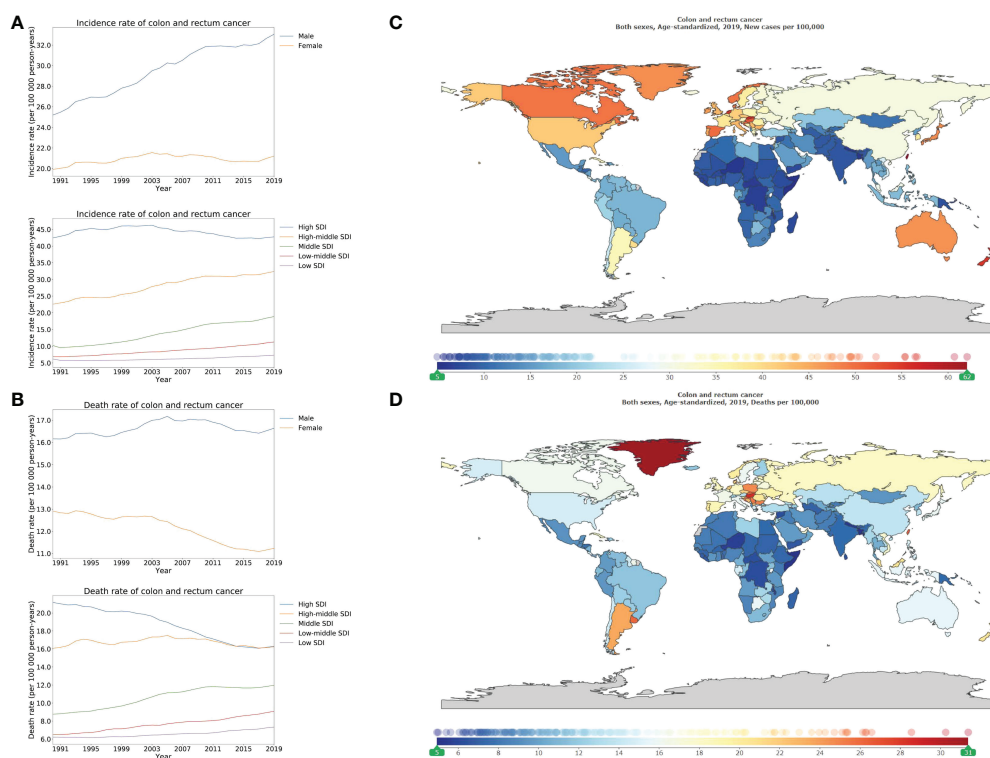


FIGURE 1

Burden of colorectal cancer for 204 countries and territories. Age-standardized incidence (A) and death (B) rate per 100,000 population of colorectal cancer from 1990 through 2019 by country and territory, stratified by sex or SDI; age-standardized incidence (C) and death (D) rate of colorectal cancer per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by GBD 2019 tool.

stomach cancer, there were 16.6 [14.8–18.3], and 7.9 [7.1–8.8] per 100 000 person-years in male and female, respectively (appendix p 123). The highest ASIR and ASDR were noted in the high-middle, and middle SDI locations compared to those that were lower in high, low-middle, and low SDI locations (Figures 3A, B; appendix pp 113–121; 124–132). In 2019, Mongolia, Bolivia (Plurinational State of), and several East Asia countries such as China, Republic of Korea, and Japan outlined the highest ASIR of stomach cancer, whereas Maldives, Namibia, and Malawi elucidated the lowest ASIR (Figure 3C; appendix pp 168–171). Additionally, Mongolia exhibited the highest ASDR (46.4 [36.3–57.5]), followed by Bolivia (36.1 [28.8–44.3]), and Afghanistan (29.3 [21.3–36.5]). Lastly, the lowest ASDRs were recorded in Maldives, Malawi, Kuwait, and United States of America (Figure 3D; appendix pp 141–144).

The burden of esophageal cancer

Stratified using SDI, the higher ASIRs were revealed in the high-middle, and middle SDI locations compared to those that were lower in high, low-middle and low SDI locations

(Figure 4A). A similar pattern was also observed for the ASDR (Figure 4B). Geographical variance by SDI locations of esophageal cancer corresponded to that of stomach cancer. In 2019, the highest ASIR was 7.1 (5.5–8.2) per 100 000 person-years for high-middle SDI locations while that of high SDI locations was 5.2 (4.7–5.7) per 100 000 person-years. For the ASDR, there were 6.6 (5.3–7.6) per 100 000 person-years for high-middle SDI locations while that of high SDI locations was 4.2 (3.9–4.4) per 100 000 person-years in 2019 (Figure 4B; appendix pp 154–162). Remarkably, the highest incidence rates came from Malawi (24.5 [18.7–32.5] per 100 000 person-years), then Mongolia and Uganda. Furthermore, Malawi (25.8 [19.8–33.9] per 100 000 person-years), Mongolia, and Uganda exhibited the highest mortality rates (Figures 4C, D; appendix pp 163–166, 167–170).

The burden of pancreatic cancer

Similar to the geographical variance in colon and rectum cancer, the ASIR and ASDR of pancreatic cancer increased along with increases in SDI values. Both the highest ASIR and ASDR were reported in the high SDI locations, followed by the high-

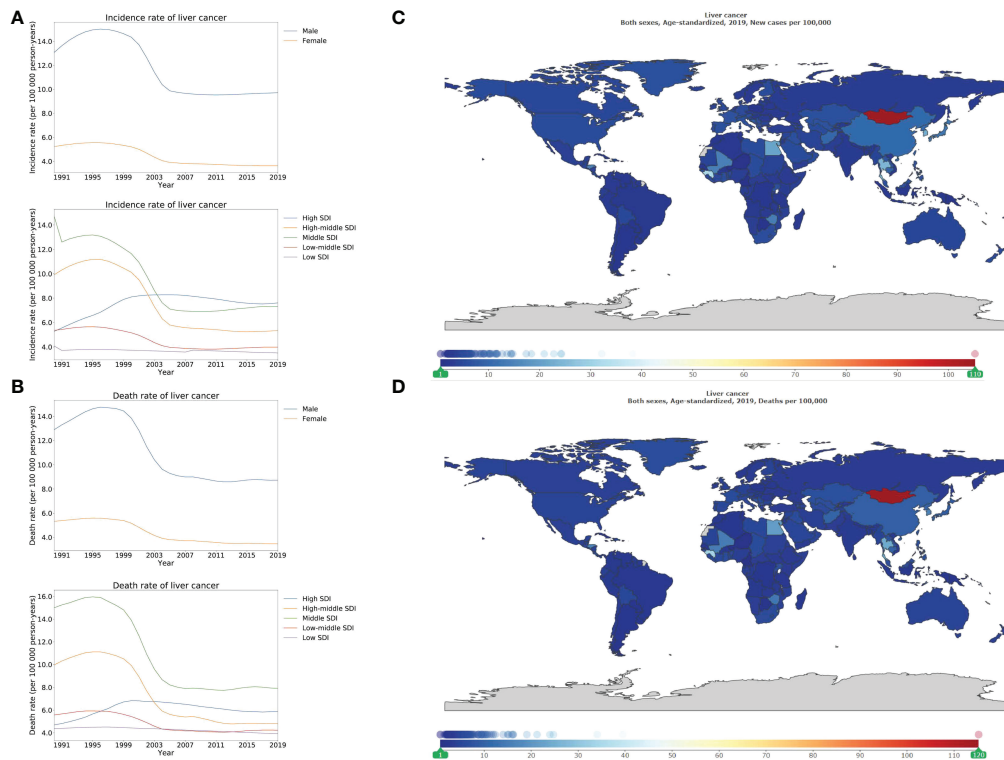


FIGURE 2
Burden of liver cancer for 204 countries and territories. Age-standardized incidence (A) and death (B) rate per 100000 population of liver cancer from 1990 through 2019 by country and territory, stratified by sex or SDI; age-standardized incidence (C) and death (D) rate of liver cancer per 100000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by GBD 2019 tool.

middle, middle, low-middle, and low SDI locations, as the decreasing order of SDI (Figures 5A, B). In high SDI locations, the ASIR and ASDR were 10.2 (9.1–11.1), and 9.6 (8.8–10.2), per 100 000 person-years, respectively, in 2019. Whilst in low SDI locations, ASIR and ASDR were 2.4 (2.1–2.7), and 2.7 (2.4–3.1), per 100 000 person-years, respectively, in 2019 (appendix pp 173–181, 184–192). The ASIR and ASDR in high SDI locations tripled the rates in low SDI locations. Greenland (18.9 [15.5–22.3]) depicted the highest ASIR, followed by Monaco, United Arab Emirates (Figure 5C; appendix pp 193–196). Similar to the order of ASIR, Greenland (19.3 [15.7–22.8]), Monaco, and United Arab Emirates enumerated the highest ASDR (Figure 5D; appendix pp 197–200).

Discussion

Colon and rectum cancer

According to GLOBOCAN 2018, for both sexes combined, colon and rectum cancer (9.2%) ranks the first leading cause of mortality except lung cancer due to tumors (11). However, the

morbidity and mortality of colon and rectum cancer vary greatly between different countries or regions. The incidence rates of colon and rectum cancer in highly developed countries such as North America (12) and Europe (13) is much higher compared to low-developed countries such as Africa and South-Central Asia (14).

According to the data from GBD 2019, high SDI locations exhibited the greatest burden of colon and rectum cancer in the world. By contrast, this study demonstrated that the ASDR of colon and rectum cancer has declined in the past three decades, which agrees with the findings of Arnold et al, which were based on several high HDI countries such as Canada, Denmark, UK, and Singapore (15). Another study by Doubeni et al. (16) noted that a higher prevalence of adverse health behaviors in the populations with low socioeconomic status would further contribute to the socioeconomics related-disparity in the risk of new-onset colon and rectum cancer. Therefore, given the economic resources and healthcare structure, relatively cheaper screening measures such as fecal occult blood tests in these areas may be a feasible strategy to reduce the burden of colon and rectum cancer. Lastly, organized screening and early detection programs, followed by the removal of precancerous polyps, may help to curb the mortality rate of colon and rectum cancer (17).

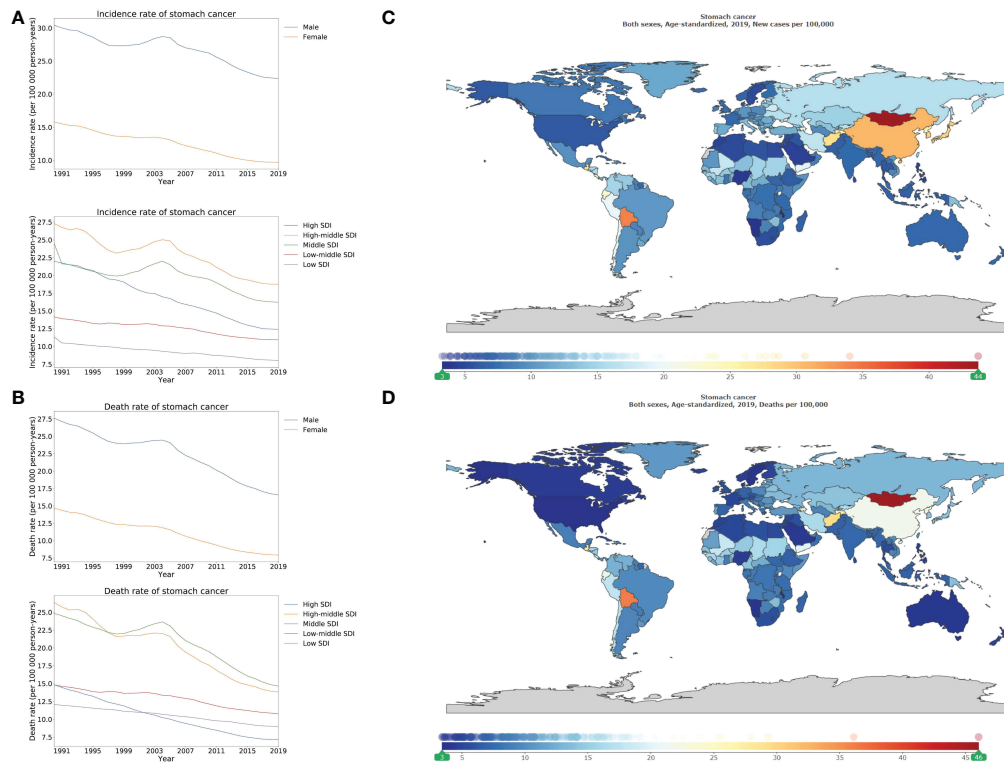


FIGURE 3

Burden of stomach cancer for 204 countries and territories. Age-standardized incidence (A) and death (B) rate per 100,000 population of stomach cancer from 1990 through 2019 by country and territory, stratified by sex or SDI; age-standardized incidence (C) and death (D) rate of stomach cancer per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by GBD 2019 tool.

Liver cancer

Liver cancer related-risk factors include hepatitis B virus (HBV), hepatitis C virus (HCV), metabolic syndrome, alcohol consumption, diabetes, and so on (18). Globally, HBV accounts for 33% of liver cancer deaths, while alcohol accounts for 30%, HCV for 21%, and other causes for 16% of liver cancer deaths (6). Should be noted, there is profound association between socioeconomics and attributable etiology of liver cancer (19). Unfortunately, treatment options for advanced stages of hepatocellular carcinoma, the most common form of liver cancer, remain scarce (20).

According to the SDI quintile, in all SDI locations except high SDI locations, over 35% burden of the ASDR of liver cancer was caused by hepatitis B virus infection between 1990 and 2015 (6). Considering the heavy burden of liver cancer in middle SDI, and high SDI locations, universal vaccination against the hepatitis B virus in these areas is a feasible strategy to reduce the liver cancer burden. In high SDI, high-middle SDI, and middle SDI locations, which also report the highest-burden of colon and rectum cancer, over 30% burden of liver cancer in terms of ASDR can be attributed to alcohol consumption (6).

Stomach cancer

Overall, the ASIR and ASDR of stomach cancer have been gradually decreasing in both males and females in the past three decades. Unlike colon and rectum cancer, ASIR and ASDR of stomach cancer in high-middle SDI, and middle SDI locations surpass those of high SDI locations. The reported ASIR is lowest in the low-middle, and low SDI locations. However, this may be caused by inadequate screening since the socioeconomic factor has a critical influence on feasibility on upper endoscopy (21, 22). Population-based upper endoscopy screening, eradication of *Helicobacter pylori* infection, and improvements in food preservation, access to clean water, and household hygiene, would help reduce the global incidence of noncardia stomach cancer, especially in countries with a higher burden, e.g. high-middle SDI, and middle SDI locations.

Esophageal cancer

Similar to the geographical variance observed in stomach cancer, the ASIR of esophageal cancer, or to be more exact,

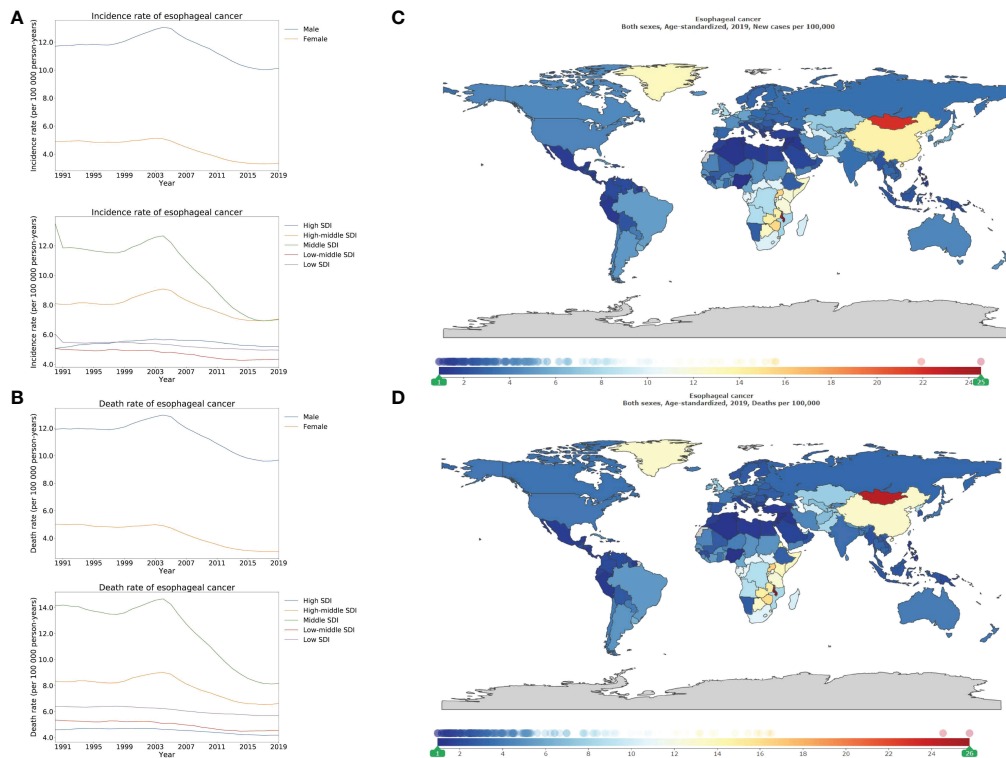


FIGURE 4

Burden of esophageal cancer for 204 countries and territories. Age-standardized incidence (A) and death (B) rate per 100,000 population of esophageal cancer from 1990 through 2019 by country and territory, stratified by sex or SDI; age-standardized incidence (C) and death (D) rate of esophageal cancer per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by GBD 2019 tool.

esophageal squamous cell carcinoma, tends to be higher in the middle, and high-middle SDI rather than high SDI locations, which is consistent with several other studies. Lower socioeconomic status has consistently linked to increased risk of esophageal squamous cell carcinoma (23, 24). Although there is an overall inverse association between socioeconomic status and ASIR of esophageal squamous cell carcinoma (4, 25–27), the higher socioeconomic status has a positive association with esophageal adenocarcinoma (28). It is important to note that the reported ASIR of esophageal cancer is lowest in the low-middle, and low SDI locations, which is similar to that of stomach cancer. Overtly underestimated incidence and mortality of esophageal cancer can be attributed to inadequate upper endoscopy-based screening. Further, an investigation from China has shown that lower socioeconomic status has strong association with elevated risks of esophageal cancer-related deaths (29). In countries with a high incidence of both stomach and esophageal cancer, for example, China and Mongolia, efforts of mass endoscopic screening in the population at high risk might be beneficial for early detection of both cancers.

Pancreatic cancer

Globally, high-income North America, e.g. Greenland, and the United States, Central Europe, and Eastern Europe have the highest incidence rates of pancreatic cancer. The risk of pancreatic cancer is positively associated with socioeconomic status (11, 30) and resembles the geographical variance in colon and rectum cancer. The high SDI locations have the highest incidence of pancreatic cancer, which gradually decreases with a decrease of SDI stratification. The remarkable geographical variance can be attributed to higher exposure to the well-known or suspected risk factors of pancreatic cancer in high-income countries as well as the scarcity of feasible diagnostic tools in low-income, and middle-income countries. The ageing population and several potential risk factors, including smoking, high fasting plasma glucose, high BMI, may contribute to the higher incidence of pancreatic cancer in high SDI countries (5). Like other major cancers of the gastrointestinal tract, pancreatic cancer also has a predilection for males. However, the ratio of male to female in the incidence of pancreatic cancer is nearly 1.3, which is much lower than those in other major cancers of the

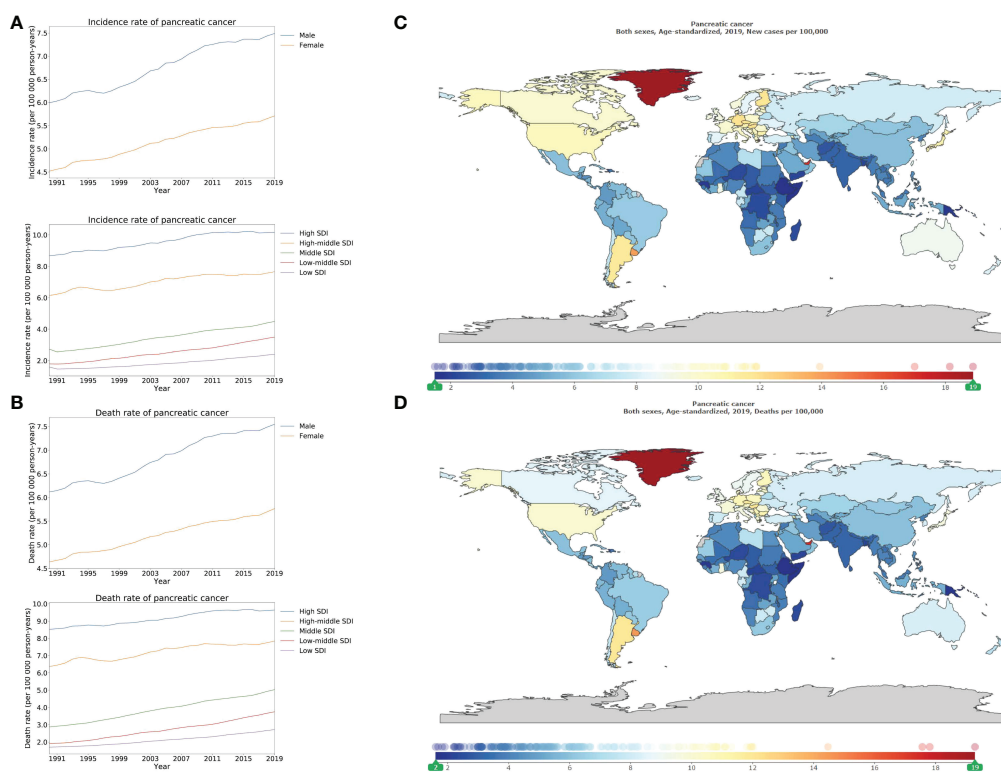


FIGURE 5
Burden of pancreatic cancer for 204 countries and territories. Age-standardized incidence (A) and death (B) rate per 100,000 population of pancreatic cancer from 1990 through 2019 by country and territory, stratified by sex or SDI; age-standardized incidence (C) and death (D) rate of pancreatic cancer per 100,000 person-years by country and territory, in 2019. The maps in (C) and (D) were generated by GBD 2019 tool.

gastrointestinal tract, such as 2.8 in liver cancer. Typically, pancreatic cancer is a disease in older people, with age being the most critical risk factor in developing pancreatic cancer. Usually, the actual or projected female life expectancy advantage over men is significant (31, 32). The higher proportion of aging women partially counteracts the impact of other risk factors such as smoking, on the development of pancreatic cancer. As a result, gender disparity in the incidence of pancreatic cancer shrinks. Although pancreatic cancer is one of the deadliest cancers, unfortunately, no data have the benefits of pancreatic cancer screening in asymptomatic adults (33, 34). It is still in need of effective serum or image-based screening for pancreatic cancer.

Major cancers of the gastrointestinal tract

An understanding of the temporal and geographical trends in five major cancers originating from the gastrointestinal tract is important since these account for over 35% of neoplasms-related deaths. Trends in the burden of major gastrointestinal tract cancers have underwent substantial changes across the world

because of the expanding screening programs, including ultrasound, gastroscopy, and colonoscopy, as well as changes in the related risk factors associated with the major gastrointestinal tract cancers.

Overall, four patterns of change arise in the five types of cancers: firstly, both ASIR and ASDR decrease, e.g. in the stomach and esophageal cancer; secondly, ASDR decrease, while ASIR increase, e.g. colon and rectum cancer; thirdly, both ASIR and ASDR remain stable, e.g. liver cancer; fourthly, both ASIR and ASDR increase, e.g. pancreatic cancer (S. Figures 1A, 1B).

Strong correlation, positive or negative, exists between socioeconomic status and burden of major gastrointestinal tract cancers. Stratified by SDI locations, significant binary polarization of the tumor burden related to major gastrointestinal tract cancers can be observed. The high SDI and high-middle SDI locations tend to have the highest ASIR and ASDR of colon and rectum cancer, and pancreatic cancer compared with that in low-middle SDI, and low SDI locations have the highest ASIR and ASDR of stomach cancer, and esophageal cancer (S. Figure 2).

In clinical practice, colorectal and pancreatic cancer represents a kind of “disease of richness” whereas stomach cancer and esophageal cancer are associated with poverty.

Further, it should be noted that almost all the major gastrointestinal tract cancers related to incidence and mortality from low-middle SDI, and low SDI locations have been overtly underestimated. Since lower socioeconomic status remarkably hinders the accessibility and compliance to cancer screening, it is not surprising that the burden of tumors from these areas is seriously underestimated.

Significant gender variance exists in the burden of major gastrointestinal tract cancers. Regarding the incidence of major gastrointestinal tract cancers, males have a higher burden in all these cancers, with the ratios of male to female ranging from 1.3 in pancreatic cancer to 2.8 in liver cancer. Although women have a longer life expectancy, men may have a higher prevalence of cancer-related risk factors such as smoking and alcohol consumption, which leads to a higher burden of cancers in men. This indicates the importance of controlling cancer-related risk factors.

Limitations

There are several limitations, including the possible underestimation of cancer burden in low-middle SDI, and low SDI locations due to inadequate cancer screening. Second, insufficient revelation about geographical variance in large countries such as USA and China. Cancer burden was reported by country or region in the GBD. However, a large country usually has a significant geographical variance of cancer burden in the urban or rural region. Third, no finer data is available for complex cancer. For example, stomach cancer can be divided into cardia cancer and noncardia cancer whereas esophageal cancer includes adenocarcinoma and squamous cell carcinoma. These subgroups of cancer tend to exhibit different features in terms of ASIR and ASDR. Fourth, racial disparities and inequities in the medical system are not rarely seen worldwide. Colored races may suffer insufficient medical care (35). However, GBD 2019 has no race-related information. Despite these limitations, data of GBD 2019 are valuable to implement cost-effective interventions, address modifiable risks, carry out efficient prevention for gastrointestinal tract cancers.

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.

Author contributions

J-SP and L-LG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; J-SP and L-LG were responsible for its conception and design; M-ZH, L-LG, J-ML, Z-JC, and X-YL were responsible for the acquisition, analysis, or interpretation of data; J-SP drafted the manuscript; M-ZH and L-LG made critical revision of the manuscript for important intellectual content; J-ML and J-SP conducted the data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.942035/full#supplementary-material>

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Real-world assessment of attenuated dosing anti-PD1 therapy as an alternative dosing strategy in a high-income country (as defined by World Bank)

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The rising cost of oncological drugs poses a global challenge to patients, insurers, and policy makers, with the leading drugs worldwide by revenue from immune checkpoint inhibitors (ICIs). Despite its cost, ICI is marked as a paradigm shift, offering the potential of a long-term cure. To reduce cost, an attenuated dose of ICI based on pharmacological principles can be used while maintaining efficacy. This real-world study aims to examine the prescribing patterns, the effect of financial constraints, and the outcomes in non-small cell lung cancer (NSCLC). All patients receiving palliative intent ICI treatment for advanced NSCLC between January 2014 and April 2021 in National University Hospital, Singapore were recruited. Demographics, prescription trends, factors affecting the prescription of attenuated dose ICI (AD ICI) *versus* standard dose ICI (SD ICI), and the effect of dose on survival outcomes, toxicities, and costs were examined. Two hundred seventy-four received ICI. The majority of them were treated in first-line setting. One hundred sixty-two (59%) of patients received AD ICI, whereas 112 (41%) received SD ICI. Patients who did not have a supplemental private as-charged health insurance plan were more likely to have received AD ICI (OR: 4.53 [2.69–7.61] $p < 0.001$). There was no difference in progression-free survival (PFS) and overall survival (OS)—adjusted HR 1.07 CI [0.76, 1.50] $p = 0.697$ and HR 0.95 CI [0.67, 1.34] $p = 0.773$, respectively, between patients who received AD *versus* SD ICI. A cost minimization analysis evaluating the degree of cost savings related to drug costs estimated a within

study cost saving of USD 7,939,059 over 7 years. Our study provides evidence for AD-ICI as a promising strategy to maximize the number of patients who can be treated with ICI. This has the potential to make significant economic impact and allow more patients to benefit from novel therapies.

KEYWORDS

PDL1, attenuated, lung cancer, immunotherapy, immune check inhibitor (ICI), dose, non-small cell lung cancer

Introduction

Breakthroughs in anti-cancer treatment have altered the treatment paradigm in oncology. However, the costs of treatment pose a global challenge to patients, insurers, and policy makers. Global sales of oncology drugs reached USD 176 billion in 2021. This is more than double that of the next most costly item, vaccines. By 2026, cancer drug sales are expected to almost double to USD 320.6 billion and approach 22% of the pharmaceutical market (1–4). The leading drugs worldwide by revenue currently comes from immune checkpoint inhibitors (ICIs) (5, 6).

Singapore is a high-income economy as defined by World Bank with a gross national income of USD 54,539 per capita. Singapore's healthcare system is also ranked one of the best in Asia and the world, focusing on quality, efficiency, and cost (7). However, rising national health expenditures is receiving increasing attention. With cancer being the nation's leading cause of death and rising cost of cancer drugs, the country's spending on cancer drugs has grown at a compound annual growth rate of 20% between 2017 and 2021. This poses a challenge to the nation's co-payment healthcare system. Singapore's healthcare system revolves around a mixed financing system. The country's public statutory insurance system, MediShield, is a basic insurance plan that covers a portion of hospitalization and outpatient treatment. This is complemented by government subsidies, as well as a compulsory savings account Medisave for each citizen, which pays for inpatient care and selected outpatient services (8–10).

Despite its cost, ICI targeting program death 1 (PD-1) and PD-ligand 1 (PD-L1) are marked as a paradigm shift in cancer treatment and offer the possibility of long-term survival (11–18). However, cost effectiveness and sustainability of these drugs are important issues to be considered in the real world (19, 20). Financial toxicity has not only shown to reduce quality of life, increase symptom burden, and potentially affecting survival of patients (21, 22), but it also threatens the financial sustainability of our healthcare system. The potential impact is the lack of access to drugs and benefits of novel therapies.

With the widespread use of ICI, these escalating healthcare costs are necessitating the practice of value-based oncology. An alternative strategy is the development of lower cost off-label treatment regimens, based on pharmacological rationale. This approach of interventional pharmacoeconomics seeks to decrease costs while maintaining equivalent efficacy (23, 24).

In our study, we looked at the real-world use of ICI in non-small cell lung cancers (NSCLC) in our institution since its approval in 2014 and examined the demographics, factors affecting the prescribing patterns, the effects of financial toxicity, and the survival outcomes of patients treated with ICI.

Methods

Patients and treatment

A retrospective cohort study was carried out for all patients receiving palliative intent ICI treatment for advanced NSCLC between January 2014 and April 2021 in an academic tertiary cancer center (National University Cancer Institute, Singapore; NCIS). NSCLC was selected as ICI has been widely approved for use. All patients were identified retrospectively. Patients receiving ICI and enrolled into clinical trials were excluded from the study. Baseline patient demographics, tumor, and treatment characteristics were extracted from electronic medical records. Local protocols continue treatment until disease progression, unacceptable toxicities, death, patient's decision to stop treatment, or after 2 years of treatment, although some patients who remained progression free after 2 years continued treatment.

Response evaluation

Chest and/or abdominal computed tomography (CT) scans were performed by clinicians every 8–12 weeks, as part of routine clinical care, to evaluate patient's response and assess for disease progression. Progression-free survival (PFS) was

measured from time of initiation of drug to disease progression by RECIST or death due to any cause. Overall survival (OS) was measured from time of initiation of drug to death due to any cause. Safety analysis examined the incidence of \geq Grade 3 immune-related adverse events (irAEs) and adverse events (AEs) as recorded by clinicians.

Statistics and economic analysis

Continuous and categorical variables were summarized as median (inter-quartile range) and frequency (percentage), respectively. The differences in baseline characteristics of patients receiving attenuated dose ICI (AD ICI) and standard dose ICI (SD ICI) were evaluated using the multinomial logistic regression model. SD ICI was defined as the FDA-approved dose of pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks, nivolumab 240 mg every 2 weeks, or 480 mg 4 weeks, atezolizumab 1200 mg every 3 weeks, and durvalumab 10 mg/kg every 2 weeks. AD ICI was defined as a lower than FDA-approved dose of ICI. In our study, AD ICI was given based on an approximate 2 mg/kg weight-based dose of pembrolizumab and 3 mg/kg weight-based dose of nivolumab. The differences in toxicities of the two doses of ICI were tested using the chi-square or Fisher's exact test whenever applicable.

We also plotted the Kaplan–Meier curve to find a difference in PFS and OS between the AD ICI and SD ICI. Univariate and multivariable Cox proportional hazard regression model was used to find variables associated with PFS and OS in this population. Quantitative association from Cox regression was expressed as hazard ratio (HR) with its corresponding 95% confidence interval (CI). All the tests used in this study were two sided, and P -values < 0.05 were considered as statistically significant. All these tests were performed using Stata version 17.

Based on an acceptance of non-inferior survival and toxicity outcomes, a limited economic evaluation was carried out using a cost-minimization approach (25). This assessed the monetary savings available from the use of AD ICI instead of SD ICI across the entire study population based on the total cycles received by the study population and price of ICI. A fixed price of ICI was assumed. Sensitivity analysis considered the potential savings within the study population if all patients were to receive AD ICI. The dose of AD ICI for this analysis was calculated at pembrolizumab 100 mg and nivolumab 180 mg based on an approximate weight-based dosing of 2 and 3 mg/kg, respectively, vial size and median weight of 56 kg in our population. Given the identical regimens and observed clinical outcomes, all other costs were assumed to remain constant. This analysis was only performed for patients receiving pembrolizumab and nivolumab, as none of the patients who received durvalumab and atezolizumab were treated at attenuated dose.

Results

Patient characteristics

Two hundred seventy-four patients received immunotherapy in for advanced NSCLC from 2014 to April 2021 at NCIS. Baseline demographics are shown in Table 1. Median age was 65.1 (range: 28.3–92.2). Majority of the patients were Chinese (214, 78%), Singaporeans (239, 87%), men (202, 73%), had an ECOG status of 0/1 (236, 86%), were current/ex-smokers (177, 65%), married (240, 88%), had children (240, 88%), and worked in the service and sales sector (879, 29%) according to the International Standard Classification of Occupations (ISCO) 8 structure. The average body weight was 56 kg (range: 31–103).

In terms of healthcare services, most patients were government subsidized (214, 78%), had Medisave (234, 85%), had MediShield (244, 89%), and did not have a supplemental private health insurance plan (169, 62%).

Treatment characteristics are summarized in Table 2. The majority of the patients received pembrolizumab (229, 84%), received ICI monotherapy (164, 60%), and were treated in the first-line setting (169, 62%).

Figures 1A, B illustrate the increasing trend of ICI usage in our study population since its approval in 2014 and the shift in the use of ICI in first-line setting, respectively. One hundred sixty-two (59%) of patients received AD-ICI, whereas 112 (41%) received SD-ICI. Using the multinomial logistics regression model, we found that patients who did not have a supplemental private as-charged health insurance plan were more likely to have received LD-ICI (OR: 4.53, 95% CI [2.69, 7.61] $p < 0.001$) (Table 1).

Survival analysis

All patients were included in the survival analysis. Median follow-up duration was 25.1 months.

All variables were analyzed to find independent variables associated with PFS (Table 3) and OS (Table 4). Univariate analysis showed that male gender and a heavier weight were associated with improved PFS, whereas a poorer ECOG status and a later line of treatment were associated with a decreased PFS. For OS, foreigners, heavier weight, and private-paying patients was associated with an improved OS, whereas a poorer ECOG status and a later line of treatment were associated with a decreased OS.

Multivariate logistic regression analysis was conducted to elucidate associations between significant variables found in univariate analysis between PFS and OS. Only a poorer ECOG status and a later line of treatment continued to be associated with both a decreased PFS and OS.

TABLE 1 Patient demographics.

		Total	Attenuated dose ICI	Standard dose ICI	Odds ratio (95% CI)	P- value
		274 (100%)	162 (59%)	112 (41%)		
Median age (range)		65 (28-92)	67 (43-92)	62 (28-80)	1.05 [1.02, 1.07]	$p = 0.001$
Median weight (range)		56 (31-103)	54 (31-83)	65 (38-103)	0.94 [0.91, 0.96]	$p < 0.001$
Ethnicity	Chinese	214 (78%)	132 (81%)	82 (73%)	1.18 [0.79, 1.76]	$p = 0.420$
	Malay	32 (12%)	20 (12%)	12 (11%)		
	Indian	9 (3%)	6 (4%)	3 (3%)		
	Others	19 (7%)	4 (2%)	15 (13%)		
Nationality	Singaporean	239 (87%)	150 (93%)	89 (79%)	1.18 [0.44, 3.19]	$p = 0.743$
	Singaporean PR	10 (4%)	5 (3%)	5 (4%)		
	Foreigner	25 (9%)	7 (4%)	18 (16%)		
Gender	Female	72 (26%)	46 (28%)	26 (23%)	0.76 [0.44, 1.33]	$p = 0.339$
	Male	202 (73%)	116 (72%)	86 (77%)		
ECOG	0/1	236 (86%)	134 (83%)	102 (91%)	1.30 [0.81, 2.08]	$p = 0.280$
	2	20 (7%)	17 (11%)	3 (3%)		
	3	17 (6%)	10 (6%)	7 (6%)		
	Unknown	1 (1%)	1 (1%)	0 (0%)		
Smoking status	Current smoker	97 (36%)	58 (36%)	39 (35%)	0.97 [0.73, 1.28]	$p = 0.819$
	Ex-smoker	80 (29%)	49 (30%)	31 (28%)		
	Never smoker	92 (33%)	51 (32%)	41 (37%)		
	Unknown	5 (2%)	4 (2%)	1 (1%)		
Marriage status	Married	240 (88%)	140 (86%)	100 (89%)	1.064 [0.72, 1.58]	$p = 0.760$
	Divorced/Separated	10 (4%)	7 (4%)	3 (3%)		
	Single	22 (8%)	15 (9%)	7 (6%)		
	Unknown	2 (1%)	0 (0%)	2 (2%)		
Have children	Yes	240 (88%)	147 (91%)	93 (83%)	0.45 [0.25, 0.81]	$p = 0.008$
	No	26 (9%)	15 (9%)	11 (10%)		
	Unknown	8 (3%)	0 (0%)	8 (7%)		
Paying class	Private	60 (22%)	18 (11%)	42 (38%)	0.21 [0.11, 0.39]	$p < 0.001$
	Subsidized	214 (78%)	144 (89%)	70 (63%)		
Medisave	Yes	234 (85%)	144 (89%)	70 (62%)	0.31 [0.16, 0.63]	$p = 0.001$
	No	40 (15%)	18 (11%)	42 (38%)		
MediShield	Yes	244 (89%)	153 (94%)	91 (81%)	0.26 [0.11, 0.58]	$p = 0.001$
	No	30 (11%)	9 (6%)	21 (19%)		
Supplemental as charged private health insurance	Yes	105 (38%)	39 (24%)	66 (59%)	4.53 (2.69-7.61)	$p < 0.001$
	No	169 (62%)	123 (76%)	46 (41%)		
Occupation (ISCO-8 structure)	Manager	28 (10%)	10 (6%)	18 (16%)	1.02 [0.95, 1.09]	$p = 0.602$
	Professionals	44 (16%)	21 (13%)	23 (21%)		
	Technician	6 (2%)	4 (2%)	2 (2%)		
	Clerical support workers	6 (2%)	5 (3%)	1 (1%)		
	Service and sales	79 (29%)	55 (34%)	24 (21%)		

(Continued)

TABLE 1 Continued

	Total	Attenuated dose ICI	Standard dose ICI	Odds ratio (95% CI)	P-value
Skill, agricultural, forestry, and fishery workers	2 (1%)	1 (1%)	1 (1%)		
Craft and related trades workers	5 (2%)	3 (2%)	2 (2%)		
Plant and machine operator	19 (7%)	10 (6%)	9 (8%)		
Elementary operations	23 (8%)	14 (9%)	9 (8%)		
Arm forces operation	2 (1%)	0 (0%)	2 (2%)		
Unemployed	18 (7%)	14 (9%)	4 (4%)		
Unknown	42 (15%)	26 (15%)	17 (15%)		

The Kaplan–Meier curves for PFS and OS are demonstrated in [Figures 2A, B](#). The median PFS and OS for AD ICI and SD ICI were 4.6 and 6.1 months and 11.9 and 17.9 months, respectively. The univariate Cox regression model demonstrates no significant difference in PFS (raw HR 1.21, 95% CI [0.91, 1.61], $p = 0.183$, and OS (raw HR 1.34, 95% CI

[0.99, 1.83], $p = 0.0060$). When adjusted for significant variables found in the univariate analysis, the multivariate Cox regression model shows no significant difference in PFS (adjusted HR 1.07, 95% CI [0.76, 1.50], $p = 0.843$) and OS (adjusted HR 0.95, 95% CI [0.67, 1.34], $p = 0.773$) between AD ICI and SD ICI.

TABLE 2 Treatment characteristics.

		Lung cancer (N = 274)		
		Total	Attenuated dose ICI (n = 162)	Standard dose (n = 112)
Histology	Squamous	43 (16%)	26 (16%)	17 (15%)
	Non-squamous	231 (84%)	136 (84%)	95 (84%)
Tumor PDL1 TPS	0%	51 (19%)	29 (18%)	23 (21%)
	1–49%	57 (21%)	28 (17%)	29 (26%)
	≥50%	103 (38%)	68 (42%)	35 (31%)
	Unknown	62 (23%)	37 (23%)	25 (22%)
EGFR	Positive	27 (9%)	14 (9%)	13 (12%)
	Negative	247 (84%)	148 (91%)	99 (88%)
ALK	Positive	3 (1%)	2 (1%)	1 (1%)
	Negative	271 (92%)	160 (99%)	111 (99%)
ROS	Positive	3 (1%)	0 (0%)	3 (3%)
	Negative	271 (92%)	162 (100%)	109 (97%)
Line of treatment in the palliative setting	First line	169 (62%)	98 (60%)	71 (63%)
	Second line	72 (26%)	44 (27%)	28 (25%)
	Third line	20 (7%)	11 (7%)	9 (8%)
	Fourth line and beyond	13 (5%)	9 (6%)	4 (4%)
Partner drug	Monotherapy	164 (60%)	115 (71%)	51 (45%)
	Combined with chemotherapy	110 (40%)	47 (29%)	61 (54%)
Type of immunotherapy used	Pembrolizumab	229 (84%)	142 (88%)	87 (78%)
	Nivolumab	31 (11%)	20 (12%)	11 (10%)
	Atezolizumab	12 (4%)	0	12 (11%)
	Durvalumab	3 (1%)	0	2 (2%)
Median dose of immunotherapy (mg/kg)	Pembrolizumab	2.22 (1.20–4.98)	1.92 (1.20–3.23)	2.99 (1.94–4.98)
	Nivolumab	3.01 (2–8.18)	2.86 (2–3.18)	4 (2.63–8.18)
	Atezolizumab	17.91 (13.17–27.27)	–	17.91 (13.17–27.27)
	Durvalumab	10	–	10

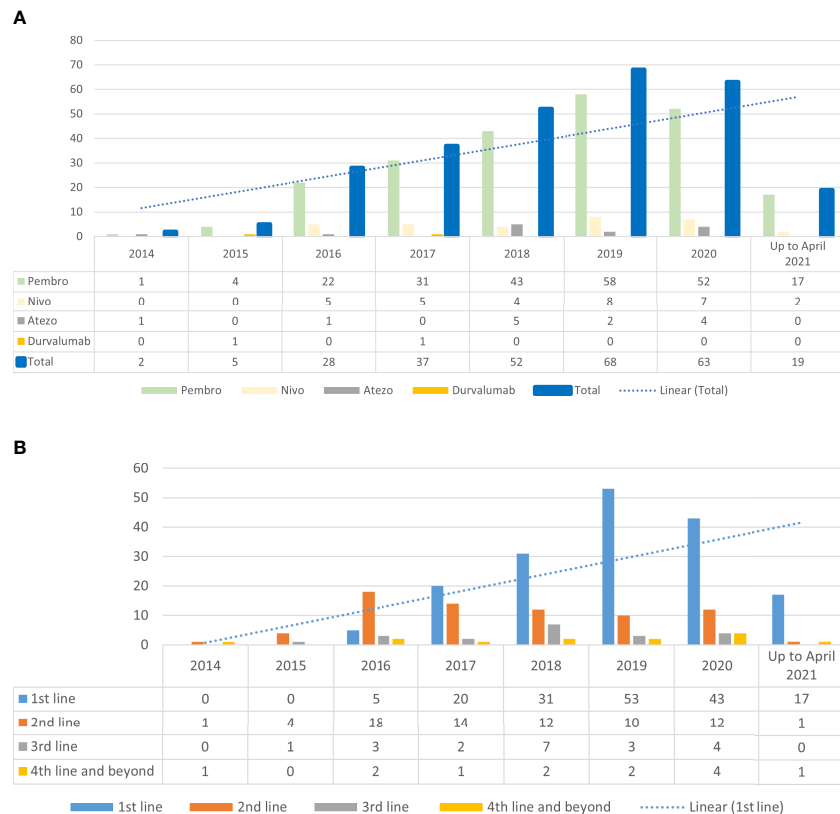


FIGURE 1

(A) Trend of immune checkpoint inhibitor use since 2014 (B) Immune checkpoint inhibitor and line of treatment.

Toxicities

Thirty-seven (12%) of the patients discontinued treatment because of toxicities. There was no dose relationship between ICI and serious irAEs or deaths. The rates of G3 or more AEs and deaths were 10% *versus* 18% ($p = 0.056$) and 3% and 4% ($p = 0.0386$) for AD and SD treatments, respectively (Table 5).

Treatment costs

In our study, a lower than FDA-approved dose of ICI was routinely delivered based on an approximate 2 mg/kg weight-based dose of pembrolizumab and 3 mg/kg weight-based dose of nivolumab for patients who did not have adequate financial reimbursement plan or based on physician's preference. None of the patients who received durvalumab or atezolizumab received a lower than approved dose (Table 2).

In our institution, a 100-mg vial of pembrolizumab costs USD 3,778, whereas a 100- and 40-mg vial of nivolumab costs USD 976 and 433, respectively, in Singapore. The total number of cycles of pembrolizumab and nivolumab received in our study

was 3,743, median cycles 8 and 7, respectively. Cycles (2,313 *vs.* 1,430) were delivered in the AD ICI and SD ICI groups. We estimated a total cost savings in our study population of USD 7,939,059 based on the total number of cycles of ICI received in the AD ICI group. This translates to cost savings per cycle for each patient of USD 3,778 and USD 433 for pembrolizumab and nivolumab, respectively.

The cost minimization analysis demonstrates a cost saving of USD 12,863,264 if a weight-based dose of AD ICI was used instead of SD ICI. This would translate to a cost saving of USD 55,692 and USD 5,335 per patient receiving pembrolizumab and nivolumab, respectively (Table 6).

Discussion

To our knowledge, our study represents the largest cohort to date to evaluate the real-world use of ICI and the efficacy of an attenuated dose of ICI in NSCLC.

The overall use of ICI and the use in the first-line setting have increased over the years in our institution since its approval in 2014 for use in NSCLC, which is reflective of the global trend

TABLE 3 Univariate and multivariate Cox regression for progression free survival.

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age		1.00	[0.99, 1.013]	0.916			
Ethnicity (reference: Chinese)	Malays	1.305	[0.86, 1.97]	0.210			
	Indians	0.84	[0.34, 2.05]	0.699			
Race (reference: Singaporean)	Singapore PR	1.32	[0.62, 2.8]	0.476			
	Foreigners	.68	[0.39, 1.20]	0.184			
Male gender		0.72	[0.53, 0.96]	0.028	0.973	[0.68, 1.37]	0.846
ECOG (reference: ECOG 0/1)	2/3	2.16	[1.69, 2.75]	<i>p</i> < 0.001	2.29	[1.77, 2.96]	<i>p</i> < 0.001
Smoking status (reference: current smokers)	Former smoker	0.82	[0.58, 1.16]	0.266	1.12	[0.93, 1.37]	0.246
	Non-smokers	1.33	[0.96, 1.85]	0.084			
Weight		0.99	[0.98, 1.00]	0.045	1.00	[0.98, 1.01]	0.309
Private patient		0.79	[0.56, 1.13]	0.204			
No private as charge insurance		0.93	[0.71, 1.23]	0.623			
PDL1 TPS score (reference: PDL1 0%)	PDL1 1-49%	1.23	[0.80, 1.899]	0.352			
	PDL1 ≥ 50%	1.00	[0.67, 1.49]	0.995			
Line of treatment	2nd line	1.53	[1.11, 2.10]	0.009	1.50	[1.25, 1.79]	<i>p</i> < 0.001
	3rd line	1.77	[1.09, 2.88]	0.021			
	4th line and beyond	3.06	[1.55, 6.07]	<i>p</i> < 0.001			
Immunotherapy combined with chemotherapy (reference: immunotherapy alone)		0.70	[0.53, 0.94]	0.015	0.98	[0.70, 1.36]	0.882
Driver mutation positive (reference: driver mutation negative)		1.92	[1.29, 2.87]	0.001	1.14	[0.703, 1.85]	0.593
Attenuated dose immunotherapy (reference: standard dose immunotherapy)		1.21	[0.91, 1.61]	0.183	1.07	[0.76, 1.50]	0.697

TABLE 4 Univariate and multivariate Cox regression for overall survival.

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age		1.018	[1.00, 1.03]	0.056			
Ethnicity (reference: Chinese)	Malays	1.06	[0.68, 1.64]	0.804			
	Indians	.421	[0.13, 1.31]	0.133			
Nationality status (reference: Singaporean)	Singapore PR	1.32	[0.54, 3.23]	0.537	0.57	[0.35, 0.92]	0.021
	Foreigners	0.19	[0.059, 0.58]	0.004			
Male gender		0.81	[0.58, 1.129]	0.199			
ECOG (reference: ECOG 0/1)	2/3	2.26	[1.77, 2.88]	<i>p</i> < 0.001	2.22	[1.72, 2.87]	< 0.001
Smoking status (reference: current smokers)	Former smoker	0.83	[0.57, 1.20]	0.315			
	Non-smokers	1.00	[0.69, 1.42]	0.959			
Weight		0.98	[0.97, 0.99]	0.004	0.99	[0.98, 1.00]	0.055
Private patient		0.58	[0.38, 0.89]	0.013	0.90	[0.56, 1.45]	0.654
No private as charge insurance		1.06	[0.79, 1.44]	0.686			
PDL1 TPS score (reference: PDL1 0%)	PDL1 1-49%	1.26	[0.78, 2.03]	0.354			
	PDL1 ≥ 50%	1.12	[0.72, 1.74]	0.612			
Line of treatment	2nd line	1.26	[0.89, 1.78]	0.185	1.45	[1.23, 1.71]	<i>p</i> < 0.001
	3rd line	1.29	[0.75, 2.23]	0.356			
	4th line and beyond	2.27	[1.15, 4.51]	0.019			
Immunotherapy combined with chemotherapy (reference: immunotherapy alone)		0.74	[0.54, 1.01]	0.060			
Driver mutation positive (reference: Driver mutation negative)		1.31	[0.84, 2.05]	0.236			
Lower dose immunotherapy (reference: approved dose immunotherapy)		1.34	[0.99, 1.83]	0.060	0.95	[0.67, 1.34]	0.773

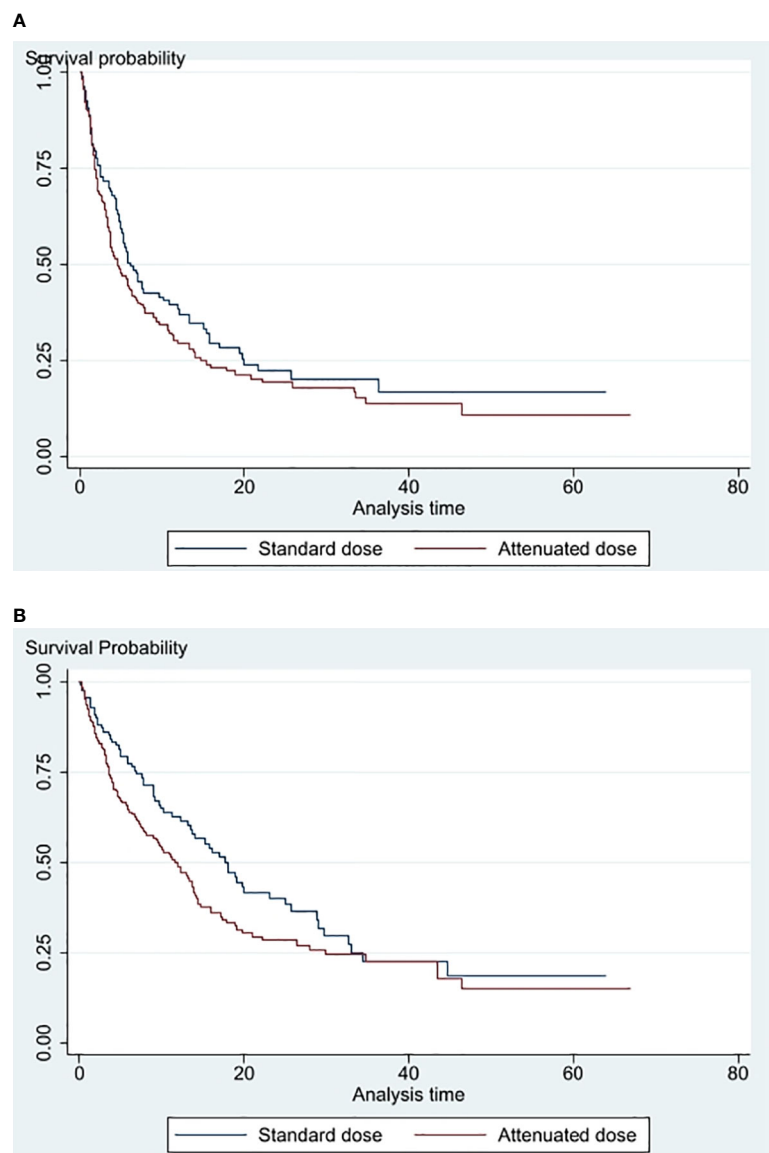


FIGURE 2
(A) PFS of standard dose vs attenuated dose immune checkpoint inhibitors (B) Overall survival of standard dose versus attenuated dose immune checkpoint inhibitors.

TABLE 5 Toxicity analysis of attenuated dose *versus* standard dose immune checkpoint inhibitors.

	Total	Attenuated dose ICI (<i>n</i> = 165)	Standard dose (<i>n</i> = 109)	<i>P</i> -value
No. of patients with G3 or more adverse events	37 (14%)	17 (10%)	20 (18%)	0.056
No. of patients who discontinued treatment because of irAE	32 (12%)	15 (9%)	17 (16%)	0.101
No. of deaths from irAE	8 (3%)	6 (4%)	2 (2%)	0.386

TABLE 6 Cost analysis of attenuated dose *versus* standard dose pembrolizumab and nivolumab.

	Pembrolizumab			Nivolumab	
	Total	Attenuated dose ICI (<i>n</i> = 142)	Standard dose ICI (<i>n</i> = 86)	Attenuated dose ICI (<i>n</i> = 20)	Standard dose ICI (<i>n</i> = 11)
Total number of cycles received	3743	2074	1287	239	143
Median number of cycles			8	7	
Cost (USD)	18,237,950	7,835,572	9,724,572	336,751	341,055
In study savings (USD)	7,939,059	7,835,572	–	103,487	–
In study savings (USD)/cycle	–	3778	–	433	–
Amount of savings if attenuated used for all patients (USD)	12,863,264	7,835,572	4,862,286	103,487	61,919

(26–28). The majority of patients also received ICI upfront in their treatment, in line with FDA's approval of ICI in NSCLC (29).

However, 162 (59%) of patients in our institute did not receive SD ICI. Only 105 (38%) of the patients had a supplemental as-charged private insurance plan on top of Singapore's public statutory insurance system, and this was significantly associated with the use of SD ICI with odds ratio of 4.53. Despite financial barriers to prescribing SD ICI, multivariate analysis showed no significant differences in PFS and OS despite the discrepancy in the doses of ICI with an adjusted HR of 1.07 and 0.95, respectively. Only a poorer ECOG status and treatment in later lines were significantly associated with both a poorer PFS and OS, which were within expectations.

Pharmacological principles for dose reduction and weight-based dosing were employed for patients who did not have adequate financial reimbursement. It is known that there are nonlinear relationships between dose of ICI and clinical outcomes. The pharmacokinetic analysis of doses of 200 mg and 2 mg/kg of pembrolizumab has shown similar exposure distributions with no advantage to either dosing approach. Pembrolizumab kinetics has also shown that there is 95% trough target engagement with dosing of 0.8 mg/kg every 3 weeks with saturation of PD-1 receptors at a dose of ≥ 1 mg/kg. Similarly, for nivolumab, a dose ranging phase 1b study showed that PD-1 receptor occupancy was already saturated at a dose of 0.3 mg/kg (30–38). In our study, the median dose of patients receiving AD ICI was close to 2 and 3 mg/kg for pembrolizumab and nivolumab, respectively. This could explain why we did not see an efficacy difference between the AD ICI and SD ICI.

A weight-based dosing of ICI also appears to be cost efficient. Goldstein et al. demonstrated huge cost savings to the U.S. healthcare system by using a personalized dosing of 2 mg/kg of pembrolizumab (20). In our study population, an estimated in study cost savings was USD 8,154,100. This could increase to USD 13,207,243 if all patients received AD ICI. Other than cost savings, adoption of a weight-based dosing approach will also decrease the dosage drugs needed and may allow more global

access to effective yet value-driven therapeutics. While the development of ICI has improved the survival of people with several kinds of cancer, it is not available to most people in low- and middle-income countries (39). In fact, while the importance of immune-oncology drugs was recognized, it is not listed in the World Health Organisation essential medical list (WHO EML) at the 23rd WHO meeting on essential medicines held in September 2021 due to their high cost (40). In a study to evaluate the concordance of medications included in the WHO EML and availability on the frontline of clinical care, striking barriers to accessing high-priority medicines in low- and middle- income countries remain. Core medications such as doxorubicin, cisplatin, and tamoxifen continue to be associated with risks of catastrophic out-of-pocket expenditure (41). The fact that substantial proportion cannot even afford older generic cytotoxic drugs, let alone ICI, highlights a major barrier in access to core medicines. The result of our study reinforces the sustainability and efficacy of use of weight-based dosing approach and may be a step toward addressing the affordability of oncology drugs, allowing more uniform global access to effective yet value-driven therapeutics.

Our study has its limitations. The PFS and OS were numerically better in SD ICI group but the retrospective nature of the study, differing baseline characteristics and limited sample size does not allow for valid efficacy comparison among different dosing strategies. In addition, the relatively small sample size limits the power of the study to demonstrate a statistically significant difference. Given the uncertainty of clinical outcome between the 2-dose groups, a prospective randomized controlled clinical trial is needed to clarify this. The use of SD-ICI was more likely in patients who had a supplemental as-charged private insurance plan on top of Singapore's public statutory insurance system. This is a potential source of bias due to a positive relationship between health insurance coverage and health-related outcomes (42, 43). Other ICI such as tislelizumab, a China-developed anti-PD1 antibody, has also shown improve PFS in advanced non-squamous NSCLC when combined with chemotherapy (44) and was also

reported to be cost effective (45) but is not yet approved or available in Singapore and, hence, not used in this study. Data to support the use of these newer anti-PD1 antibodies to the currently approved ones will also take time to accumulate. Finally, given no differences were identified in the clinical outcomes of the two regimens, a cost minimization analysis was used to examine the cost savings provided by AD ICI. This was not pre-planned and simply provides an indication of cost savings. The costs assessed are only those of the drug and do not include regimen-related costs such as drug administration, pre-medications, clinic visits, subsequent therapy, and management of AEs. While the costs are not anticipated to vary based on the study outcomes, further formal assessment of cost utility of AD ICI should be considered alongside future prospective randomized study.

Despite these limitations, our study reflects the real-world application of ICI where cost is prohibitive, outside the controlled setting of conventional clinical trials (39). It also suggests the efficacy of an attenuated dose of ICI, which can provide considerable cost savings to both patients and the healthcare system.

Conclusion

Increasing cost of drugs contributes to the increasing cost of healthcare. This problem needs to be urgently tackled. Our real-world study demonstrates efficacy of AD ICI, based on a pharmacological rationale, which has the potential to make significant economic impact yet allow our patients to benefit from novel therapies. With the expanding role of ICI in various tumor types, this value driven approach will be highly relevant to patients, oncologists, and policy makers.

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.

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Ethics statement

The studies involving human participants were reviewed and approved by National Health Group Domain Specific Review Board (NHG DSRB) (Reference number: 2017/012654). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JL, YH, KS, and ZC participated in data acquisition and collection. JL analyzed the data. JL, WY, SL, and BG contributed to manuscript writing. 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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Unmet supportive care needs and associated factors: Evidence from 4195 cancer survivors in Shanghai, China

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Background: Cancer survivors at different stages of life often have different needs that make it challenging for services to provide satisfactory care. Few studies have considered whether services are truly meeting the needs of cancer patients by exploring and identifying their perspectives on unmet needs.

Objective: The aim of this study was to identify the unmet needs of cancer survivors and to further determine the potential impact of socio-demographic factors.

Methods: A cross-sectional study that included 4195 cancer patients was conducted in Shanghai, China. Using Maslow's hierarchy of needs theory as a conceptual framework, the questionnaire included five dimensions: information, life and finances, continuing care, emotions, and self-actualization. Correlation analysis and ordered logistic regression analysis was used to explore the relationship between demographic sociological factors and unmet needs for supportive care.

Results: The most common unmet supportive care needs include information needs (2.91 ± 1.32), self-actualization needs (2.69 ± 1.32) and continuing care needs (2.59 ± 1.30). Unmet needs for life and finances were more pronounced among cancer participants in the 45-69 age group. After adjusting for confounders, we found that each 6-month increase in the time since diagnosis was associated with a 0.8% (OR: 0.992, 95% CI: 0.985-0.998) reduction in high need for continuing care and a 0.9% (OR: 0.991, 95% CI: 0.983-0.999) reduction in high need for self-actualization, respectively.

Conclusions: Information needs are the most important concern among the diverse unmet needs of cancer survivors. Time since diagnosis is associated with unmet supportive care needs of cancer survivors. The findings highlight the large gap between actual health services and patients' unmet need for supportive care, which will provide the basis for a patient-centered supportive care system for cancer survivors.

KEYWORDS

cancer survivors (MeSH term), unmet supportive care needs, Shanghai, different life stage, patient – centered care

Introduction

Cancer, as the leading cause of death and an important obstacle to increasing life expectancy in all countries (1), causes a serious burden on the healthcare economy (2). Technological advances such as early cancer screening, targeted therapies, and immunotherapy have contributed to a general increase in the survival period of cancer patients, and the number of cancer survivors has consequently increased (3). However, China ranks first in the world in both the number of new cancer cases and cancer deaths (4, 5), objectively reflecting the poor survival of oncology patients, and there is an urgent need for China to adopt a comprehensive strategy to address the changing cancer burden profile (6).

Patient-centeredness has become the gold standard in the delivery of healthcare worldwide, and effective health policies will help patients to reduce their burden in terms of social life and mental health, including access to health information, financial assistance, social isolation or the burden of caregivers (7, 8). In addition to treatment, comprehensive care for cancer patients should focus on the needs of patients at different levels to facilitate their recovery. Current evidence on the need for health services for cancer survivors remains mixed and incomplete (9). Fiszer et al. reviewed 23 studies on breast cancer patients and found that the information needs and psychological needs of Asian and Western women differed significantly due to their cultural backgrounds (10). Another review suggested that patients with rare cancers have unmet needs throughout their disease trajectory, and their supportive care needs should be addressed individually, depending on the rare cancer subdomain and phase of the disease and from diagnosis onwards (11).

Research studies related to cancer patients in some countries have shown that cancer patients typically have greater unmet needs, which are positively associated with cancer-specific distress (12, 13). The long-term unmet need may substantially reduce patients' treatment adherence, leading to serious

consequences of poorer treatment outcomes, shorter survival, poorer prognosis, and higher risk of recurrence (14–16). A national survey study that included 8,935 Japanese cancer patients showed that younger patients were significantly less satisfied with positive communication with medical staff and with items related to their survivorship in post-treatment care (16). In addition, for patients with rare cancers, delays and extensions in diagnosis were often associated with reduced trust in the professionalism of the patient's doctor (17).

Previous unmet-need studies conducted in high-income countries such as the US (18), UK (19) and Canada (20) have limited applicability due to the wide variation in healthcare systems and socio-demographic factors. Studies conducted in China (21–24) have been based on qualitative interviews focusing on specific populations, with small sample sizes that do not objectively reflect the comprehensive needs of Chinese cancer survivors and related influencing factors (25). Therefore, we aimed to identify the unmet needs of Chinese cancer survivors, determine the influencing factors, and explore whether there are differences in the needs of survivors at different stages of survival. Based on Shanghai, the largest economic city in China, where 4,195 cancer patients were included, a multidimensional questionnaire was used to analyze the current situation of cancer patients' needs and to explore the relationship between socio-demographic factors and unmet needs.

Method

Study design and data collection

Since 1995, the China Anti-Cancer Association has designated April 15–21 each year as the National Cancer Prevention and Treatment Publicity Week (26). The campaign calls for community-wide attention to the health management of cancer patients and aims to achieve “integrated medicine” from

the resources of the medical profession and new technological tools. We surveyed the needs of cancer patients in Shanghai during the 28th National Cancer Awareness Week in 2022 using the online questionnaire. We used quota sampling in the survey, which is a sampling method in which the investigator classifies or stratifies the overall survey sample according to certain markers, determines the sample size for each type (stratum) of units, and draws the sample arbitrarily within the quota. Quota sampling allows for a more balanced distribution of the sample or is more consistent with the overall characteristics (27). Quota sampling was conducted in all areas of Shanghai (16 districts), and 300 questionnaires were distributed by trained research assistants in each district (28). After excluding invalid questionnaires, 4195 questionnaires were included in the final statistical analysis, with a valid response rate of 99.4%.

We recruited adult participants with cancer who had lived in Shanghai for the past three months. Patients were identified and recruited based on their health status at follow-up visits in the past year. The patient is in a stable survivorship phase and is not in urgent need of surgery or radiotherapy (29). The study received ethical approval from the Shanghai Health and Health Development Research Center (Shanghai Institute of Medical Science and Technology Information) under protocol number SHDRC2022005. Due to the restrictions on social distance during the pandemic period, all participants provided informed consent confirmed by electronic signature. Details of the questionnaire can be obtained by contacting the corresponding author.

Questionnaire

Basic demographic and sociological information on study participants included age, sex education level, marital status, work status, income, and physical activity. The medical information included the location of cancer, time since diagnosis, treatment plan and duration of therapy. The unmet supportive care needs questionnaire for this study was referenced from the Supportive Care Needs Survey-Short Form (SCNS-SF34) (30) and the Short Form for Unmet Needs of Cancer Patients (SF-SUNS) (31). And we simplified and adapted the questionnaire due to language and cultural differences between countries that may affect the measurement of patient-reported outcomes (32, 33).

We conducted Delphi expert consultations to revise our questionnaire in December 2021, January 2022, and March 2022. Experts suggested that we should include cancer survivors' needs for disease burden and commercial health insurance in the questionnaire scale. Also, it should be ensured that all the contents of the questionnaire are easy to understand for participants with different levels of education. In addition, a

pre-survey including 60 participants was conducted to ensure that each question in the questionnaire scale was set to match the Chinese population.

The questionnaire consisted of five need dimensions, information needs (5 entries), living and financial needs (5 entries), continuity of care needs (6 entries), emotional needs (6 entries), and self-actualization needs (2 entries). A five-point Likert scale was used to evaluate these questions, with a maximum score of 5 and a minimum score of 1. A higher score indicates that the patient has a higher level of unmet needs. The total Cronbach's alpha coefficient of the scale was 0.874, and the coefficients of all dimensions were greater than 0.80. Validity analysis showed that the Kaiser-Meyer-Olkin (KMO) value was 0.978 and was significant ($p < 0.05$), which could be used for factor analysis (34).

Statistical analyses

Quantitative data from normal distribution were expressed as mean and standard deviation, and differences between groups were compared by double independent samples t-test or one-way ANOVA test. Correlation analyses were performed using Pearson tests of patients' needs scores in different dimensions. Besides, after adjusting for covariates such as age and sex, we used an ordered logistic regression model to explore the association between time since diagnosis and the unmet need of cancer patients across dimensions. All statistical analyses were performed using R 4.2.1 software with "psych", "mass", and "multcomp" packages (35–37). Statistical significance of the tests was reported at $p < 0.05$.

Result

Demographic characteristics

Table 1 summarized the demographic characteristics of the study participants. The mean age (\pm SD) of participants was 63.2 ± 7.43 and the age at first diagnosis of cancer was 53.5 ± 8.52 . There were more female than male participants (80.4% vs. 19.6%), and more participants with carcinoma *in situ* than metastatic cancer (82.3% vs. 5.5%). The overall unmet supportive care needs score was 61.9 ± 27.9 , with significant differences between age groups, for example, participants in the 45–74 age group had higher needs than those in the 18–44 age group (62.4 vs 54.4 , $p < 0.05$). The most prevalent cancer diagnosis was breast cancer (39.0%), followed by colorectal cancer (12.8%) and tracheobronchial and lung cancer (10.2%). Details of the cancer diagnoses of the study participants are shown in Table S1.

TABLE 1 Basic information and needs scores of study participants.

	Number	%	Total need score (SD)	t/F-value	P-value
Total participants	4195		61.9 (27.9)		
Age, years, mean (SD)	63.2 (7.43)				
Time from initial diagnosis, years, mean (SD)	9.72 (6.42)				
Age at initial diagnosis, years, mean (SD)	53.5 (8.52)				
Age group (years)				2.50	0.04
18-44	65	1.55	54.4 (24.7)		
45-74	3927	93.6	62.4 (28.1)		
≥ 75	203	4.84	58.9 (28.0)		
Sex				0.20	0.58
Males	823	19.6	62.3 (28.6)		
Females	3372	80.4	61.8 (27.8)		
Marital status				0.00	0.76
Married	3636	86.7	61.8 (27.9)		
Single/widowed	559	13.3	61.9 (28.2)		
Education level (years)				0.00	0.99
≤ 9	1933	46.1	61.9 (27.8)		
9-12	1645	39.2	62.0 (28.2)		
≥ 12	617	14.7	61.8 (27.8)		
Working status				0.70	0.54
Employed	162	3.9	59.4 (27.6)		
Retired	3653	87.1	61.9 (28.2)		
Unemployed	380	9.1	62.5 (26.3)		
Average monthly income (RMB)				0.77	
≤ 3000	977	23.3	63.0 (27.8)		
3001 - 6000	2376	56.6	62.2 (28.0)		
6001 - 9000	577	13.8	61.6 (28.1)		
≥ 9000	265	6.3	61.2 (28.2)		
Medical insurance				0.91	0.44
Basic medical insurance	1467	35.0	62.4 (28.1)		
Employee medical insurance	2536	60.5	61.5 (27.9)		
Commercial medical insurance	181	4.3	63.1 (28.2)		
None	11	0.3	71.9 (28.4)		
Physical activity				0.76	0.52
Active	835	19.9	62.5 (28.2)		
Moderately active	744	17.7	61.9 (28.2)		
Mildly active	1751	41.7	61.7 (27.5)		
Sedentary	865	20.6	59.5 (28.4)		
Tumor status				2.50	0.10
Primary tumor	3451	82.3	61.4 (27.9)		
Metastatic tumor	231	5.5	64.1 (28.0)		
Not sure	513	12.2	63.9 (28.6)		
Disease stage				0.70	0.66
Stage I	1629	27.7	62.9 (28.1)		
Stage II	1255	29.9	61.7 (27.8)		
Stage III	752	17.9	61.5 (27.5)		
Stage IV	171	4.1	62.3 (29.5)		
Not sure	855	20.4	61.1 (28.1)		

Unmet supportive care needs

The results of the descriptive statistics for unmet supportive care needs across the five dimensions are presented in Table 2. The most common unmet supportive care needs include information needs (2.91 ± 1.32), self-actualization needs (2.69 ± 1.32) and continuing care needs (2.59 ± 1.30). In the information needs dimension, 32.7% of patients indicated that it was very important to know about cancer risk factors, with a need score of 3.35, which ranked first in this dimension. In the dimension of the living and financial need, 76.9% and 71.3% of patients indicated a need for detailed information about health insurance reimbursement (Need score: 3.06) and how to receive financial benefits (Need score: 2.89) respectively. Only 29.6% of patients indicated that they needed guidance on sexuality (Need score: 1.71). In the continuity of care dimension, the need for doctors' appointments was high (Need score: 2.89), with 66.9% and 67.0% of participants indicating the need for care from a

community-based family doctor (Need score: 2.63) and reminders for follow-up examinations (Need score: 2.66) respectively.

Regarding psychological and emotional well-being, more than half of the participants expressed an urgent need to talk to someone about their feelings and 82.2% of the patients wanted to talk to someone who had similar experiences (Need score: 2.70). In the dimension of self-actualization, 71.5% of patients would like to set new life goals and realize their life aspirations, and 74.9% of patients are willing to share their treatment experience and guide and help their patients.

Differences in survivor needs between groups

As shown in Table 3, age significantly influenced cancer survivors' need for life and finances, with participants in the 45-

TABLE 2 Results of descriptive statistics on unmet need for supportive care across five dimensions.

	Frequency (percentage)					Need score (SD)
	No Need	Low Need	Medium Need	Medium-high Need	High Need	
A. Information needs						2.91 (1.32)
A1. Oncologist	1185 (28.3)	810 (19.3)	456 (10.9)	707 (16.9)	1037 (24.7)	2.90 (1.57)
A2. Current disease status	1027 (24.5)	892 (21.3)	533 (12.7)	825 (19.7)	918 (21.9)	2.93 (1.50)
A3. Latest treatment	1438 (34.3)	807 (19.2)	529 (12.6)	639 (15.2)	782 (18.6)	2.65 (1.53)
A4. Heredity of the disease	1536 (36.6)	680 (16.2)	422 (10.1)	660 (15.7)	897 (21.4)	2.69 (1.60)
A5. Cancer risk factors	714 (17.0)	742 (17.7)	470 (11.2)	899 (21.4)	1370 (32.7)	3.35 (1.50)
B. Living and financial needs						2.49 (1.23)
B1. Time required for treatment	1491 (35.5)	813 (19.4)	478 (11.4)	698 (16.6)	715 (17.0)	2.60 (1.52)
B2. Health insurance reimbursement	971 (23.2)	791 (18.9)	500 (11.9)	896 (21.4)	1037 (24.7)	3.06 (1.52)
B3. Financial benefits	1206 (28.8)	763 (18.2)	492 (11.7)	740 (17.6)	994 (23.7)	2.89 (1.56)
B4. Work situation	2059 (49.1)	711 (17.0)	455 (10.9)	442 (10.5)	528 (12.6)	2.21 (1.45)
B5. Sexual life guidance	2955 (70.4)	399 (9.5)	299 (7.1)	205 (4.9)	337 (8.0)	1.71 (1.27)
C. Continuing care needs						2.59 (1.30)
C1. Family doctor care	1390 (33.1)	890 (21.2)	540 (12.9)	627 (15.0)	748 (17.8)	2.63 (1.51)
C2. Follow-up visits	1386 (33.0)	827 (19.7)	525 (12.5)	724 (17.3)	733 (17.5)	2.66 (1.51)
C3. Doctor's appointment	1239 (29.5)	712 (17.0)	491 (11.7)	767 (18.3)	986 (23.5)	2.89 (1.57)
C4. Rehabilitation care	1545 (36.8)	808 (19.3)	554 (13.2)	633 (15.1)	655 (15.6)	2.53 (1.49)
C5. Psychological support	1958 (46.7)	683 (16.3)	518 (12.4)	447 (10.7)	589 (14.0)	2.29 (1.48)
C6. Privacy protection	1648 (39.3)	712 (17.0)	516 (12.3)	541 (12.9)	778 (18.6)	2.54 (1.55)
D. Emotional needs						2.32 (1.23)
D1. Anxiety and depression	2021 (48.2)	762 (18.2)	512 (12.2)	442 (10.5)	458 (10.9)	2.18 (1.41)
D2. Appearance change	1899 (45.3)	843 (20.1)	568 (13.5)	422 (10.1)	463 (11.0)	2.22 (1.39)
D3. Talking about feelings	2038 (48.6)	861 (20.5)	540 (12.9)	372 (8.9)	384 (9.2)	2.09 (1.34)
D4. Communication with patients	974 (23.2)	1217 (29.0)	708 (16.9)	675 (16.1)	621 (14.8)	2.70 (1.37)
D5. Respect	1686 (40.2)	879 (21.0)	613 (14.6)	530 (12.6)	487 (11.6)	2.35 (1.41)
D6. Uncertainty	1535 (36.6)	991 (23.6)	641 (15.3)	498 (11.9)	530 (12.6)	2.40(1.40)
E. Self-actualization needs						2.69 (1.32)
E1. Setting new goals	1197 (28.5)	927 (22.1)	674 (16.1)	725 (17.3)	672 (16.0)	2.70 (1.45)
E2. Guidance to help others	1054 (25.1)	1065 (25.4)	805 (19.2)	679 (16.2)	592 (14.1)	2.69 (1.37)

TABLE 3 Results of univariate analysis of need scores for five dimensions of study participants.

	A. Information needs		B. Living and financial needs		C. Continuing care needs		D. Emotional needs		E. Self-actualization needs	
	Mean Score	P-value	Mean Score	P-value	Mean Score	P-value	Mean Score	P-value	Mean Score	P-value
Age (years)		0.07		0.03		0.14		0.10		0.14
18-44	2.52		2.10		2.31		2.09		2.48	
45-74	2.92		2.51		2.63		2.37		2.74	
≥ 75	2.80		2.37		2.48		2.18		2.54	
Sex		0.53		0.62		0.25		0.45		0.82
Males	2.91		2.50		2.60		2.36		2.74	
Females	2.90		2.49		2.59		2.32		2.68	
Tumor status		0.06		0.07		0.03		0.43		0.54
Primary tumor	2.88		2.47		2.57		2.31		2.68	
Metastatic tumor	2.99		2.57		2.77		2.37		2.75	
Not sure	3.02		2.59		2.67		2.38		2.74	
Disease stage		0.72		0.57		0.70		0.45		0.73
Stage I	2.94		2.54		2.63		2.38		2.72	
Stage II	2.89		2.48		2.58		2.32		2.70	
Stage III	2.91		2.48		2.59		2.27		2.65	
Stage IV	2.94		2.50		2.61		2.31		2.77	
Not sure	2.86		2.46		2.55		2.30		2.69	
Marital status		0.85		0.57		0.77		0.68		0.66
Married	2.92		2.47		2.61		2.34		2.73	
Single/widowed	2.90		2.50		2.59		2.33		2.70	
Education level (years)		0.71		0.57		0.87			2.66	
≤ 9	2.89		2.51		2.59		2.25		2.64	
9-12	2.91		2.47		2.61			0.44		0.53
≥ 12	2.94		2.48		2.58		2.35		2.73	
Working status		0.28		0.14		0.47		2.30		2.67
Employed	2.75		2.34		2.47		2.36		2.74	
Retired	2.91		2.49		2.60		2.74		3.00	
Unemployed	2.94		2.57		2.58			0.68		0.99
Average monthly income (RMB)		0.45		0.20		0.59		2.30		2.70
≤ 3000	2.91		2.54		2.62		2.33		2.70	
3001 - 6000	2.90		2.49		2.59			0.88		0.96
6001 - 9000	2.95		2.48		2.59		2.32		2.69	
≥ 9000	2.79		2.36		2.50		2.33		2.70	
Medical insurance		0.61		0.54		0.27		2.30		2.69
Basic medical insurance	2.91		2.51		2.63			0.86		0.44
Employee medical insurance	2.90		2.48		2.57		2.27		2.74	
Commercial medical insurance	2.96		2.59		2.62		2.33		2.69	
None	3.38		2.71		3.17		2.32		2.77	
Physical activity		0.50		0.54		0.81		0.42		0.38
Active	2.95		2.54		2.61		2.38		2.75	
Moderately active	2.93		2.51		2.60		2.33		2.73	
Mildly active	2.88		2.48		2.60		2.31		2.67	
Sedentary	2.89		2.47		2.56		2.29		2.67	

74 age group having a higher need for life and finances, and those in the 18-44 age group having a relatively lower need (Need score: 2.51 vs. 2.10, $p < 0.05$). The results showed that participants with metastatic cancer had a higher need for continuity of care than those with *in situ* cancer (Need score: 2.77 vs. 2.57, $p < 0.05$). No significant differences in patients' needs were found between sex, monthly income, health insurance, and stage of disease. The five dimensions of unmet supportive care needs for information needs, living and financial needs, continuity of care, emotional needs, and self-actualization were correlated with Pearson coefficients of 0.805, 0.812, 0.750, and 0.679, respectively (Figure S1).

Unmet supportive care needs of survivors at different stages

The intensity of unmet needs among cancer survivors varies at different stages. Our results showed that the need for continuing care needs and emotional needs dimensions peaks 3-5 years after the cancer diagnosis and gradually decline thereafter. Notably, patients who were first diagnosed less than three years ago (Need score: 2.35) and those diagnosed more than ten years ago (Need score: 2.26) had lower emotional need scores, and those diagnosed 3-5 years ago and 5-10 years ago had higher emotional needs with need scores of 2.38, 2.36, respectively. Other dimensions of cancer survivors' needs decline over time (Figure 1).

After adjusting for age, sex, tumor status, and disease stage, we found that each 6-month increase in the time since diagnosis was associated with a 0.8% (OR: 0.992, 95% CI: 0.985-0.998) reduction in high need for continuing care and a 0.9% (OR: 0.991, 95% CI: 0.983-0.999) reduction in high need for self-actualization, respectively (Figure 2). Although logistic regression analyses of the other need dimensions were not statistically significant, they reflect that cancer patients' unmet needs may show dynamic changes with time since diagnosis (Table S2). The results of the reliability and validity analysis of the questionnaire in this study were presented in Table S3, S4, respectively.

Discussion

This study identified the current needs and influencing factors of cancer survivors through a population-based survey study in Shanghai, China. We analyzed the blind spots in the current cancer survivorship management model and explored the differences in the unmet needs of cancer patients at different stages of survivorship. The findings will provide evidence for future exploration to develop a "patient-centered" long-term follow-up management system for cancer survivors.

In our study, the most common unmet supportive care needs include information needs (2.91 ± 1.32), and 32.7% of patients indicated that the cancer risk factors information was very important. Similar results have been reported in other

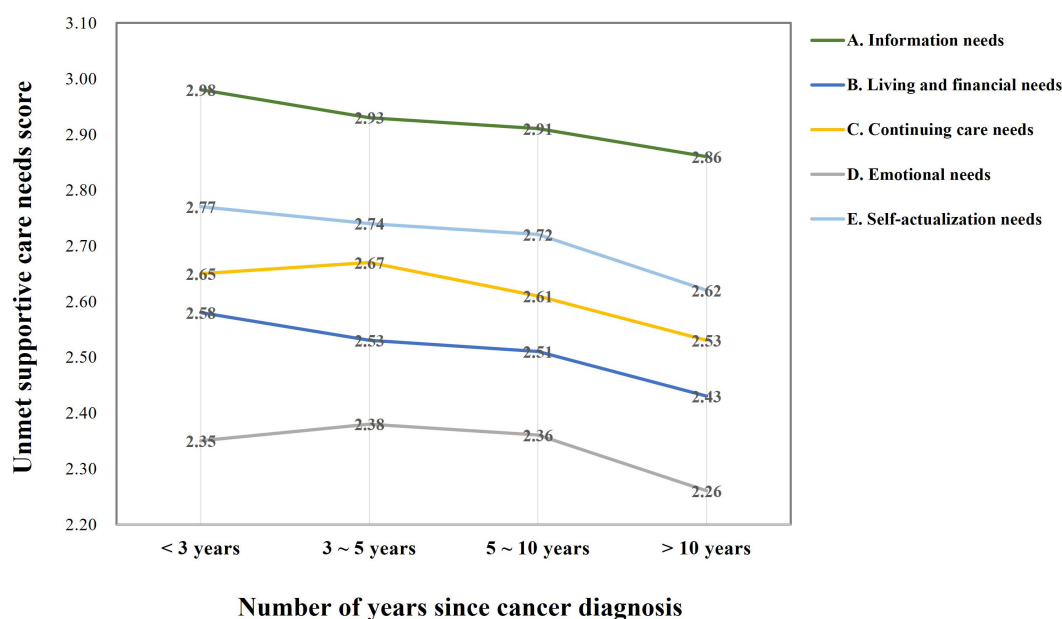


FIGURE 1
Unmet supportive care needs by time since cancer diagnosis.

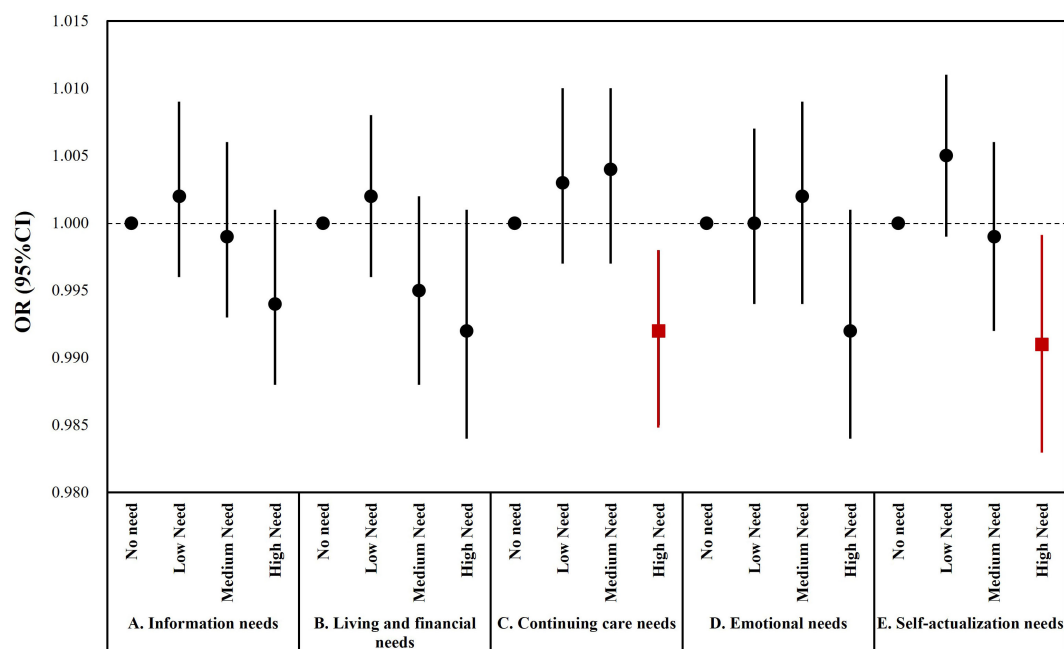


FIGURE 2

Results of multivariate ordered logistic analysis of the post-diagnosis time and participants' need level. *Red symbols represent $p < 0.05$. The model was adjusted for age, sex, tumor status, and disease stage.

studies. Icomomou et al. found that Greek cancer patients had a high need for information, particularly about the consequences of chemotherapy, prognosis, how chemotherapy works, how to manage emergencies, everyday preventive measures, and patient psychological support (38). A German study involving 280 participants showed that patients with a high perception of their own control over the disease more often used any source of information available to them and were more often interested in acquiring additional information. Information needs seem to be higher in patients with a high external locus of control and low self-efficacy (39). There is growing agreement that we need to meet the high demand for information from cancer survivors to reduce pessimism and panic due to uncertainty of information (23, 40). However, the quality, availability and visibility of information is difficult to ensure for the various forms of media available. MacLennan et al. proposed a web-based platform to alleviate information silos for cancer survivors in the form of multi-stakeholder engagement, by building a professional community, identifying survivor needs and allowing individuals to actively participate in the design and delivery of supportive care and appropriate information (41). As patients have different perceptions of self-efficacy and control, and information needs vary with these perceptions, future research is expected to take into account and respect these

differences when providing structured recovery information guidance to cancer survivors.

Our findings suggested that age factors influence the living and financial needs of cancer patients, with those in the 45-74 age group having significantly higher needs than those in the 18-44 age group and those older than 75 years. Contrary to our research, a retrospective study involving 1129 breast cancer patients did not find differences in financial need across age groups (22). And a study conducted in the Middle East indicated that the score of financial need gradually decreased with increasing age of cancer survivors, but the difference was not statistically significant (42). However, evidence from a review of the quality of survival and unmet need in patients with head and neck cancer, which could support our findings, suggested that older patients have less self-reported unmet needs and lower financial burden compared to younger patients (14). And a cross-sectional international comparative study reported that survivors aged 15-59 years at diagnosis had significantly higher odds of reporting a 'high/very high' unmet need for the financial item than survivors aged 60 years and over (43). There are possible explanations for the differences in the level of living and financial needs of cancer survivors across age groups. As younger patients have a lower symptom burden, a better performance status, and a higher quality of life, can return to

work more quickly and with relatively less financial stress (44), whereas patients over the age of 45 have a more difficult time returning to work after cancer treatment, they have higher stress levels in terms of forced retirement and have difficulty affording high health insurance (45). Besides, a Canadian study of nasopharyngeal cancer survivors who had completed treatment for more than four years showed that only 62% of patients within working age were still working after diagnosis (≤ 65 years), and nearly a third worked fewer hours than before diagnosis (median decrease of 12 h/week; range, 4–30) (46). The reduction in daily working hours is usually associated with a decline in income, accompanied by ongoing expenses for treatment and rehabilitation, resulting in increased living and financial demands.

Increasing time since diagnosis was associated with a general decline in the need for each dimension among cancer survivors. In our survey, cancer survivors' need for continuity of care and self-actualization increased up to 5 years after diagnosis, but then declined. Similar to our results, Tzelepis et al. reported that being diagnosed in the last 2 years was significantly associated with an increase in unmet continuity of care need scores (47). An international study conducted in the Asia-Pacific region suggested that higher levels of unmet need were associated with fewer months post-treatment, lower perceived quality of life and higher overall symptom scores ($p < 0.01$) (48). Clinically, the first five years after treatment (transition and extended survival) is a fragile period in which survivors may be caught up in adverse reactions, fatigue, anxiety about the risk of relapse, and life stress (49). One research suggested that cancer survivors have significantly lower needs for supportive care in treatment and at follow-up than at the newly diagnosed stage (22). Some studies in countries with well-developed healthcare systems have also shown high unmet needs among survivors who have just finished treatment, and a decrease among those in recovery (50). Contrary to the above views, a survey of 320 breast cancer survivors in Korea indicated that the level of unmet needs of the advanced cancer patient group was higher than that of the early cancer group in terms of psychological and physical symptoms, social support and hospital services. They attributed this difference to the fact that cancer patients experienced longer and more complex treatments and their side effects at a later stage, and therefore have a greater fear of cancer recurrence and more needs in terms of social and medical resources (51). Cancer type (e.g. *in situ* versus metastatic) and patient mental status also have a greater impact on patients' unmet needs, and patients with chronic illness or disability tend to be at greater risk and have higher needs later in life (52–54).

One of the strengths of this study is that a quota sample of cancer patients from the whole of Shanghai (16 districts) was

included, reducing regionally-induced differences and providing a representative picture of the general situation in the city. As one of the most urbanized cities in China, Shanghai is a model area for healthcare policy with its rich medical resources and level of disease control. Our findings on the unmet needs of cancer patients will provide an evidence-based basis for healthcare decision-making and health service practice. However, there are still limitations to our study. Based on the cross-sectional study design, the inference of causal effects is limited and we cannot further speculate on changes in unmet needs of cancer patients over time. Secondly, adolescent patients were not included in this study and the results may be subject to selection bias. Finally, we used a representative sample of regions rather than a specific cancer dataset. While such a decision strengthens the generalizability of our findings, future efforts should also investigate similar themes using specific cancer datasets to see if our findings are sustained.

Conclusions

Our findings suggest that the unmet needs of cancer survivors are diverse and complex in China. Information needs were the unmet needs of greatest concern to survivors. An increase in the time since diagnosis was associated with a decrease in patients' need for continuity of care and self-actualization. We expect that future models of care support for cancer patients should shift from detecting cancer recurrence to improving the quality of life, functional outcomes, experience and survival of cancer survivors, reducing the risk of cancer recurrence and neoplastic disease, improving the management of comorbidities and reducing costs to patients and payers.

Data availability statement

The datasets presented in this article are not readily available because data sets may violate participants' privacy. Requests to access the datasets should be directed to chenminxing@shdrc.org.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Shanghai Health Development Research Center (Shanghai Medical Information Center), approval no.: SHDRC2022005. Informed consent was obtained from all subjects involved in the study.

Author contributions

Writing—original draft preparation: RL. Writing—review and editing: MC. Visualization: YC. Supervision: GD. Investigation: JS and XH. Project administration: CJ. 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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Supplementary material

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Healthcare coverage affects survival of *EGFR*-mutant Thai lung cancer patients

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Background: Despite significant benefits of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in patients with *EGFR*-mutated NSCLC, access remains limited in Thailand and elsewhere.

Methods: Retrospective analysis of patients with locally advanced/recurrent NSCLC and known *EGFR* mutation (*EGFR*m) status treated at Ramathibodi Hospital (2012–2017). Prognostic factors for overall survival (OS), including treatment type and healthcare coverage, were analyzed using Cox regression.

Results: Of 750 patients, 56.3% were *EGFR*m-positive. After first-line therapy (n=646), 29.4% received no subsequent (second-line) treatment. *EGFR*-TKI-treated *EGFR*m-positive patients survived significantly longer than *EGFR*m-negative patients without *EGFR*-TKIs (median OS [mOS] 36.4 vs. 11.9 months; hazard ratio HR=0.38 [95%CI 0.32–0.46], $P<0.001$). Cox regression indicated significantly longer OS in patients with comprehensive healthcare coverage that included reimbursement of *EGFR*-TKIs, versus basic coverage (mOS 27.2 vs. 18.3 months; adjusted HR=0.73 [95%CI 0.59–0.90]). Compared with best supportive care (BSC; reference), *EGFR*-TKI-treated patients survived significantly longer (mOS 36.5 months; adjusted HR (aHR)=0.26 [95%CI 0.19–0.34]), and versus chemotherapy alone (14.5 months; aHR=0.60 [95%CI 0.47–0.78]). In *EGFR*m-positive patients (n=422), relative survival benefit of *EGFR*-TKI treatment remained highly significant (aHR[*EGFR*-TKI]=0.19 [95%CI 0.12–0.29]; aHR(chemotherapy only)=0.50 [95%CI 0.30–0.85]; reference:BSC), indicating that healthcare coverage (reimbursement) affected treatment choice and survival.

Conclusion: Our analysis describes *EGFR*m prevalence and survival benefit of EGFR-TKI therapy for *EGFR*m-positive NSCLC patients treated from 2012–2017, one of the largest such Thai datasets. Together with research by others, these findings contributed evidence supporting the decision to broaden erlotinib access on healthcare schemes in Thailand from 2021, demonstrating the value of local real-world outcome data for healthcare policy decision-making.

KEYWORDS

EGFR-TKI, non-small cell lung cancer, drug reimbursement, targeted therapy, Thailand, healthcare coverage

Introduction

Cancer is the leading cause of death, and lung cancer is the second most diagnosed cancer, and cause of cancer deaths after liver cancer in Thailand (1, 2). The NSCLC treatment landscape has evolved with the clinical development and approval of molecular-targeted therapies for patients with specific molecular features, notably epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI), accompanied by *EGFR* mutation testing (3). The results have been encouraging and are of particular importance in Asian countries as 76% of all activating *EGFR* mutations (*EGFR*m) are detected in Asian patients, with southern Asian patients showing the highest *EGFR*m frequencies (46–52%) (4, 5). In Thailand, *EGFR* mutations were detected in 57–68% of lung adenocarcinoma patients, and the most common mutations were also exon 19 and exon 21 (L858R) point mutation (6, 7). A meta-analysis of seven clinical trials reported prolonged PFS in patients with advanced-stage *EGFR*m-positive NSCLC treated with 1st generation EGFR-TKIs versus chemotherapy, with the greatest benefit observed in patients with exon 19 mutations (8). First-line treatment with 2nd and 3rd generation EGFR-TKI, was associated with significantly longer median PFS compared with 1st generation EGFR-TKI in patients with common sensitizing *EGFR* mutations (9, 10). Currently, the longest OS of *EGFR* mutant lung cancer patients treated by single agent EGFR-TKI is 38.6 month from the FLAURA study which proved the concept and the clinical benefit of EGFR-TKI as the first-line treatment (11).

Despite evidence for the benefits of prescribing EGFR-TKIs as first-line treatment, patient access to EGFR-TKIs in Southeast Asia remains limited. Even though EGFR-TKIs (erlotinib, gefitinib and afatinib) were assessed to have considerable clinical benefit, subsidies or reimbursement for these agents are limited in several Southeast Asian countries, including Myanmar (afatinib unavailable), Laos, and Cambodia as of 2015 (12). Some exceptions included Indonesia that fully subsidized erlotinib, and Vietnam that offered a subsidy of up to 75% for its citizens (12).

In Thailand, access to EGR-TKIs, defined by both costs and availability, has also been limited to varying degrees under the existing healthcare coverage schemes. The three public health insurance schemes in Thailand are the Civil Servant Medical Benefit Scheme (CSMBS; started in 1975), the Social Security Scheme (SSS; started in 1990), and Universal Coverage (UC; started in 2002). The CSMBS

and SSS insure individuals employed in the government and private sectors respectively, whereas the UC scheme covers individuals not eligible for the CSMBS or SSS (13, 14).

A medication included in the National List of Essential Medicines (NLEM) is reimbursable for the specified indication under all three healthcare schemes. In the case of certain high-cost drugs, including molecular targeted drugs, these have been reimbursable only for patients with CSMBS coverage, under the Oncology Prior Authorization Program (OCPA). Since 2006, CSMBS-insured patients could reimburse gefitinib and erlotinib for third-line treatment of NSCLC under the OCPA (no *EGFR* mutation testing required). From 2018 onwards, under the OCPA, CSMBS-insured individuals could reimburse gefitinib as first-line treatment (*EGFR*m-positive patients only), and in 2019 osimertinib as second- or third-line treatment (*T790M*-positive patients after 1st generation EGFR-TKI treatment failure). Prior to December 2020, individuals with only UC or SSS coverage could not receive reimbursement for EGFR-TKI treatment (any line).

The decision to include a medication into the NLEM is made based on the Thai Health Technology Assessment guidelines, which evaluate the benefits of the medication based on available data on costs and health outcomes (12, 15). To help national healthcare policy-makers in Thailand and other Southeast Asian countries make informed and up-to-date decisions that affect cancer care, it is highly important that treatment outcomes in real-life practice with important medicines, such as EGFR-TKIs, are explored and well documented. Our study analyzed treatment outcomes for NSCLC patients in Thailand, particularly real-world clinical benefit of EGFR-TKI therapy for *EGFR*m-positive NSCLC patients at the time of EGFR-TKI could not reimburse for UC and SSS patients in Thailand. This data was contributing to a body of data essential for evaluation and improvement of EGFR-TKI reimbursement programs in Thailand. We hope this real-world evidence could provide the useful data for helping improvement of EGFR TKI reimbursement policy in the other developing countries as well.

Patients and methods

Study participants and data collection

This retrospective study included patients with locally advanced/recurrent NSCLC treated at Ramathibodi hospital from 9 May 2012 to

30 April 2017, and who had known *EGFR* mutation status (tissue test). Patients with early-stage NSCLC (stage I, II or IIIA), insufficient medical data, or those found to have non-*EGFR* driver mutations were excluded. The Human Research Ethics Committee of the Ramathibodi Hospital approved the study (IRB No. MURA2020/304) and waived the requirement for informed patient consent. Clinical data from the time of diagnosis to time of death were obtained from electronic database records.

Patients were categorized into four groups based on their *EGFR* mutation status and type of treatment received (Figure 1). Mutations were categorized as: Common *EGFR* activating mutations including exon 19 (*del19*) or *L858R*; uncommon activating mutations including *G719X*, *L861Q*, *del19 + L858R*, *del19 + S768I*, *L858R + S768I*, *G719X + S768I*; and uncommon resistance mutations including exon 20 insertions (*20ins*), *del19+T790M*, *L858R+T790M*, *L858R+20ins* and *L861Q+T790M*.

Outcomes

Overall survival (OS) was defined as the time from diagnosis of advanced-stage disease to death from any causes, or the end of the data collection period (November 30, 2019). Time to treatment failure (TTF) of *EGFR*-TKI was defined as the time from initiation of *EGFR*-TKI treatment to the time of stopping *EGFR*-TKI.

Statistical analysis

Patient characteristics were summarized using descriptive statistical techniques. Chi-square or Fisher's exact tests were used to analyze association between categorical variables. The Kaplan-Meier method was used to estimate survival probabilities over time. Univariate and multivariate Cox proportional hazards regression models were used to analyze relationships between prognostic factors and survival outcomes. All statistical analyses were performed using Stata software (version 15). Significance tests were two-sided, and performed at the 5% significance level ($\alpha=0.05$).

Results

Patient characteristics

Of 1,192 NSCLC patients with available *EGFR* mutation test results diagnosed/treated at our institution from May 2012 to April 2017, 442 patients (37.1%) were excluded from the analysis due to insufficient medical data (28.7%), presence of *ALK* mutations (2.2%), or stage I–IIIA at diagnosis without recurrent disease (6.2%) (Figure 1). The final analysis population included 750 patients with locally advanced, advanced, or recurrence (stage I–III at diagnosis with recurrent disease), and known *EGFR* mutation status (Table 1; Figure 1).

For the total NSCLC patient population ($n=750$), the median follow-up time was 24.9 months (range, 22.0–27.5) and the median follow-up time for patients diagnosed with stage IV NSCLC was 21.4 months (range, 19.6–23.4). Half of the patients (54.3%) were female, and the majority had adenocarcinoma histology (83.2%) (Table 1). Slightly over half of all patients (54.0%) had CSMBs or state enterprise (CSMBs/SE) healthcare coverage, 22.3% had UC/SSS healthcare coverage, and 23.7% were self-paying. The profile of healthcare coverage status was similar in the *EGFRm*-positive and *EGFRm*-negative groups (Table 1).

Over half of the patients (56.3%; $n=422$) were *EGFRm*-positive. *EGFRm*-positive patients were predominantly never-smokers (75.4%) and female (64.5%). Most patients had common *EGFR* activating mutations (55.2% with exon 19 deletion; 32.7% with *L858R* point mutation), and 12.1% had double mutations or uncommon mutations (Supplementary Table A).

Systemic therapy

Within the overall NSCLC patient population ($n=750$), most patients (58.4%) received chemotherapy as their first-line treatment, mainly platinum-doublet regimens (Supplementary Table B). Two-hundred and eight patients (27.7%) received first-line *EGFR*-TKI therapy, and 13.9% did not receive any systemic therapy. Sixty-three

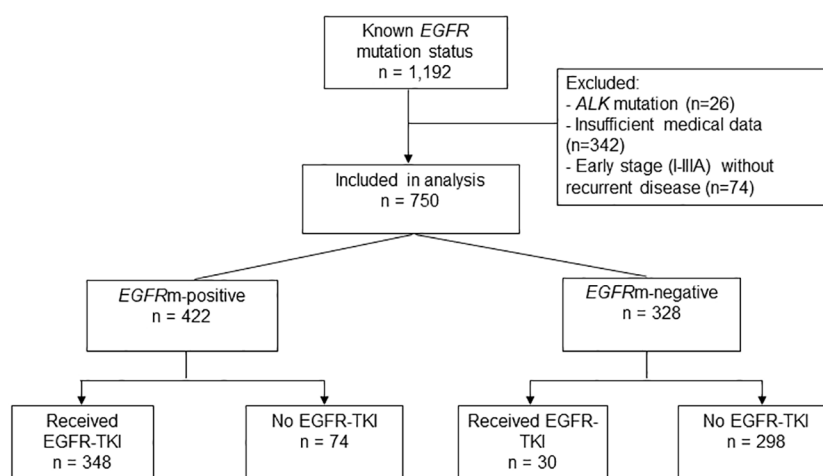


FIGURE 1
Flowchart of patient selection in the study.

TABLE 1 Demographic characteristics.

Characteristics	All patients N = 750	EGFRm+ N = 422	EGFRm– N = 328	P [†]
Age (mean ± SD) years	64.5 ± 11.4	64.0 ± 11.1	64.5 ± 11.8	0.596
Gender				<0.001
Male	343 (45.7)	150 (35.5)	193 (58.8)	
Female	407 (54.3)	272 (64.5)	135 (41.2)	
Histology subtype				<0.001
Adenocarcinoma	624 (83.2)	377 (89.3)	247 (75.3)	
Adenosquamous carcinoma	14 (1.9)	6 (1.4)	8 (2.4)	
Squamous cell carcinoma	17 (2.3)	5 (1.2)	12 (3.7)	
Other NSCLC/unknown	95 (12.7)	34 (8.1)	61 (18.6)	
Stage at diagnosis				0.043
I	58 (7.7)	39 (9.2)	19 (5.8)	
II	50 (6.7)	26 (6.2)	24 (7.3)	
III	89 (11.9)	40 (9.5)	49 (15.0)	
IV	553 (73.7)	317 (75.1)	236 (71.9)	
Smoking status				<0.001
Current/Ex-smoker	277 (36.9)	104 (24.6)	173 (52.7)	
Never-smoker	473 (63.1)	318 (75.4)	155 (47.3)	
Healthcare coverage status				0.567
UC/SSS	167 (22.3)	89 (21.1)	78 (23.8)	
CSMBS/SE	405 (54.0)	228 (54.0)	177 (54.0)	
Self-pay	178 (23.7)	105 (24.9)	73 (22.2)	
Lines of treatment received				<0.001
No treatment	104 (13.9)	33 (7.8)	71 (21.7)	
1	192 (25.6)	93 (22.1)	99 (30.2)	
2	176 (23.5)	109 (25.8)	67 (20.4)	
≥3	278 (37.1)	187 (44.3)	91 (27.7)	
EGFR-TKIs received	N = 378	N = 348	N = 30	0.009
1 agent	229 (60.6)	203 (58.3)	26 (86.7)	
2 agents	127 (33.6)	123 (35.4)	4 (13.3)	
≥3 agents	22 (5.8)	22 (6.3)	0 (0)	

n (%) unless otherwise stated.

[†]P-value from chi-squared or Fisher's exact test. P-values <0.05 were considered statistically significant.

UC, Universal Coverage; SSS, Social Security Scheme; CSMBS, Civil Servant Medical Benefit Scheme; SE, State Enterprise Scheme; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitor; EGFRm+, positive for EGFR activating mutation, EGFRm–, wild-type EGFR; SD, standard deviation.

patients received erlotinib, 111 patients received gefitinib, 20 patients received afatinib, 7 patients received osimertinib, and the other 7 patients received EGFR-TKI in clinical trial as the first-line treatment (Supplement Table B). There was a 29.4% drop-off rate from first-line to second-line treatment, and a 38.4% drop-off rate from second-line to third-line treatment (Supplementary Table B).

Among EGFRm-positive patients (n=422), 109 patients (25.8%) received two lines of treatment, and 187 (44.3%) received three or more lines of treatment, including chemotherapy. The majority

(58.3%) of EGFRm-positive patients received only one type of EGFR-TKI (Table 1).

Overall survival according to EGFRm status and EGFR-TKI treatment

Since EGFR-TKI treatment is indicated specifically for NSCLC patients with activating EGFR mutations, we first investigated the

influence of EGFR-TKI treatment on survival. *EGFR*m-positive patients treated with EGFR-TKIs survived significantly longer than the reference group of *EGFR*m-negative patients not treated with EGFR-TKIs (median OS 36.4 vs. 11.9 months; HR=0.38 [95% CI 0.32–0.46], $P<0.001$) (Figure 2A). Survival of *EGFR*m-positive patients who did not receive EGFR-TKI treatment was not significantly different from the reference group (median OS: 9.8 vs. 11.9 months; HR=1.15 [95% CI 0.87–1.52], $P=0.330$).

Overall survival according to treatment type

One hundred and four patients underwent best supportive care alone due to poor performance status and rapid progression of disease. Compared with best supportive care alone (median OS 4.8 months), EGFR-TKI treatment significantly prolonged survival (median OS 36.5 months, HR=0.40 [95% CI 0.28–0.57, $P<0.001$]) (Figure 2B) for the whole population ($n=750$). Notably, EGFR-TKI-treated patients also survived longer than those who only received chemotherapy, who had a median OS of 14.4 months (HR=0.58 [95% CI: 0.46–0.75, $P<0.001$] versus best supportive care) (Figure 2B).

Our analysis of the subset of *EGFR*m-positive patients ($n=422$) revealed a similar trend (Figure 2C). Once again, EGFR-TKI treatment was associated with longer survival than chemotherapy alone (median OS: 36.4 months and 11.0 months, respectively), with non-overlapping 95% CIs of their hazard ratios versus best supportive care: HR(EGFR-TKI)=0.21 [95% CI: 0.14–0.32], HR(chemotherapy) =0.58 [95% CI: 0.35–0.91]. Taken together, these results indicate that appropriate EGFR-TKI treatment according to mutation status (i.e., for *EGFR*m-positive patients) significantly prolonged overall survival, compared with chemotherapy alone or best supportive care.

Overall survival according to healthcare coverage scheme

Since healthcare coverage directly affects drug reimbursement and access to treatments such as EGFR-TKIs, we next investigated whether healthcare coverage status was related to survival outcomes. Among patients with more comprehensive coverage (CSMBS/SE), median OS was significantly longer than for those with basic coverage (UC/SSS): median OS 27.2 versus 18.3 months, HR=0.72 [95% CI 0.58–0.88], $P<0.001$ (Figure 3A). Overall survival among self-paying patients was not significantly different from those with only UC/SSS healthcare coverage. Similarly, among *EGFR*m-positive patients, CSMBS/SE patients showed longer significantly longer survival than UC/SSS patients: median OS 36.6 versus 24.0 months, HR=0.72 [95% CI 0.54–0.96], $P=0.030$ (Figure 3B). In both the total patient population and in the *EGFR*m-positive subset, having more comprehensive healthcare coverage (CSMBS/SE) was associated with significantly longer survival than basic UC/SSS coverage.

Clinical outcomes in EGFR-TKI-treated patients with different EGFR mutation subtypes

Among patients with *EGFR* activating mutations who were treated with EGFR-TKIs, median OS was 35 months or longer, and did not differ significantly across mutation subtypes (Supplementary Figure A). Time to EGFR-TKI treatment failure was similar in patients with common *EGFR* activating mutations only (approximately 13 months for those with exon 19 deletion or

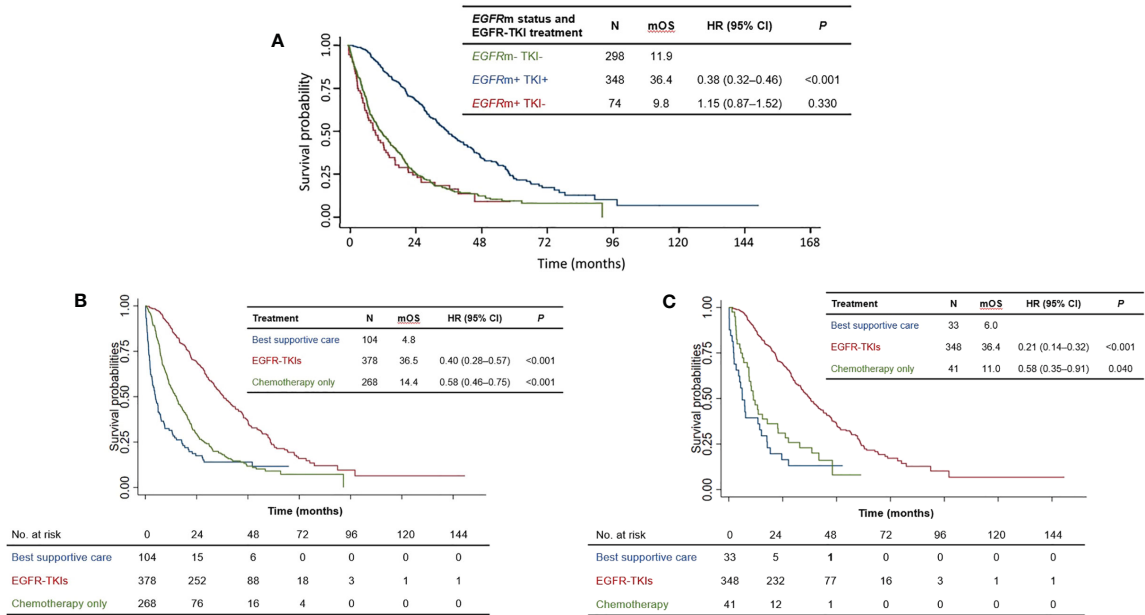


FIGURE 2
(A) Overall survival of patients according to *EGFR*m status and EGFR-TKI treatment. (B) Overall survival of patients according to treatment type for the total patient population. (C) Overall survival of patients according to treatment type for *EGFR*m-positive patients. mOS = median overall survival; HR, hazard ratio; CI, confidence interval; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitor; *EGFR*m+, positive for EGFR activating mutation, *EGFR*m-, wild-type EGFR.

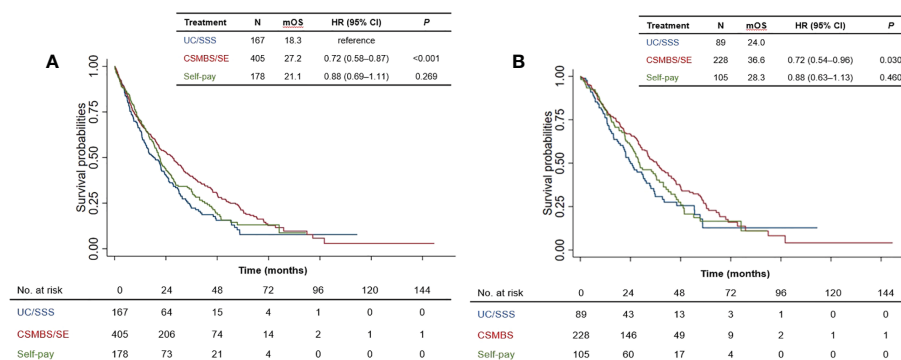


FIGURE 3

Overall survival of patients according to healthcare coverage scheme for (A) total patient population, and (B) *EGFRm*-positive patients. mOS, median overall survival; HR, hazard ratio; CI, confidence interval. UC, Universal Coverage; SSS, Social Security Scheme; CSMB/SE, Civil Servant Medical Benefit Scheme; SE, State Enterprise Scheme.

L858R), but significantly shorter in those who also had the T790M resistance mutation (T790M+: 7.6 months) (Supplementary Table C).

In the subset of T790M+ patients, treatment with osimertinib significantly prolonged survival: median OS was 57.4 months with osimertinib treatment versus 25.2 months without osimertinib (HR=0.24 [95% CI 0.13–0.44, $p<0.001$]) (Supplementary Figure B).

Cox regression analysis of prognostic factors for survival

To study the range of factors that potentially impact the survival of NSCLC patients, we performed multivariate Cox regression to analyze prognostic factors for survival in the total NSCLC patient population, and in the subset of *EGFRm*-positive patients.

In the total NSCLC patient population ($n=750$), potentially significant prognostic variables identified from univariate analyses included age, gender, smoking status, type of healthcare coverage, *EGFRm* status and treatment type. Of these, only age, gender, healthcare coverage type and treatment type remained statistically significantly related to OS in multivariate analyses (Table 2). The largest survival benefit was observed in patients who were female (adjusted HR=0.79 [95% CI: 0.63–0.99]), those who had CSMB/SE healthcare coverage (adjusted HR=0.73 [95% CI: 0.59–0.90] versus UC/SSS), or were treated with EGFR-TKIs (adjusted HR=0.26 [95% CI: 0.19–0.34] versus best supportive care only).

In the subset of *EGFRm*-positive patients ($n=422$), the potentially significant prognostic variables identified from univariate analyses were gender, smoking status, healthcare coverage status and treatment type. Of these, only gender and treatment type remained significant prognostic factors for OS in multivariate analyses (Table 3). The CSMB/SE group also showed a trend toward longer OS compared with the UC/SSS or self-paying groups in multivariate analyses (Table 3). As observed in the total NSCLC patient population, survival with EGFR-TKI treatment in *EGFRm*-positive patients was also longer than with chemotherapy alone (adjusted HR[EGFR-TKI]=0.19 [95% CI: 0.12–0.29], adjusted HR (chemotherapy)=0.50 [95% CI: 0.30–0.85]), and both significantly prolonged OS compared with best supportive care.

These results indicate that the observed influence of healthcare coverage status on survival can be attributed to drug reimbursement and access to EGFR-TKI therapy, especially for *EGFRm*-positive patients.

Discussion

The clinical development of EGFR-TKIs offered a more efficacious and tolerable alternative to standard cytotoxic chemotherapy for patients with *EGFR*-mutated lung cancer, and this has profoundly altered the NSCLC treatment landscape in the past decade. Like other molecular targeted therapies, EGFR-TKIs have the potential to improve clinical outcomes for large numbers of NSCLC patients in Asia and other regions where the prevalence of actionable molecular alterations is high (4, 5). Studies suggest that *EGFR* mutations are present in ≥ 40 –68% of Thai NSCLC patients, with higher frequencies among those with adenocarcinoma histology (6, 7, 16).

Clinical trials provide evidence of significant benefit with 1st/2nd-generation EGFR-TKIs in early-line treatment of *EGFRm*-positive NSCLC (8–11, 17, 18), additionally, these agents are recommended in numerous clinical practice guidelines and are included in the WHO Essential Medicines List (19). Even so, reimbursement and access to EGFR-TKI therapy remain limited in a number of countries, even where these agents have been approved by national health authorities for treating advanced-stage NSCLC. Examples include reimbursement of selected agents only under certain healthcare schemes, and/or only after failure of multiple lines of other therapy, as was the case in Thailand for 1st generation EGFR-TKIs prior to 2021.

Moreover, in real-world practice, a substantial proportion of patients diagnosed with advanced NSCLC remain untreated, or receive only limited therapy. Due to factors such as rapid disease progression, decline in PS, and/or toxicity from previous therapy, high drop-off rates after first-line therapy (≥ 20 –30% or more with successive lines) have been reported in a number of countries (20–24). We noted similar trends in our analysis, with drop-off rates of 29% and 38% after first-line and second-line therapy, respectively; in fact, 14% of our patients received no active anticancer treatment at all

TABLE 2 Cox regression analysis of prognostic factors associated with overall survival of all patients.

Prognostic factors	N	Overall survival (months)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	<i>P</i> [†]	Adjusted HR (95% CI)	<i>P</i> [†]
Age	750		1.01 (1.00–1.02)	0.004*	1.01 (1.00–1.02)	<0.001*
Gender						
Male	343	17.1	1		1	
Female	228	28.5	0.67 (0.57–0.79)	<0.001*	0.79 (0.63–0.99)	0.041*
Smoking status						
Current/Ex-smoker	277	14.6	1		1	
Never-smoker	473	27.8	0.64 (0.55–0.77)	<0.001*	0.99 (0.79–1.25)	0.950
Healthcare coverage status						
UC/SSS	167	18.3	1		1	
CSMBS/SE	405	27.2	0.72 (0.58–0.87)	<0.001*	0.73 (0.59–0.90)	0.003*
Self-pay	178	21.1	0.88 (0.69–1.11)	0.269	1.00 (0.79–1.27)	0.990
EGFR mutation						
No	328	13.8	1		1	
Yes	422	32.0	0.51 (0.43–0.60)	<0.001*	1.03 (0.81–1.32)	0.790
Treatment						
Best supportive care	104	4.8	1		1	
Chemotherapy alone	268	14.5	0.58 (0.46–0.75)	<0.001*	0.60 (0.47–0.78)	<0.001*
EGFR-TKI treatment	378	36.5	0.40 (0.28–0.57)	<0.001*	0.26 (0.19–0.34)	<0.001*

[†]*P*-values calculated from Cox proportional hazards model.

**P*-values <0.05 were considered statistically significant.

UC, Universal Coverage; SSS, Social Security Scheme; CSMBS, Civil Servant Medical Benefit Scheme; SE, State Enterprise Scheme; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitors; CI, confidence interval; HR, hazard ratio.

TABLE 3 Cox regression analysis of prognostic factors associated with overall survival in EGFRm-positive patients.

Prognostic factors	N	Overall survival (months)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	<i>P</i> [†]	Adjusted HR (95% CI)	<i>P</i> [†]
Age	422		1.00 (0.99–1.01)	0.740	1.00 (0.99–1.01)	0.960
Gender						
Male	150	25.8	1		1	
Female	272	35.8	0.74 (0.59–0.94)	0.010*	0.70 (0.52–0.95)	0.021*
Smoking status						
Current/Ex-smoker	104	24.4	1		1	
Never-smoker	318	34.9	0.75 (0.58–0.97)	0.030*	0.96 (0.68–1.34)	0.790
Healthcare coverage status						
UC/SSS	89	24.0	1		1	
CSMBS/SE	228	36.6	0.72 (0.54–0.96)	0.030*	0.76 (0.56–1.03)	0.070
Self-pay	105	28.3	0.88 (0.63–1.13)	0.460	1.01 (0.72–1.42)	0.950
Treatment						
Best supportive care	33	6.0	1		1	

(Continued)

TABLE 3 Continued

Prognostic factors	N	Overall survival (months)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	<i>P</i> [†]	Adjusted HR (95% CI)	<i>P</i> [†]
Chemotherapy alone	41	11.0	0.58 (0.35–0.91)	0.040*	0.50 (0.30–0.85)	0.010*
EGFR-TKI treatment	348	36.4	0.21 (0.14–0.32)	<0.001*	0.19 (0.12–0.29)	<0.001*

[†]*P*-values calculated from Cox proportional hazards model.

**P*-values <0.05 were considered statistically significant.

UC, Universal Coverage; SSS, Social Security Scheme; CSMBS, Civil Servant Medical Benefit Scheme; SE, State Enterprise Scheme; EGFR-TKI, Epidermal growth factor receptor-tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio.

(supportive care only). Cost barriers and limited access to superior agents for early-line therapy may exacerbate such problems with under-treatment.

In many regions, the real-world impact of limited or differential access on clinical outcomes has not been well quantified, potentially hindering national-level decision-making that could improve cancer care. Our analysis of real-world treatment patterns and outcomes in Thai NSCLC patients (2012–2017) was the largest to date for this time period, and was significant because it highlighted that patients' survival was significantly associated with their healthcare coverage status and especially the type of treatment received. Specifically, for *EGFR*m-positive patients, receiving EGFR-TKI therapy (reimbursable only under the more comprehensive CSMBS/SE schemes) was associated with longer survival than chemotherapy alone or best supportive care. Our results showed that, for *EGFR*m-positive NSCLC patients who received EGFR-TKI treatment, real-world clinical outcomes (median OS approximately 35 months, median TTF approximately 12 months) were comparable with those reported in other countries (20, 21, 23, 25, 26). However, some of the clinical factors that might affect the survival of *EGFR*m-positive patients such as performance status, brain metastases, and post EGFR-TKI treatment were not retrieved from our database. This is one of the limitations of this report. In contrast, *EGFR*m-negative NSCLC patients (who are not considered to benefit from EGFR-TKI therapy), our analysis suggested a possibility that choice of treatment based on healthcare coverage status may also influence survival, and this possibility may need to be explored in future work. For example, pemetrexed and vinorelbine could not reimburse in UC and SSS patients which might affect the survival of patients. Although not explored in the present analysis, the influence of healthcare coverage on *EGFR* mutation testing practice is a related issue that also warrants investigation.

Along with others, these findings on the clinical benefit of EGFR-TKI treatment contributed real-world evidence to support re-evaluation of EGFR-TKI reimbursement. In 2020, with the combined efforts and cooperation of other oncologists and healthcare policy-makers, a decision was reached to include erlotinib (generic) in the Thai NLEM as a first-line treatment for patients with advanced *EGFR*m-positive NSCLC from 2021 onwards (27). This potentially broadens access to EGFR-TKI first-line therapy on all healthcare schemes in Thailand. Following the update, the CSMBS scheme now reflects the recognition of erlotinib as the preferred first-line EGFR-TKI, in line with other national healthcare schemes. For CSMBS-insured individuals,

reimbursement of gefitinib can still be requested under the OCPA if the patient is unable to tolerate the side effects of erlotinib first-line therapy. However, given that over two-thirds of the population (72.2%) are only covered by the UC scheme, many patients could still have limited access to 2nd and 3rd generation EGFR-TKI therapies such as afatinib, dacomitinib, and osimertinib. Only CSMBS patients could reimburse osimertinib as the second-line treatment in *T790M*-positive patients.

The landscape of lung cancer treatment continues to evolve rapidly. Currently, there was a study (ADUARA) significantly demonstrated increasing of disease-free survival (DFS) of 3-year osimertinib in adjuvant treatment for stage IB – stage IIIA *EGFR*m-positive patients. This indication of osimertinib also approved by Thai FDA, but the patients could not reimburse from all healthcare schemes. Therefore, it will be important to continue generating high-quality data on the local impact of treatments, to support national healthcare policy-makers in timely evaluation and up-to-date decisions on first-line treatments in metastatic disease or adjuvant treatment in early stage disease, their indications and extent of subsidies.

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 Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University COA. MURA2020/304. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KKh : Investigation, methodology, patient enrollment, data curation, validation, data interpretation, project administration, resources, formal analysis, original draft. SO: Investigation, methodology, software, validation, formal analysis, review & edit

manuscript. KKa : Investigation, patient enrollment, data curation, review & edit manuscript. PK: patient enrollment, data curation. PS: Investigation, patient enrollment, review & edit manuscript. NT: investigation, patient enrollment, review & edit manuscript. PP: Patient enrollment, data curation, review & edit manuscript. JW: patient enrollment, data curation, review & edit manuscript. TT: Visualization, patient enrollment, data curation, review & edit manuscript. TD: Study design, conceptualization, visualization, patient enrollment, data analysis, data interpretation, conclusion, suggestion, review & edit manuscript. ES: Visualization, data curation, review & edit manuscript. TR: Supervision, study design, conceptualization, visualization, investigation, methodology, analysis, data curation, validation, conclusion, data interpretation, original draft, writing - review & editing. 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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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2023.1047644/full#supplementary-material>

SUPPLEMENTARY FIGURE A

Overall survival by EGFR mutation subtype. mOS = median overall survival; HR = hazard ratio; CI = confidence interval.

SUPPLEMENTARY FIGURE B

Overall survival in patients with acquired T790M mutation with and without osimertinib treatment. mOS = median overall survival; HR = hazard ratio; CI = confidence interval.

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Global research trends of acupuncture therapy on cancer pain: A bibliometric and visualized study

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Background: The number of publications on acupuncture for cancer pain is increasing rapidly with an upward tendency. Considering that no bibliometric articles related to this topic have been published yet. It is necessary to evaluate the global scientific output of research in this field, and shed light on the direction of clinical cancer pain management in the future.

Methods: Research publications regarding acupuncture on cancer pain from inception to 2022 were downloaded from the Web of Science Core Collection. Bibliometric analyses were performed using CiteSpace software, the bibliometrix R package, and VOSviewer software. Network maps were generated to assess the collaborations between different countries, institutions, authors, and keywords. And clusters map was generated to evaluate reference.

Results: A total of 790 articles related to acupuncture therapy for cancer pain were identified. We observe that the number of publications is gradually increasing over time. China and the United States were the main contributors. Mem Sloan Kettering Canc Ctr (38 papers) and Beijing Univ Chinese Med (28 papers) contributed the most publications, becoming the leading contributors in this field. Although J Clin Oncol (28 articles) ranked ninth in terms of publication volume, it was the journal with the most citations and the highest number of IF (50.717) and H-index (494) at the same time. MAO J from Mem Sloan Kettering Canc Ctr was the most prolific author (23 articles). The main hot topics included matters related to acupuncture (239 times), pain (199 times), management (139 times), quality of life (107 times), electroacupuncture (100 times), and breast cancer (82 times).

Conclusion: Our bibliometric analysis provides a comprehensive overview of the development of acupuncture for cancer pain, enabling relevant authors and

research teams to identify the current research status in this field. At the same time, acupuncture for breast cancer (BC) pain, aromatase inhibitor-induced arthralgia (AIA), and chemotherapy-induced peripheral neuropathy (CIPN) may soon become prospective focus.

KEYWORDS

acupuncture, cancer pain, bibliometric analysis, VOSviewer, web of science

Introduction

Pain continues to be the most common, burdensome and problematic symptoms encountered by patients with cancer, with an incidence rate of 50.7% (1, 2). Physical, emotional and cognitive functioning can be affected by chronic pain, resulting in a decrease in overall quality of life and an increased risk of mortality. The possible causes of widespread pain in cancer patients are as follows: 1) pain caused by tumor metastasis to bones and organs, 2) musculoskeletal symptoms caused by chemotherapy, 3) pain caused by diagnostic examination and drug treatment, and 4) comorbidities (3–5).

The successful management of pain in cancer patients presents a considerable clinical challenge (6). Analgesics have significant adverse effects which not only cause respiratory depression and constipation, but also lead to addiction and tolerance, further reducing the quality of life (7). The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) released in 2019 paid special attention to the theme of cancer pain management, which integrated non-drug methods (8).

Acupoints are sensors of body information. Acupuncture is well-tolerated with little risk of serious side effects. Acupuncture has been shown to have analgesic effects in studies of many other pain diseases, such as knee osteoarthritis, migraine, dysmenorrhea and low back pain (9–12). Due to the multimorphism of cancer pain, multiple investigators have already reported that acupuncture, as an integrative or complementary therapy, can provide effective therapeutic advantages to alleviate cancer-related pain, whether it is acute or chronic pain (13–17). Therefore, despite the positive effect of current therapeutic strategies in improving the survival time, necessary precautions should be adopted along with other treatments to manage cancer pain in the clinical setting (18).

In the current study, we retrieved relevant literature on acupuncture for cancer pain to conduct a statistical analysis by utilizing CiteSpace and VOSviewer. Our study aimed to shed light on the direction of cancer pain management research *via* acupuncture and provide inspiration for researchers to cooperate in their future studies.

Research methodology

Sources of data and search strategy

This study collects bibliometric data on acupuncture and cancer pain research for its review. To avoid omissions, the authors conducted the synonyms for “cancer” and “acupuncture” through the MeSH Database in PubMed. All data were collected from the online database Science Citation Index-Expanded (SCI-E) of the Web of Science (WOS). The search time was from database inception to 12 October 2022. The language was restricted to English. There were no restrictions in terms of document type, data category, or document year. The specific search strategy and results are shown in Table 1. There were 841 original records in total, including articles, editorial materials, letters, meeting abstracts, and reviews. Finally, we imported these articles into CiteSpace for de-duplication, which removed 51 documents, and thus, 790 results were retained.

Assessing

To evaluate the final corpus of 790 articles related to acupuncture for cancer pain, this study adopts a bibliometric analysis approach for its review. Bibliometrics on acupuncture and cancer pain were visualized by using CiteSpace (Version 6.1 R3), R software (version 4.2.1), the bibliometrix R package, VOSviewer (Version 1.6.18), and Microsoft Excel 2019. Two researchers independently completed the literature selection, data extraction, and analysis to ensure the reliability of the results. CiteSpace was used for co-authorship network of countries, institutions, authors, cited journals, and references. In order to have a more comprehensive understanding of topics and research frontiers in this field, we used the bibliometrix R package and VOSviewer to analyze keywords at the same time.

The parameters of CiteSpace were set as follows: time slices were 1985–2022, the number of years in each slice was 1, the term source was selected for all selections, and Pruning was Pathfinder and Pruning sliced Networks.

TABLE 1 The Topic Search Query.

Set	Results	Search Query
#1	24,575	TS=(Acupuncture)) OR TS=(Electroacupuncture))
		OR TS=("electro-acupuncture")) OR TS=(Acupressure)) OR
		TS=(Moxibustion)) OR TS=("Acupoint Injection")) OR
		TS=(Acupoints)) OR TS=(Pharmacopuncture)) OR
		TS=("Needle knife")) OR TS=("catgut embedding")) OR
		TS=("catgut implantation at acupoint")) OR
		TS=("embedding thread")
#2	4,297,341	(TS=(tumor*)) OR TS=(tumour*)) OR TS=(cancer*))
		OR TS=(carcin*) OR TS=(oncolog*) OR TS=(neoplas*)
		OR TS=(malignan*)
#3	614,101	TS=(pain)
#4	841	#1 AND #2 AND #3

Results

Publication output and temporal trend

Based on the above search methods and data processing, a total of 790 publications were obtained, which were published from 1985 to 2022. There were 584 articles (73.92%) and 208 reviews (26.33%) among the 790 included documents, averaging 21 publications per year. The annual distribution of the number of publications is shown in Figure 1, showing an increasing growth trend. Before 2005, the annual number of research articles on acupuncture for cancer pain was less than 10 documents. Since then, the publications of related literature on acupuncture and cancer pain showed a small fluctuating upward trend, reaching three peaks in 2014, 2018, and 2021. And 2021 (97 publications, 12.28%) was the most prolific year for publications.

To ensure whether the growth of publications on studies of acupuncture for cancer pain conformed to Price's law, the acquired data were exponentially adjusted and linearly fitted. We obtain the equation $y = -1.6 + 2.6e^{((x-1985)/6.47)}$ ($R^2 = 0.98$) from its exponential curve, with the result of good fitting. As a result, the continuous increase in publications over time indicates that the cancer pain aspect of acupuncture therapy is attracting increasing attention, which can provide recommendations for future research.

Leading countries

A country collaboration network map was generated by CiteSpace (Figure 2). The top 5 most productive countries are presented in Table 2. This research involved a set of 54 countries

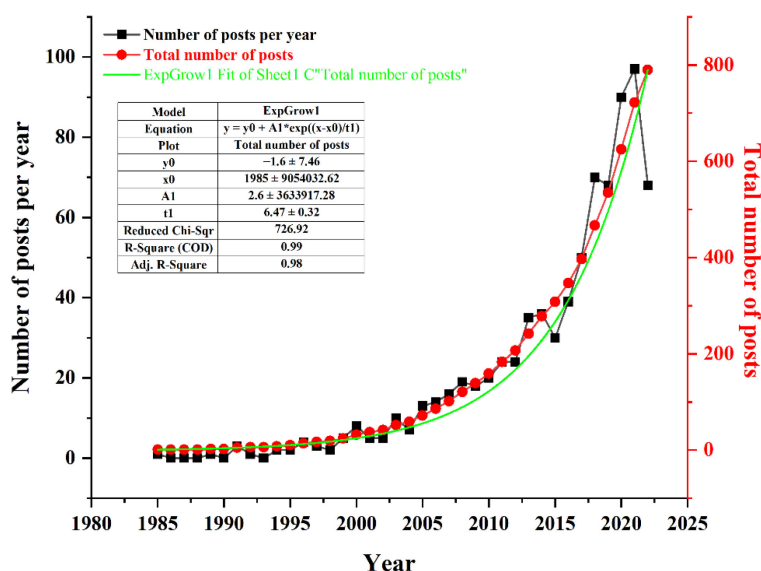


FIGURE 1
Annual publications covering research on acupuncture for cancer pain.

with 118 links. The countries with the most publications were mainly China and the United States. China contributed the highest number of articles (288, 36.46% of all articles), followed by the United States (281, 35.57%), South Korea (67, 8.49%), and England (53, 6.71%). The top five countries by centrality were the United States (0.42), China (0.26), Japan (0.15), Italy (0.09) and Saudi Arabia (0.09). As seen from it, the United States and China have published a large amount of relevant literatures and established collaborative relationships with many countries. Meanwhile, the United States also showed the highest centrality.

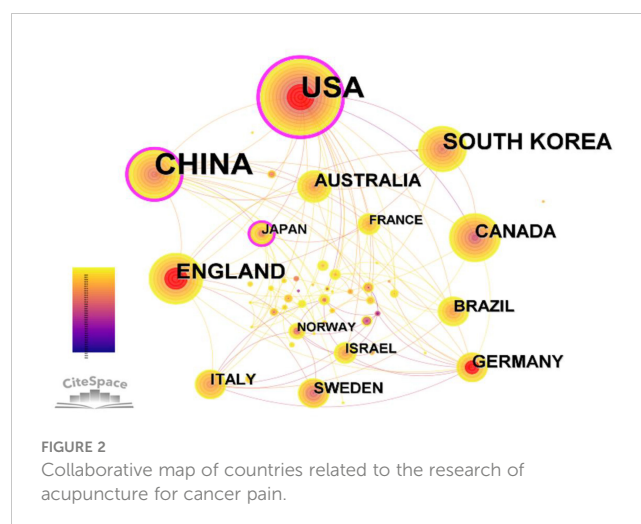
Institutions

According to the CiteSpace, a total of 458 institutions were involved in this field (Figure 3). The 10 institutions with the highest number of articles were obtained (Table 3). Mem Sloan Kettering Canc Ctr (38 records, 4.81% of all articles) contributed the most publications, followed by Beijing Univ Chinese Med (28, 3.54%), Kyung Hee Univ (25, 3.16%), Guangzhou Univ Chinese Med (18, 2.28%), and Nanjing Univ Chinese Med (17, 2.15%). Beijing Univ Chinese Med showed the highest centrality (0.19). Thus, we can see institutions with the most publications and high centrality are mainly distributed in China and the the United States. The purple circle around the nodes reflects the centrality of the network, indicating that Mem Sloan Kettering Canc Ctr and Beijing Univ Chinese Med played a pivotal role in the cooperative relationships among institutions.

Authors and cited authors

The CiteSpace software was used to generate a co-author map containing 671 nodes and 1233 links (Table 4; Figure 4). In terms of the number of published papers, MAO J was the most prolific author, with 23 articles (2.91%), followed by WANG Y (22, 2.78%), LEE J (18, 2.28%) and LIU Y (17, 2.15%). LEE J and DENG G showed the highest centrality, each with the centrality of 0.09. By observing the visualization map, we could find the authors with more publications and higher central position tend to cooperate closely with other authors.

An author co-citation map was generated displaying 969 nodes and 3444 links (Table 5; Figure 5). The top 5 most cited authors were Molassiotis A (102), Vickers AJ (101), Ernst E (93), Lu WD (93), and Hershman DL (92). The top 5 authors in centrality were



Cassileth BR (0.2), Ernst E (0.19), Vickers AJ (0.1), Molassiotis A (0.09), and, Shen JN (0.09).

Leading journals and cited journals

In total, 297 academic journals published papers about acupuncture for cancer pain. Table 6 lists the top 10 most popular journals contributing to articles on acupuncture and cancer pain topics, and shows the countries of origin and the impact factor of the top 10 journals. The top 10 journals published about 34.43% of the documents in the field. Among them, the average impact factor (IF) was 7.5572. Evid-Based Compl Alt was the leading journal, publishing the most papers (42 articles, England), followed by Integr Cancer Ther (40 articles, United States), Medicine (33 articles, United States), Supportive Care In Cancer (30 articles, United States), J Altern Complem Med (30 articles, United States), J Pain Symptom Manag (28 articles, United States), Acupuncture In Medicine (26 articles, England), Complement Ther Med (15 articles, England), J Clin Oncol (14 articles, United States), and Acupuncture Electro (14 articles, United States). The impact factor (IF) of Evid-Based Compl Alt (the most published journal) was 2.650 (2021), and the H-index was 72. Among the top 10 journals, the journal with the highest IF (50.717), which also had the highest H-index (494), was J Clin Oncol from the United States. It indicates that the articles published in this journal are influential in the field of acupuncture for cancer pain.

TABLE 2 Top 5 Countries with the highest frequency and centrality related to the research of acupuncture for cancer pain.

Ranking	Frequency	Country	Ranking	Centrality	Country
1	288	China	1	0.42	USA
2	281	USA	2	0.26	China
3	67	South Korea	3	0.15	Japan
4	53	England	4	0.09	Italy
5	30	Canada	5	0.09	Saudi Arabia

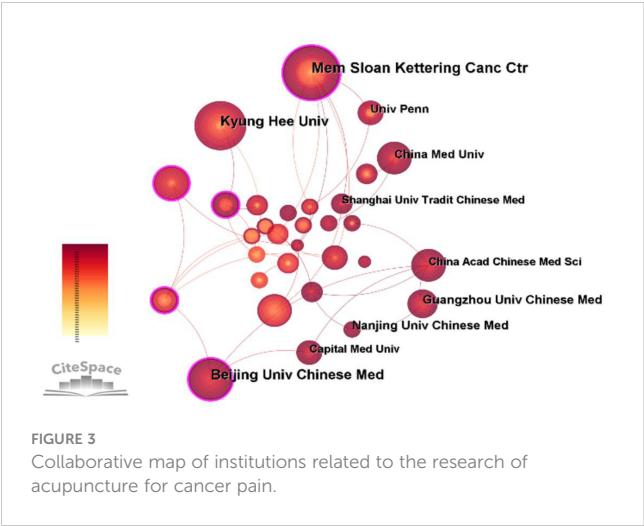


FIGURE 3 Collaborative map of institutions related to the research of acupuncture for cancer pain.

Table 7 and Figure 6 present the top 5 cited journals on acupuncture for cancer pain research. J Clin Oncol was cited in the most journals (391 counts), followed by Pain (360 counts). The highest citation counts of this journal may be due to it being the journal with the highest IF and the highest H-index. This also provides a direction for us to find related articles in the future. Evid-Based Compl Alt ranked third, with 324 counts. The fourth and fifth, with more than 250 citations, were Acupunct MED (285 counts) and Support Care Cancer (275 counts), respectively. A node represents a journal, the purple ring outside the node indicates the size of the centrality of the journal. Brit MED J has the highest centrality (0.15).

Reference

We used CiteSpace to obtain a reference co-citation map related to studies on acupuncture for cancer pain (Figure 7), with 916 nodes and 2522 links. Table 8 enumerates the basic information of the top 10 most cited references. These highly cited studies were mainly published between 2013 and 2020. The most cited reference was

Hershman DL’s paper, which was a randomized clinical trial (RCT) of the acupuncture effects on joint pain related to aromatase inhibitors among women with early-stage breast cancer, published in JAMA in 2018. It was cited 41 times. Chiu HY (2017) wrote the second most highly cited paper, with 37 citations. He YH (2020) wrote a systematic review, ranked third, with 33 citations. The fourth position was occupied by Garcia MK (2013), with 29 citations. Followed by Mao JJ (2014), Paley CA (2015), and Vickers AJ (2018), with 23 citations. A total of 24 clusters were obtained. The largest cluster was “pain management” which contains 104 references. The color of the cluster “complementary medicine”, “nonpharmacological management”, and “insured cancer patient” were red, indicating the latest research direction of research on acupuncture in treating cancer pain.

Keywords

Co-occurrence analysis of keywords can identify research hotspots and trends. We analyzed a total of 90 keywords among 2937 keywords related to the research of acupuncture for cancer pain that were identified as having occurred more than fifteen times. The top 90 keywords are visualized in Figure 8A, showing that predominant words were divided into three clusters, represented by three colors (red, green, and blue).

We can see a visualization of each cluster of keywords over time (Figures 8B–D). Cluster 1 refers to acupuncture therapy method for cancer pain, indicated by red, with the main keywords of acupuncture, management and breast cancer. Cluster 2 refers to electroacupuncture therapy method for cancer pain, indicated by green, with the main keywords of electroacupuncture, induced peripheral neuropathy and postoperative pain. Cluster 3 refers to disease, indicated by blue, with the main keywords of chemotherapy, chemotherapy induced periphara, neurotoxicity, and multiple myeloma, which were the latest topics. The development trend and strategic coordinate map are shown in Figure 9. The high-occurrence words (Figures 9A, B) include acupuncture (239 times), pain (199 times), management (139 times), quality of life (107 times),

TABLE 3 Top 10 institutions related to the research of acupuncture for cancer pain.

Ranking	Frequency	Institution	Country	Centrality	Institution	Country
1	38	Mem Sloan Kettering Canc Ctr	USA	0.19	Beijing Univ Chinese Med	China
2	28	Beijing Univ Chinese Med	China	0.17	Columbia Univ	Canada
3	25	Kyung Hee Univ	South Korea	0.16	Univ Maryland	USA
4	18	Guangzhou Univ Chinese Med	China	0.13	Mem Sloan Kettering Canc Ctr	USA
5	17	Nanjing Univ Chinese Med	China	0.12	Korea Inst Oriental Med	South Korea
6	15	China Med Univ	China	0.09	Dana Farber Cane Inst	USA
7	15	Univ Penn	USA	0.08	Harvard Univ	USA
8	14	Capital Med Univ	China	0.08	Natl Cheng Kung Univ	China
9	14	Shanghai Univ Tradit Chinese Med	China	0.08	British Acupuncture Council	England
10	13	China Acad Chinese Med Sci	China	0.07	Kyung Hee Univ	South Korea

electroacupuncture (100 times), breast cancer (82 times), therapy (77 times), cancer (66 times), women (61 times), complementary (60 times). It can be seen that the covered groups with the need to treat cancer pain by acupuncture mainly existed in women, and their negative emotions were mainly anxiety and depression. Acupuncture was most likely to be considered as an alternative therapy to provide effective palliative treatment for cancer pain patients, and improve their quality of life. The cancer pain categories treated by acupuncture were mainly breast pain, neuropathic pain, and low back pain, which were characterized by chronic pain. In addition, we can also see that these treatments were mostly achieved through RCTs. Figure 9C shows that the frequency of the above top 10 keywords increased over time. The keyword “acupuncture” grew the fastest, followed by “breast cancer”. Through the thematic map of keywords (Figure 9D), internal organ, o-ring test, and clinical application were highly developed and isolated themes; acupuncture point was emerging or declining themes; acupuncture, pain; electroacupuncture were basic and transversal themes. In addition, we can predict that neuropathic pain, mechanism, expression, management, quality of life, and breast cancer will be the research trends.

Discussion

In the present research, we performed a bibliometric analyses using VOSviewer, CiteSpace, and the bibliometrix R package to characterize the current landscape and frontier topic of acupuncture for cancer pain. The contributions of countries, institutions, authors, journals, reference and keywords to this emerging field were analyzed. Thus, the general information was summarized, predicting hotspots and trends on acupuncture for cancer pain.

Basic information

Since 2005, the annual publication output in this field has increased in a steady fashion. The publication output in 2021 was the highest, accounting for 12.28% of all the included studies. It

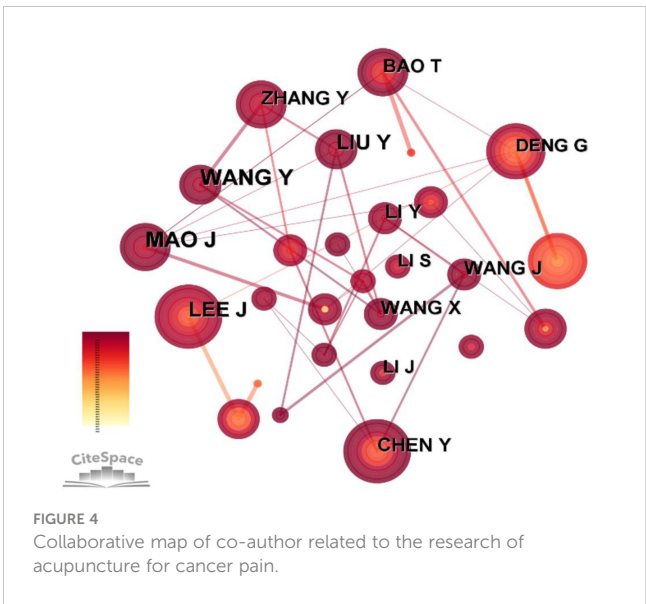


FIGURE 4 Collaborative map of co-author related to the research of acupuncture for cancer pain.

can be seen that acupuncture on cancer pain has attracted more and more attention, and various countries have begun to using acupuncture to treat patients with cancer pain. The reason why acupuncture attracts more and more attention to this field is that, on the one hand, the development of the modern medicine is more and more mature and the patients’ quality of life is concerned. On the other hand, the reason may be the widely use of acupuncture in medical fields has been proved to be effective.

China was the country with the largest number of publications, but the United States had a high centrality of 0.42, indicating that most countries in this field had direct and indirect cooperation with the United States. The institutions with the most publications were in the United States. And the institution with the largest number of publications in China is Beijing Univ Chinese Med. It may be concluded that Chinese researchers, with the advantage of the long history use of acupuncture, are equipped to conduct more studies and publish more literature, while western researchers are more influential in the study of

TABLE 4 Top 10 authors of studies on acupuncture for cancer pain.

Ranking	Frequency	Author	Centrality	Author
1	23	MAO J	0.09	LEE J
2	22	WANG Y	0.09	DENG G
3	18	LEE J	0.06	CHEN Y
4	17	LIU Y	0.05	MAO J
5	15	LI Y	0.05	ZHANG Y
6	15	ZHANG Y	0.05	BAO T
7	14	WANG J	0.05	LI Q
8	14	WANG X	0.04	LEE M
9	14	CHEN Y	0.03	LI Y
10	13	BAO T	0.03	WANG J

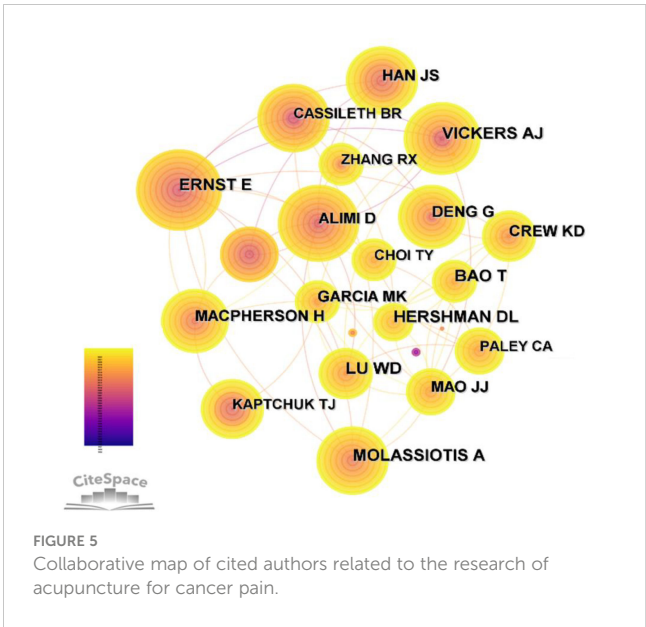
cancer pain. According to the analysis of publishing institutions, the first and second institution were Mem Sloan Kettering Canc Ctr and Beijing Univ Chinese Med respectively, both of which have very strong comprehensive strengths. Mem Sloan Kettering Canc Ctr is the largest private cancer research center in the world, making a significant contribution to the understanding, diagnosis and treatment of cancer. Beijing Univ Chinese Med is the most important medical innovation research base in China, training a large number of senior medical and health personnel. These results suggest that the two institutions mentioned above, may significantly influence the direction of studies in this field and participate in the strongest cooperation globally.

Although J Clin Oncol ranked ninth with 28 published articles, it had the most citations with the highest IF (50.717) and H-index (494) at the same time, indicating that this journal is very influential in this field, which can provide inspiration for future research. MAO J, a doctor from Mem Sloan Kettering Canc Ctr, who had the largest number of publications (23, 2.91%), is a pioneer in the field of acupuncture in the treatment of cancer pain. With the increase of cancer incidence and mortality, MAO J believed that the current cancer care had been challenged. Therefore, he proposed an integrative medicine (TCIM) including acupuncture and massage, to alleviate cancer symptoms or treatment-related adverse reactions such as pain, insomnia and fatigue (19). The author with the highest cited frequency is Molassiotis A, whose most cited paper is a RCT published in Support Care Cancer in 2002, which focused on adjuvant intervention to improve the standards of care for cancer patients with side effects of chemotherapy (20).

Research frontiers and trends

Keywords and references reflect the content of the research, which is helpful to identify hotspots and frontiers from their frequency, centrality, and clustering distribution.

Based on the co-occurrence map of keywords and references map, it can be determined that acupuncture and electroacupuncture (EA) may be the main therapeutic therapies for cancer pain. In addition, the management of cancer pain probably have received the greatest concern from researchers in this field. We can also infer that studies on the treatment of cancer pain with acupuncture have covered a variety of types, including breast pain, arthralgia, neuropathic pain, and low back pain.



Breast cancer pain

According to the global cancer statistics in 2020, female breast cancer (BC) has surpassed lung cancer to become the most commonly diagnosed cancer type and the leading cause of cancer-related deaths among women (21). To our knowledge, breast cancer increases the susceptibility to menopausal symptoms such as joint pain, headache, mood changes, depressive, paresthesia and tingling (22, 23). Post-mastectomy pain syndrome (PMPS) mainly involves the chest, axilla, and ipsilateral upper extremity (24). Chronic post-operative pain is so common among BC patients in part because it can arise for a variety of reasons, including the existence of a preoperative painful condition, axillary lymph node dissection, intercostobrachial nerve damage during surgical dissection, acute postoperative pain, and psychological factors (25, 26).

Acupuncture has demonstrated its effectiveness in managing symptoms of BC survivors (27). Existing systematic reviews have proved that acupuncture can not only relieve pain in patients with BC, but also improve hot flashes, fatigue, sleep disturbance, anxiety, and especially the quality of patients with BC (23, 28, 29). The Society for Integrative Oncology (SIO) developed an evidence-based guideline on the use of integrative therapy during and after breast cancer treatment, which recommends acupressure and acupuncture to manage adverse effects related to breast cancer treatment (30).

TABLE 5 Top 5 Cited authors of studies on acupuncture for cancer pain.

Ranking	Cocitation counts	Cited author	Centrality	Cited author
1	102	Molassiotis A	0.2	Cassileth BR
2	101	Vickers AJ	0.19	Ernst E
3	93	Ernst E	0.1	Vickers AJ
4	93	Lu WD	0.09	Molassiotis A
5	92	Hershman DL	0.09	Shen JN

TABLE 6 Top 10 journals related to studies on acupuncture for cancer pain.

Ranking	Articles	Journal	IF(2021)	H-index	Region
1	42	Evid-Based Compl Alt	2.650	72	England
2	40	Integri Cancer Ther	3.077	53	USA
3	33	Medicine	1.817	135	USA
4	30	Supportive Care in Cancer	3.359	98	USA
5	30	J Altern Complem Med	2.381	80	USA
6	28	J Pain Symptom Manag	5.576	129	USA
7	26	Acupuncture in Medicine	1.976	42	England
8	15	Complement Ther Med	3.335	55	England
9	14	J Clin Oncol	50.717	494	USA
10	14	Acupuncture Electro	0.684	24	USA

Aromatase inhibitor-induced arthralgia

Aromatase inhibitors (AIs), as a standard treatment for early-stage breast cancer, have adverse effects including headache and arthralgia, which in turn may cause poor adherence to AIs. Aromatase inhibitor-induced musculoskeletal symptoms (AIMSS) is characterized by symmetric pain or soreness in multiple joints, musculoskeletal pain and morning stiffness (31, 32). Through the analysis of keyword, we can see that RCT was the most common research method with the strongest evidence to prove its effectiveness. RCTs have reported that acupuncture or EA can significantly improve joint pain and stiffness in BC women with aromatase inhibitor-induced arthralgia (AIA) (33–35). Moreover, systematic reviews have demonstrated that acupuncture can significantly reduce pain intensity of breast cancer patients with AIA. what's more, acupuncture treatment has no significant side effects (36–40).

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a common clinical problem in cancer patients, which often leads to acral pain (41). PRICE, S put forward the treatment protocol of acupuncture as an auxiliary nursing care for chemotherapy patients as early as 2006 (42). Of concern, Rostock M and Greenlee, H respectively adopted EA protocols for cancer patients receiving chemotherapy, however, did not found a positive effect on the prevention and treatment of CIPN (43, 44). Later, BAO, T showed the efficacy and safety of acupuncture in reducing the incidence of

high-grade CIPN during chemotherapy in a single-arm phase IIA trial, but he also called for a follow-up randomized controlled trial to establish definitive efficacy (45).

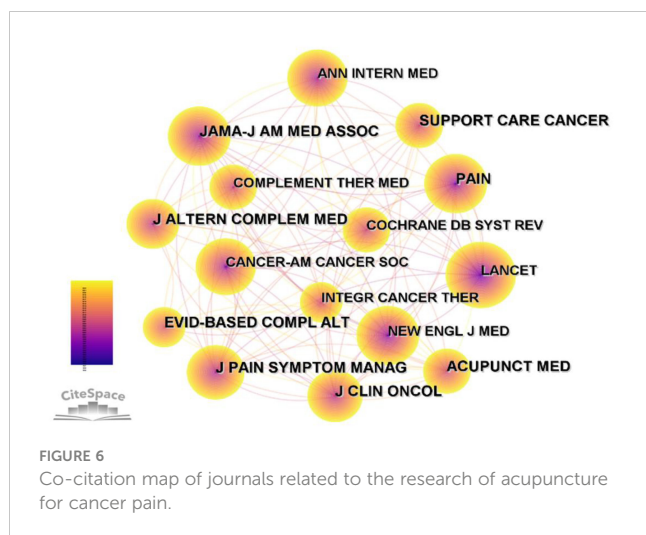
A randomized pilot study published in 2020 revealed that an 8-week acupuncture intervention could improve neuropathic sensory symptoms in breast cancer survivors with mild and moderate CIPN after the completion of taxane-containing adjuvant chemotherapy (43). Then, other RCTs also demonstrated that acupuncture can alleviate the neuropathic pain (eg, hand numbness, tingling, and pain) of CIPN and increase touch perception thresholds (46, 47). In addition, several systematic reviews have been published in 2022 to evaluate the effects of acupuncture therapies on CIPN (48–50). According to the theory of traditional Chinese medicine, the acupoints (eg, Qihai, Neiguan, Hegu, Zusanli, Sanyinjiao) selected to relieved CIPN in cancer patients are characterized by tonifying Qi, regulating Qi and blood circulation, and treating localized symptoms.

Analgesic mechanisms

The underlying mechanism of acupuncture applied to cancer pain is still not completely understood. As to acupuncture analgesia, inflammatory pain animal models actually reported that many bioactive chemicals (such as β -endorphins, IL-1 β , dynorphines, substance P) were involved in acupuncture inhibition of cancer pain (51). Regarding acupuncture for CIPN, certain studies demonstrated that it may involve stimulation of A δ and C nerve fibers or α 2 and β -adrenoceptors (52). CHOI J W found that EA

TABLE 7 Top 5 cited journals with the highest frequency and centrality related to studies on acupuncture for cancer pain.

Ranking	Cocitation counts	Cited journal	Centrality	Cited journal
1	391	J Clin Oncol	0.15	Brit MED J
2	360	Pain	0.11	Am J Chinese Med
3	324	Evid-Based Compl Alt	0.08	Anesth Analg
4	285	Acupunct MED	0.08	Am J Med
5	275	Support Care Cancer	0.07	Ann Intern Med



stimulation of the ST36 acupoint, mediated by spinal opioid receptor, alpha2- and beta-adrenoceptors, significantly reduced paclitaxel-induced neuropathic pain in mice (53). WANG F J believes that EA reduces allodynia mainly by restoring the Nrf2/HO-1 signaling pathway (54).

Psychological factors

Psychosomatic symptoms always plague most cancer patients, especially women (55). Those who survive tend to leave long-term chronic pain, often accompanied by negative emotions such as anxiety and depression, which have a significant impact on their quality of life (56). In turn, this will have a negative impact on the comprehensive treatment of cancer patients. A cross-sectional comparative study pointed out that cancer patients with pain

features showed greater psychological barriers (57). Recent systematic review indicated that psychological intervention can help reduce cancer-related pain in adults (58). In this way, we can infer that emotional factor play a key role in the management of cancer patients. Acupuncture plays a direct or indirect role in cancer pain management by increasing plasticity in the hippocampus and neural networks, reducing inflammation in the brain, and alleviating negative emotions (59, 60). Therefore, we need to strengthen interprofessional and multidisciplinary treatment and emphasize the importance of psychotherapy in cancer pain management, which requires enhanced doctor-patient communication, social support and patient cognitive behavioral therapy.

Other frontiers

Due to the emergence of low-correlation keywords, we may have ignored the latest research trends. Fortunately, we found several new trends. LEE J reported in an RCT that acupuncture could alleviate the pain and dysfunction of cancer patients with a history of neck dissection, and relieve dry mouth. In this study, LI-4, SP-6, GV-20, luozhen, auricular shenman, local ashi tender points and LI-2 were selected (61). Mao J treated cancer survivors with chronic musculoskeletal pain for 10 times with EA or auricular acupuncture, which reduced the average Brief Pain Inventory (BPI) pain severity score by 1.9 points and 1.6 points respectively. And electroacupuncture produced greater pain relief (62).

Conclusion

To the best of our knowledge, this study is the first bibliometric paper focused on publications related to acupuncture for cancer

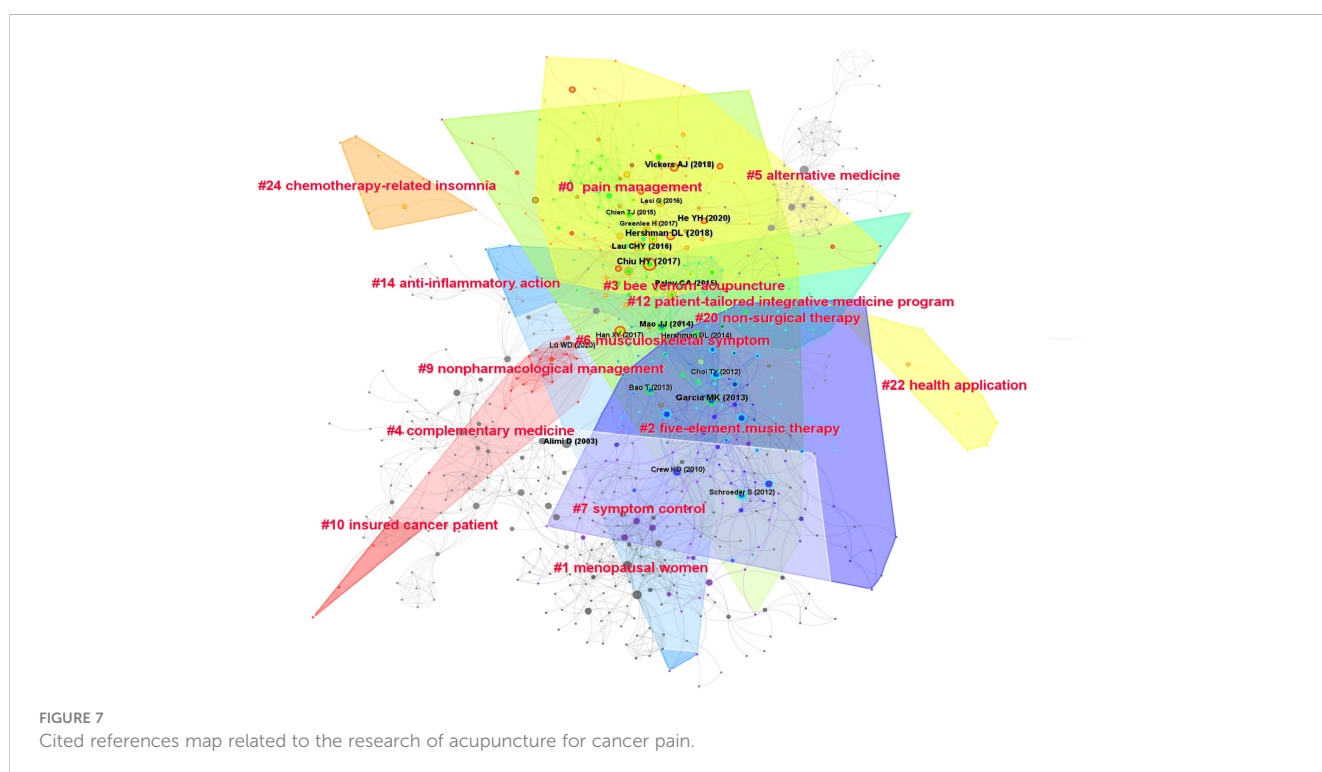
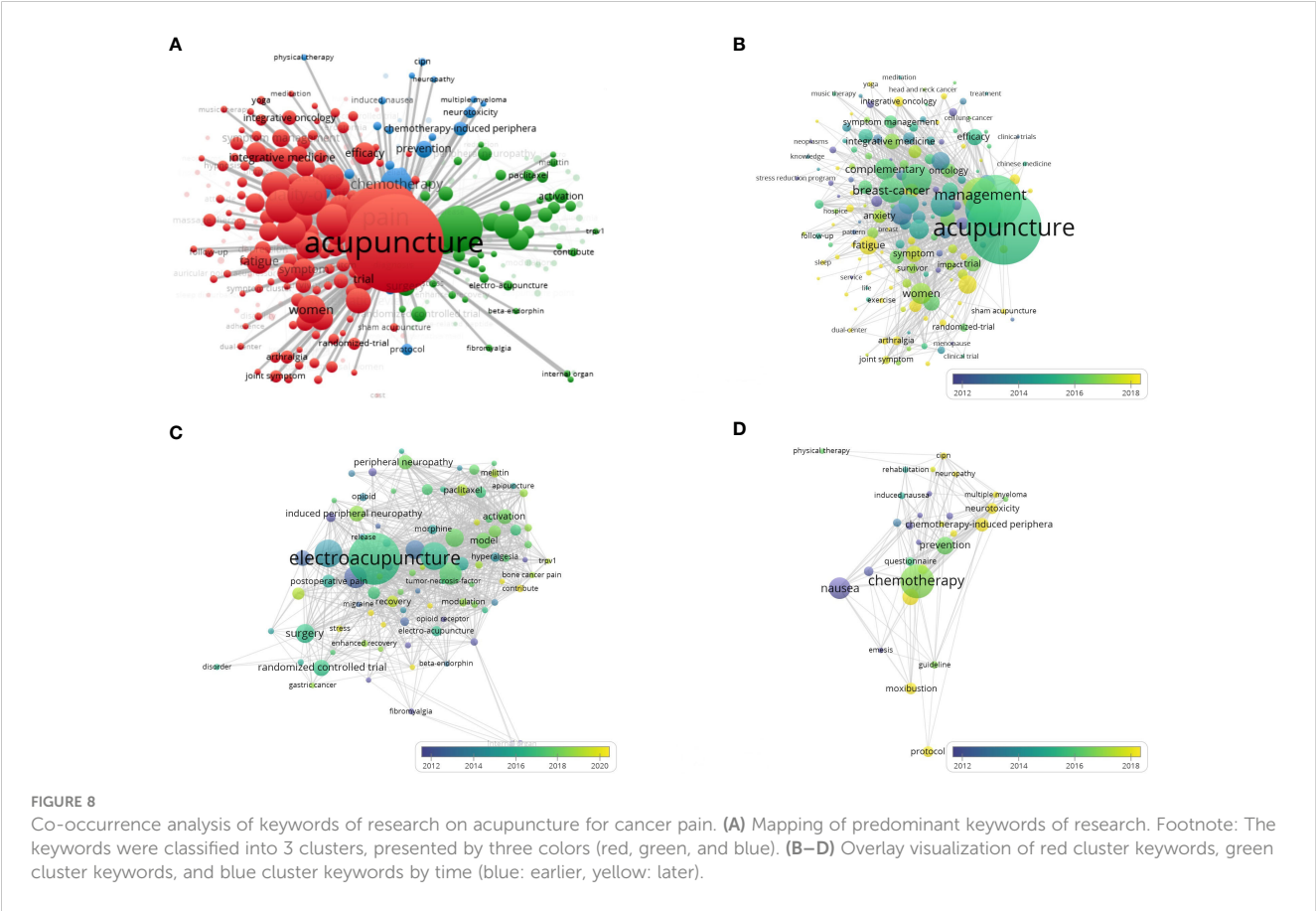
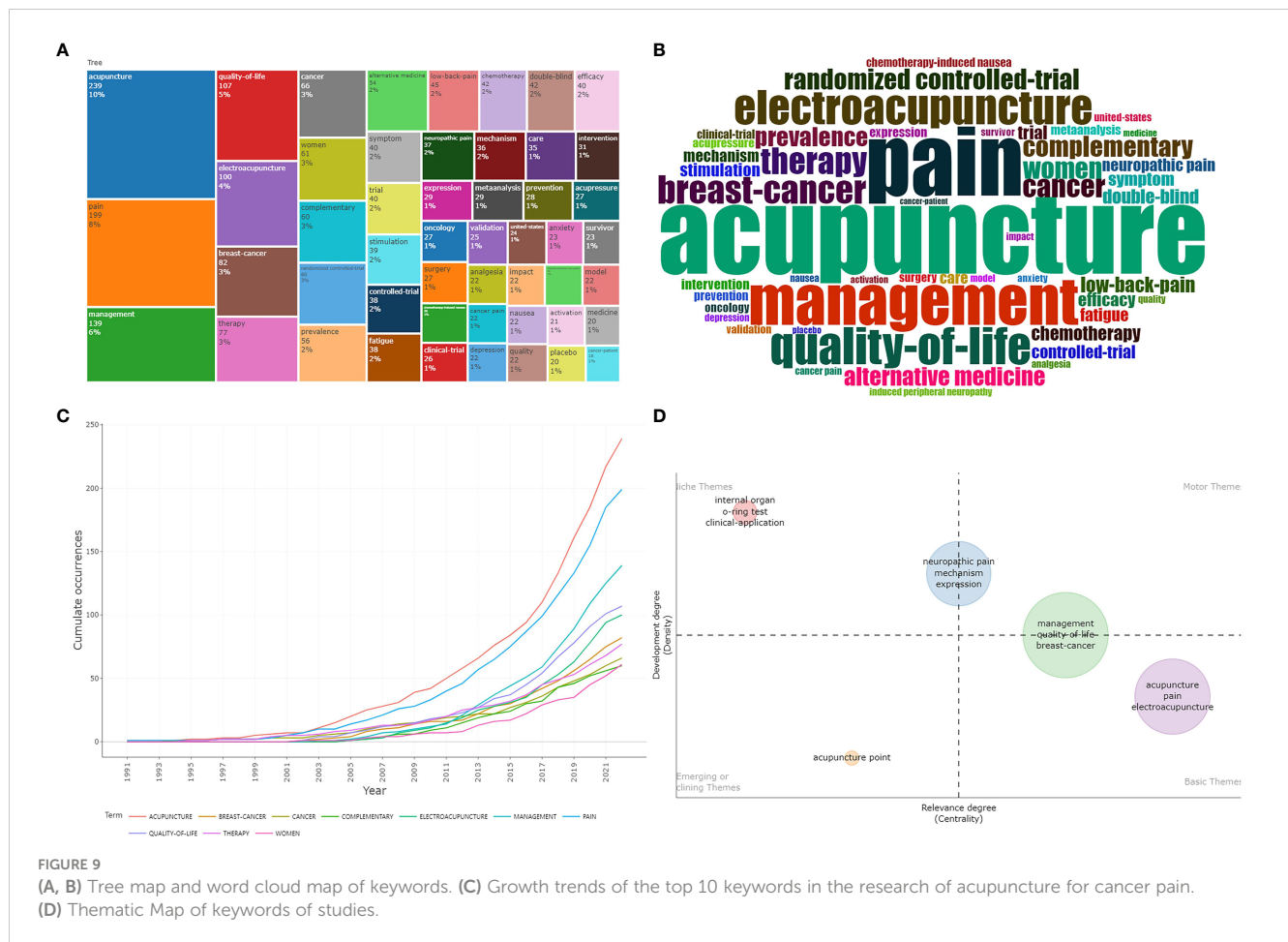


TABLE 8 Top 10 most frequently cited references related to studies on acupuncture for cancer pain.

Ranking	Frequency	Title	Author and Publication Year	DOI
1	41	Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial	Hershman DL (2018)	10.1001/jama.2018.8907
2	37	Systematic review and meta-analysis of acupuncture to reduce cancer-related pain	Chiu HY (2017)	10.1111/ecc.12457
3	33	Clinical evidence for association of acupuncture and acupressure with improved cancer pain: a systematic review and meta- analysis	He YH (2020)	10.1001/jamaoncol.2019.5233
4	29	Systematic review of acupuncture in cancer care: a synthesis of the evidence	Garcia MK (2013)	10.1200/JCO.2012.43.5818
5	23	A randomised trial of electro-acupuncture for arthralgia related to aromatase inhibitor use	Mao JJ (2014)	10.1016/j.ejca.2013.09.022
6	23	Acupuncture for cancer pain in adults	Paley CA (2015)	10.1002/14651858.CD007753.pub3
7	23	Acupuncture for chronic pain: update of an individual patient data meta-analysis	Vickers AJ (2018)	10.1016/j.jpain.2017.11.005
8	22	Acupuncture and related therapies for symptom management in palliative cancer care: systematic review and meta-analysis	Lau CHY (2018)	10.1097/MD.0000000000002901
9	21	Acupuncture and related therapies for symptom management in palliative cancer care: systematic review and meta-analysis	Alimi D (2016)	10.1200/JCO.2003.09.011
10	20	Acupuncture combined with methylcobalamin for the treatment of chemotherapy-induced peripheral neuropathy in patients with multiple myeloma	Han XY (2003)	10.1186/s12885-016-3037-z





pain in this field worldwide. More and more attention has been paid to acupuncture treatment of cancer pain. The types of cancer pain are mainly BC pain, AIA, and CIPN. The pathogenesis of acupuncture in the treatment of cancer pain remains unclear, and there is a lack of unified and recognized treatment strategies. Although the efficacy and safety of acupuncture in the treatment of cancer pain have been confirmed and recognized, the use of acupuncture points is not uniform. Acupuncture taken in different ways and evaluation methods are different, and researchers have not reached a consensus. Therefore, how to better focus on the pain status of cancer patients, integrate various auxiliary means of traditional Chinese medicine, standardize clinical operations, and care for patients' psychological health will be the direction of future research.

In conclusion, this study summarizes the data of published research papers and provides a bibliometric reference for further research in the field of cancer pain. However, the treatment of cancer pain with acupuncture still needs further exploration by scholars. Whether it is intervention mechanism, comprehensive pain assessment, management of pain crisis, or continuous care for cancer pain, it needs to be discussed and advanced. Moreover, cooperation among countries, regions, authors and disciplines can be strengthened, and more research can be done on acupuncture for cancer pain.

Limitations

There are some limitations in this study. Firstly, our retrieval time is from database inception to October 12, 2022. On the one hand, the documents before 1985 are not included in the database, and on the other hand, the database is constantly updated, which will lead to incomplete literature retrieval. Secondly, we try to use as many terms as possible as search terms, there may still be a lot of relevant terms of research may be left out, which may lead to the neglect of the latest research trends.

Data availability statement

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

Author contributions

CYL contributed to conception and design of the study. CYL and CZ collected and analyzed experimental data. CZ, MW, FRL and JJZ performed the statistical analysis. CYL wrote the paper. JWZ revised the paper for intellectual content. JWZ was responsible

for fundraising, provided administrative and material support, and supervised the study. All authors contributed to the article and approved the submitted version.

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Impact of COVID-19 pandemic on older cancer patients: Proposed solution by the International Geriatric Radiotherapy Group

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Older cancer patients are disproportionately affected by the Coronavirus 19 (COVID-19) pandemic. A higher rate of death among the elderly and the potential for long-term disability have led to fear of contracting the virus in these patients. This fear can, paradoxically, cause delay in diagnosis and treatment that may lead to a poor outcome that could have been prevented. Thus, physicians should devise a policy that both supports the needs of older patients during cancer treatment, and serves to help them overcome their fear so they seek out to cancer diagnosis and treatment early. A combination of telemedicine and a holistic approach, involving prayers for older cancer patients with a high level of spirituality, may improve vaccination rates as well as quality of life during treatment. Collaboration between health care workers, social workers,

faith-based leaders, and cancer survivors may be crucial to achieve this goal. Social media may be an important component, providing a means of sending the positive message to older cancer patients that chronological age is not an impediment to treatment.

KEYWORDS

older, cancer patients, pandemic, fear, telemedicine, spiritual treatment

Introduction

Coronavirus Disease 19 (COVID 19) is a pandemic of unprecedented and epic proportion which affects older patients disproportionately. A high rate of hospitalization and death has been reported among adults over 65 years of age (1). Among older patients who survived the infection, long-term complications such as dementia has been reported (2). Delirium during the viral infection may lead to later brain damage in this vulnerable population (3). Other studies also corroborated a higher rate of respiratory failure, fatigue, and dementia in older patients due likely to pre-existing comorbidities (4). Older cancer patients in particular, face compounded risk. They are likely to suffer a higher risk of severe illness, intensive care unit admission, mechanical ventilation, and death compared to non-cancer patients (5). Up to 28% of cancer patients admitted for COVID-19 infection died during hospital stay due to advanced age and multiple comorbidities such as high blood pressure and cardiovascular disease (6). Patients with hematologic malignancies are at a higher risk of death compared with patients with other solid tumors (7, 8). Other studies have corroborated the high mortality rate associated with old age, cancer, and COVID-19 infection (9). Thus, it is not surprising that patient fear of exposure to the virus has led to delayed diagnosis of cancer due to cancellation of diagnostic imaging procedures such as mammography or colonoscopy (10). Even though fear of virus infection was felt across the general population during the pandemic, its impact was greatest among older patients leading to anxiety and depression (11–13). Cancer patients undergoing active treatment also experienced a high level of emotional distress about the risk of infection (14). As a result, delay or avoidance of medical care increases significantly during the pandemic in the US and across the world (15). This behavior may have led to increased mortality among older cancer patients and minorities who already experience significant challenges in obtaining quality care in a reasonable time frame (16). As an international organization devoted to the care of older cancer patients, women, and minorities, the International Geriatric Radiotherapy Group (<http://www.igrg.org>) would like to propose a practical health care policy to support these vulnerable patients during the pandemic.

Pandemic fear of infection among older cancer patients

Older patients, who at higher risk for death if infected with SARS-CoV-2, expressed fear during the COVID-19 pandemic across the

globe. Using different testing scales such as the five-point fear of COVID-19 scale (FCV-19S), 44% of adults age 65 or older (n=500) admitted to fear of being exposed to the virus (12). This group of patients had preexisting comorbidities and were taking one to three medications at the survey time. Even though 98% of participants were fit, 35% suffered from loneliness, and depression. Those with a history of coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease expressed the worst fear of the virus which was compounded by social media news. In another study of 843 adults of at least 60 years of age, 28% expressed the fear of losing their lives to the virus. Their anxiety level was proportional to their age. Those who were 80 years-old or older expressed the worst fear (13). Fear of the virus is universal among older adults across the world, affecting all ethnicities (12, 17–21). The media plays a significant role in exacerbating older adults' fear (20). There was a significant correlation between fear, insomnia, and depression likely due to catastrophizing, a negative thinking style characterized by the expectation of the worst possible outcome within a situation (20–22). As a result, in one study, 81% of the participants expressed moderate to severe depression leading to a high rate of insomnia (19). Among different ethnic groups in the United States, older African Americans developed the highest fear level likely related to the odds of death if infected (23–25). Concerns about contracting the disease and fear of racial bias in testing and treatment likely compound the anxiety (26). Thus, any public policy should take into consideration the ethnic diversity and the role of socio-economic inequalities in coping with the pandemic, and provide measures that address their concerns.

Older cancer patients in particular, face dual risk. Decreased immunity, advanced age, and comorbidities significantly increase the risks of death after contracting the virus (7, 27–29). Patients with hematologic malignancies are at higher risk of death compared with those with other types of cancer (7, 29). Thus, specific recommendations are needed for this type of malignancy. Regardless of the type of cancer, patients are concerned that coronavirus infection is a more life-threatening condition than cancer. As a result, cancer patients express fear and anxiety about the risk of virus exposure and the consequences of systemic treatment on their already altered immune system (30–33). In a survey, 66% of cancer patients were alarmed by the wide community spread of COVID-19, and this was the top cause of their anxiety (30). The fear of death is compounded by the anxiety of dying alone if infected for both patients and their loved ones (31–33). In light of these fears, it is understandable that older cancer patients expressed the highest level of anxiety and depression among those surveyed (34).

Impact of COVID-19 on early cancer diagnosis

The fear of coronavirus infection has led to a significant decrease in cancer diagnosis. In a study of 82 patients with suspected breast cancer diagnosed on mammography, the rates of patients declining biopsy was 9.3% and 35.9% before and after the pandemic, respectively (35). The reason offered for refusal of the procedure was the fear of getting infected during the pandemic. In another study, the number of radiographic exams was significantly reduced during the pandemic compared with previous years, in an area affected by the pandemic. The number of radiographic exams performed was 211 in 2020 and ranged from 360 to 390 in the previous years (36). The combination of delayed biopsy procedures and radiographic exams has led to a precipitous decline in cancer diagnosis. For example, pathological diagnosis during the first six months of 2020 was reduced by 22.7% compared with the same time frame during the previous three years (37). Decreases were seen in the absolute number of pathologic specimen from all cancer sites but the lung, prostate, and gynecologic malignancies showed the steepest decline. Those three types of cancer are diagnosed with clinical exams, blood tests like PSA level, PAP smears, and radiographic exams which suggests a decline in outpatient clinic visits and/or hospital visits. Indeed, there was a significant reduction in the number of hospital visits and diagnostic procedures performed, including biopsy, colonoscopy, and mammography (38). The cancer-related hospitalization rate was reduced by 21%, and admissions were significantly reduced for all age groups. The reduction of procedures performed was 29%, 57%, and 55% for biopsies, colonoscopies, and mammograms, respectively. Other studies also corroborated a significant delay or decline in cancer diagnosis during the pandemic that was linked to a reduction in outpatient dental visits for oral cancer, and outpatient medical visits, for breast, prostate, and non-metastatic cancers, as well as various other types of cancer (39–45). Even though the decrease in cancer diagnosis was observed across all ages, individuals aged 64 or above were the most affected (42). Comparing the age groups 64 and older and younger than 64, reduction in cancer diagnosis was 35.2% and 25.2%, respectively. Another study also corroborated the significant decline in cancer diagnosis in older persons. In a multi-center cohort of 30 hospitals with specialization in the treatment of gastrointestinal cancers, the rate of cancer diagnosis in patients aged 65 or older was reduced to 42.4% and 17% during the lockdown and post lockdown period, respectively (43). This reduction in diagnosis of non-metastatic cancer in older patients is particularly worrisome because the prevalence of cancer increases with age. Early cancer diagnosis is critical to improving the survival of those vulnerable individuals with multiple comorbidities.

Zooming out to a global perspective, in Asia, delayed cancer diagnosis is often compounded by health inequalities between different socio-economic strata. In lower socio-economic strata, families are often overcrowded, with many generations living together. Older patients are at high risk of viral infection as younger family members are exposed to the virus while working full time during the pandemic (a necessity when under economic pressure). In addition, reallocation of health care workers and resources toward COVID-19 duties has further overwhelmed the

already fragile health system (46). Thus, with the onset of the pandemic, cancer screening procedures were either completely stopped or reduced to less than 25%. The number of cancer diagnosis was reduced to 54% (47). Table 1 summarizes cancer diagnosis delay during the pandemic.

In a root cause analysis of the decreased emergency room visits during the pandemic, fear of the virus was the principal cause of the patients not going to the hospital even though they had life threatening medical conditions such as myocardial infarction or stroke. The hospital was seen as a reservoir for the virus with infection spreading through coughing and aerosol-generating procedures (49). In addition, there were concerns that the hospital did not take adequate measures to protect the patients from infection. Thus, it is reasonable to postulate that older patients who may have cancer would not seek medical attention due to the fear of death from SARS-CoV-2 infection. Therefore, any proposed solution to support older cancer patients should include measures to allay their fear.

Impact of COVID-19 on cancer treatment

As a result of COVID-19 fear and/or decreased hospital admissions, the number of surgical procedures for cancer was decreased during the pandemic (38, 44). A survey of surgical oncologists across 69 European institutions revealed an average reduction of 29.3% for all types of oncologic surgery due to a reduction of outpatient clinic visits and a reduction of hospital beds or operating room availability (47). Of the physicians surveyed, 89.9% reported that fear of COVID-19 was the reason for the patients' clinic appointment cancellations. Another study (50) reported that one of the main reasons for the reduced oncologic surgical procedures was the decrease on the number of endoscopic procedures performed in older cancer patients. Compared with the previous year, only 51% of older patients underwent diagnostic endoscopies. In addition, most of older individuals underwent palliative surgery rather than curative resection which may reflect their frailty status and/or it could reflect prioritizing younger patients for treatment (50). Other studies also corroborate the reduction in cancer surgery during the COVID-19 pandemic, and the pandemic was also associated with a significant delay in surgical treatment leading to a more advanced stage at diagnosis compared with pre-pandemic years (51–53). As a result, emergency surgery and non-curative resection were performed more frequently during the pandemic (54). For various reasons ranging from COVID-19 fear to delayed elective surgery, cancer surgery for all anatomic sites was significantly reduced (47, 50–56). It is postulated that the reduction in cancer surgery was related to decreased emergency room visits due to the widespread fear of the virus. However, the issue is more complex as patients may delay treatment, and this can lead to more severe symptoms and prolonged hospitalizations due to the severity of the disease (57, 58). As an ominous sign, the decrease and/or delay of surgery for cancer patients was also associated with a delay to adjuvant treatment such as chemotherapy which may further increase mortality rate (51).

The efficacy of systemic chemotherapy depends on adherence to the treatment. Any chemotherapy postponement may lead to disease

TABLE 1 Decrease in cancer diagnosis during COVID-19 pandemic.

Study	Patient No.	Anatomic Site	Pre-COVID	Post-COVID	Reason	Country
Vanni et al. (35)	82	breast	90.7%	64.1%	Biopsy refusal	Italy
Hamilton et al. (37)	8168	all sites	4607	3561	unclear	Multiple
Fonseca et al. (38)	3, 261, 659	all sites	2, 471, 199	790, 460	Complex but virus Fear is a component	Brazil
Arduino et al. (39)	48	Oral cancer	40	8	travel restriction possible fear	Italy
Blay et al. (40)	91, 106	all sites	46, 802	44, 938	possible fear	France
Jacol et al. (41)	102, 009	all sites	54, 867	47, 142	possible fear	Germany
Coma et al. (42)	273, 379	all sites	72.8/10 ⁵	54.6/10 ⁵	Complex possible fear	Spain
Aparicio et al. (43)	3, 251	digestive	1, 866	1385	decreased endoscopy	France
Morris et al. (44)	64, 099	digestive	36, 274	27, 825	decreased endoscopy	England
Suarez et al. (45)	169	colorectal	111	58	complex possible fear	Multiple
Ranganathan et al. (48)	164, 030	all sites	112, 270	51, 760	lock down fear	India

No, number; COVID-2019, coronavirus disease 2019; NS, note specipied.

recurrence. In a study of 3661 patients who received chemotherapy on an outpatient basis, the rates of chemotherapy postponement were 11.2% and 14.2% before and after the pandemic, respectively. In patients who had chemotherapy postponement, 17.4% stated that the reason was fear of COVID-19's in light of their depressed immune system. Advanced age was the most common predictor of chemotherapy postponement (59). Importantly, among those who expressed fear and anxiety due to the virus, the introduction of telemedicine with patient education decreased the postponement rate to 4.6%, suggesting that this modality could be key to alleviating patients' anxiety and improving treatment compliance. Other studies also reported a delay or modification of chemotherapy schedule, of up to 43.6% during the pandemic (60–66). In a study of 1472 cancer patients who received treatment at a tertiary cancer center, chemotherapy was delayed or discontinued in 51.6% and 12.6% of the patients, respectively (62). Of the patients who were showing a response to therapy before the pandemic, 10.3% had disease progression, and 73% of these patients died. Older age (60+), and disease progression were risk factors for death. More patients died from cancer progression than from COVID-19 infection. Another study also highlights the impact of oncology treatment interruption on survival. Among 112 head and neck cancer patients undergoing chemotherapy either alone or combined with radiotherapy, 71 discontinued treatment during the pandemic, and 31% of these showed disease progression or death (63). Even though many factors may have influenced treatment discontinuation, in one study of patients receiving adjuvant chemotherapy for early breast cancer, old age was a significant factor influencing the decision to discontinue treatment due to the fear of getting infected with SARS-CoV-2 while undergoing chemotherapy (66). Thus, all future policy should focus on avoiding treatment interruption, while also protecting patients from COVID-19 during treatment.

Radiotherapy treatment traditionally requires a course of five to seven weeks daily treatment to be curative depending on the cancer anatomic sites and histology. Delay or discontinuation of treatment may lead to a high risk of recurrence. Because of the necessity for long treatment time, it is inevitable that due to the prolonged lock down period, cancer patients may experience delayed and/or discontinued treatment. For example, in one study of 209 cancer patients, only 46.4% completed their radiotherapy course (67). In other studies, screening of patients for viral infection during treatment may also have led to unnecessary treatment interruption as patients with low grade fever are required to stay home as a safety measure (68). Up to 88.3% of the patients experienced radiotherapy delay or interruption due to various reasons (69). Many patients experienced a treatment break of at least 45 days (70). Coronavirus infection and fear of coronavirus infection also played a part in radiotherapy disruption (71, 72). Table 2 summarizes cancer treatment delay or discontinuation during the pandemic.

It is clear that COVID-19 has affected early cancer diagnosis and has disrupted cancer treatment during the pandemic regardless of age, sex, or socio-economic status. However, the most affected were older cancer patients who, besides their fear of getting infected, also face other challenges in obtaining quality care such as social isolation, transportation difficulties, and age discrimination. While most cancer patients who contracted viral infection during the early phase of the pandemic only experienced a temporary interruption of their treatment, greater delays and modifications of treatment plans may have been considered necessary for older cancer patients (73). Thus, we propose a strategy combining modern technology such as telemedicine and spiritual support such as prayer, to improve the care of older patients during the COVID-19 pandemic, as it is very likely that the virus will remain with us in the foreseeable future.

TABLE 2 Decrease or delay in cancer treatment during COVID-19 pandemic.

Study	Treatment	Patient No.	Anatomic site	Pre-COVID	Post COVID	Reasons	Country
Morris et al. (44)	Surgery	3381	colorectal	2003	1378	reduced endoscopy	England
Xu et al. (50)	Surgery	1538	colorectal	828	710	older patients at risk for infection reduced endoscopy	China
Li et al. (51)	Surgery	8357	breast	7075	1282	quarantine	China
Choi et al. (52)	Surgery	2901	colorectal	1985	916	unclear	Korea
Metzger et al. (53)	Surgery	624	colorectal	180	121	unclear	Germany
Okuyan et al. (54)	Surgery	301	colorectal	180	121	Delay of elective Surgery, virus fear	Turkey
Guerrieri et al. (55)	Surgery	1248	genitourinary	720	528	Delay of elective surgery	Italy
Russel et al. (56)	Surgery	3889	all sites	2336	1553	Reduced surgical capacity	England
Karacin et al. (59)	Chemotherapy	3661	all sites	11.6% postponed	14.2% postponed	virus fear	Turkey
Sun et al. (60)	Chemotherapy	62	colon	unknown	50% postponed	hospital policy	China
Beypinar et al. (61)	Chemotherapy	159	lung colorectal	3.7% postponed	39.8%	hospital policy Virus fear	Turkey
Valdiviezo et al. (62)	Chemotherapy	1828	all sites	unknown	51.6% postponed 10.3% discontinued	unclear	Peru
Chen et al. (63)	Chemotherapy	117	head and neck	unknown	60.6% discontinued	Lockdown	China
Gabor et al. (64)	Chemotherapy	146	gynecologic	unknown	24.6% modification	hospital policy patient cancellation	USA
Prabhsh et al. (65)	Chemotherapy	514	Lung, CNS, urologic head and neck	unknown	16% modification	unclear	India
Gatfield et al. (66)	Chemotherapy	62	breast	unknown	16% discontinuation	Patient decision linked to old age	England
Xi et al. (67)	Radiotherapy	209	lung, breast, GI head and neck	unknown	53% discontinuation	lockdown	China
Lee et al. (68)	Radiotherapy	566	breast	6.6% interruption	8.2% interruption	COVID	Korea
Mitra et al. (69)	Radiotherapy	94	all sites	unknown	88% delay	COVID-19	India
Yu et al. (70)	Radiotherapy	140	all sites	unknown	100% discontinuation	lockdown	China
Rakici et al. (71)	Radiotherapy	195	all sites	unknown	4.6% discontinuation	COVID-19	Turkey
Koffler et al. (72)	Radiotherapy	NS	NS	8.1% discontinuation	11.3% discontinuation	unclear	USA

COVID-19, coronavirus disease 19; no, number; NS, not specified.

Potential impact of telemedicine to alleviate COVID-19 fear and for effective support of older cancer patients and their caregivers

To be effective, any measure that aims to improve older cancer patients' quality of care should include their caregivers: spouses, children, grandchildren, or friends if the patient is single. Cancer patient caregivers have to coordinate all the physicians' appointments into their work schedule, become patient advocates, provide emotional support to the patient, and manage the side effects of the

treatment such as nausea and vomiting from chemotherapy. As a result, cancer caregivers develop a high level of anxiety and depression facing a task that they are unprepared for (74). In addition, minority patients often have a higher rate of depression than Caucasians, which is likely related to a lower socio-economic status (75). They also face transportation and communication barriers with health care professionals (76). Minority patients tend to instead rely on spirituality to overcome fears and find hope, to a greater extent than other ethnic groups (77, 78). Across the world, lower socio-economic status is also associated with a higher level of mental distress and depression similar to levels in minority patients. In the time of COVID-19, prayer and faith are the coping mechanisms for

those patients. It seems logical to group them as economically disadvantaged (ED) patients to reflect the challenges that they face into obtaining quality of care.

The immediate impact of telemedicine is a reduced risk of SARS-CoV-2 infection while providing care to older cancer patients and their caregivers in the comfort of their home environment. Its real-time approach allows the patients and their caregivers active participation with the medical team which results in a high level of satisfaction (79). The Veterans Health Administration system, among the nation's largest health care system, has successfully implemented telemedicine for cancer patients (80). Both medical oncologists and radiation oncologists can conduct preliminary telehealth visit with the patients and the caregivers. Surgical oncology consultation can also be conducted virtually for low-risk procedures or in cases that require only imaging for surgical planning. If the patient is suspected to have cancer, an electronic consultation is requested by the primary care physician. The case is then reviewed by an expert or discussed through a virtual tumor board. Biopsy and further work-up can be arranged afterward. This approach is innovative because it reduces the need for transportation for patients who live in rural areas far away from medical centers. The state of Alaska also delivers a telehealth network to provide education to Native and Alaskan cancer survivors that is tailored to their culture (81). Thus, telemedicine may improve the quality of life (QOL) of minority older cancer patients and their caregivers by focusing on special aspect of their culture such as spirituality as a support mechanism.

The first message by the medical team through virtual meeting should highlight the clinic or hospital safety measures to prevent coronavirus infection such as temperature check, screening for COVID-19 exposure, personal protection equipment (PPE), full vaccination of the medical staff, a COVID-19 testing policy, and strict adherence to a clean environment. If a patient tests positive for the virus, what are the measures taken to keep the other patients safe? Those are the two main concerns expressed during a survey by patients who were afraid to seek emergency care due to the fear of the virus (49).

Once the patient and the caregiver are reassured, the medical team should introduce themselves. Ideally, the medical team should include oncologists (medical, surgical, and radiation oncologist), a geriatrician, a patient navigator, a social worker, a home health nurse, a faith-based leader, and if needed a translator for non-English speaking patients. Many telemedicine platforms are now available to provide virtual consultation with multiple health care providers at the same time for patients and their family members who may live in different states. This will give the patients and their caregivers the confidence that they will be in charge with a professional team to assess all their needs from daily transportation to spirituality. This is particularly important for ED cancer patients who often feel that their spiritual needs are not supported by their health care providers (82).

The medical team should also emphasize that the side effects that the patient may experience during treatment such as nausea, vomiting, or pain can be managed through telemedicine to avoid unnecessary visits to the emergency room which would further expose them to the virus. Caregivers' education is particularly important for older cancer patients due to their frailty and possible mental issues. Stress and anxiety should be assessed through questionnaires, and mental health referral should be initiated if needed. Patient spiritual needs can also be assessed through questionnaires. Once the patients and their caregivers are satisfied with

the initial consultation, further in-person or virtual follow-up visits can be scheduled. If a high level of religiosity is expressed by the patients and/or their caregivers, further follow-up visits can also be arranged to take place virtually with the religious representative.

Special consideration for economically disadvantaged patients and their caregivers

Compared with other socio-economic groups, ED cancer caregivers carry a higher burden in taking care of loved ones while facing many challenges such as transportation issues in getting to physician appointment or treatment sessions, lack of access to computers for disease information and education, and in the case of Latinos or other immigrant cancer patients, a language barrier (76, 83, 84). However, it has been reported that ED patients cope well with adversity through spirituality as they are traditionally very religious (77, 78, 82, 85, 86). Spirituality is defined as an individual's sense of peace, purpose, and connection to others, and beliefs about the meaning of life. In simple terms, it is a holistic belief that there is more in life than what is perceived on a sensory and physical level that connects people and the universe together. Common spiritual themes include life after death, seeking non-material happiness, and compassion for others. This aspect of their care is often overlooked by health care providers who may not be aware of cultural diversity. Thus, involvement of faith-based leaders and bilingual patient navigators in addition to health care workers, may help older ED cancer patients and their caregivers navigate through the treatment journey and improve their QOL. In contrast to the healthcare setting prevalent in the United States, in the Eastern world, spirituality, prayer, and meditation are more widely acceptable practices amongst all strata of society. The practice of prayer, meditation, and yoga, as well as other forms of spirituality have shown a definite role in reducing anxiety and improving QOL in cancer patients (87, 88). We therefore believe that inclusion of faith-based leaders in patient care is likely to be welcomed.

There is a good chance that telehealth may become widely adopted by ED older cancer patients, their caregivers, and globally. Surveys among Latinos and Africans Americans in inner cities or rural areas reveal a high level of enthusiasm for participation in telemedicine. Immediate feedback, reduced waiting time, increased access to specialists and access to multiple medical opinions are among the advantages that have been reported (89, 90). As an illustration of the popularity of telemedicine, among 10,657 adults of multiple ethnicities, Latinos and Africans Americans had a significantly higher rate of telemedicine participation than Caucasian Americans (91). Fear of COVID-19 may have accounted for the highest rate of telemedicine use among African Americans (92). A virtual environment may also be more conducive to overcoming mistrust among ED patients about discrimination by the healthcare system (92). A positive message is particularly important to encourage the COVID vaccination rate among ED cancer patients (93).

Preliminary data supports the efficacy of spiritual therapy in improving QOL in cancer patients and their caregivers, across the world (94–98). As an illustration, a randomized study of 65 breast cancer patients who underwent radiotherapy reported that those who

received spiritual therapy had significantly increased well-being as assessed by the cancer QOL C-30 and breast cancer specific questionnaire BR-23 compared with the control group (96). Even though the study was small, it highlights the impact of psychotherapy utilizing religious technique to empower the patient to attain a non-material understanding of self, universe, incidences and phenomena. Prayer reduces anxiety and help patients cope with their disease. Other studies also corroborate the importance of spiritual therapy to improve cancer patient QOL across different cultures (94, 96–98). Both cancer patients and caregivers benefit from spiritual therapy. In previous studies, cancer patients or caregivers who possess high spirituality level also enjoy better QOL, compared with those who do not, due to enhanced ability to cope with the severe distress induced by their disease (99–101). In these studies, those with a high level of spirituality are defined as those who feel the presence of God in their life and believe that God may protect and heal their suffering. This feeling was reinforced by reading of the scripture which included stories of miraculous survival in impossible circumstances (100). Thus, as ED cancer patients and their caregivers have a generally high level of spirituality, prayers conducted virtually by a faith-based leader should improve their QOL before, during, and after cancer treatment.

The feasibility of virtual based chaplaincy has been investigated in one study. In a survey of 711 cancer patients who were screened for distress level, 212 expressed a high level of spirituality. Out of those, 124 spoke on the phone with the chaplain. An in-depth survey about spirituality and chaplain intervention was conducted, and on this basis 41 patients were scheduled for further intervention either by phone (n=30), or in person (n=11) (102). Even though this study was small, it highlights efficacy of conducting spiritual therapy in a virtual mode. During the pandemic, virtual prayers were conducted successfully as a group through a Zoom or Telegram platform. Participants who experienced loneliness due to isolation and social distancing, expressed a sense of harmony and connection to others and God which helped them to cope with the pandemic stress (103). By incorporating a faith-based leader in the telemedicine team, it is feasible that cancer patients and their caregivers who express a high spiritual level may benefit from virtual spiritual therapy.

Special considerations for vaccination of older cancer patients with hematologic malignancies

COVID-19 vaccination should be recommended for older cancer patients, and in particular minorities, due to their high risk of death if infected. However, vaccine hesitancy is highest among African Americans and Hispanics. Vaccination hesitancy was 41.6% and 30.2% for African Americans and Hispanics, respectively compared with 26.3% for adult Caucasians Americans (104). The reason for vaccination hesitancy is complex but includes mistrust of the US government among other reasons (93). Thus, it is critical to promote a public health campaign about the safety and efficacy of COVID-19 vaccine to increase vaccination rate in minority cancer patients. Among those who receive vaccination, the protection rate conferred by the vaccine is not known with certainty. Even when fully vaccinated with a second boost dose, seroconversion rate in cancer patients was 88% and 70% for patients with solid tumors and

hematologic malignancies, respectively (105). However, other studies have reported a lower seroconversion rate for patients with hematologic malignancies following vaccination which may improve with a third or a fourth vaccine dose (106, 107). As those patients are at high risk of death if infected, they should avoid public exposure. The role of telemedicine is particularly important to monitor older patients with hematologic malignancies. They should take proper COVID-19 protection measures, such as social distancing and wearing an N-95 respiratory mask during clinic visits. They should also be reassured that many measures have been in place to protect them from virus exposure during their time in the clinic. Trust of the medical system is fundamental to patient adherence to treatment.

Special consideration to promote a social-media_based public campaign to reduce COVID-19 vaccine hesitancy and increase early cancer diagnosis and treatment among older cancer patients and the economically depressed population

In 1999, Ambassador Reverend Andrew Young declared in public his diagnosis of early prostate cancer to encourage young African Americans to get regular prostate cancer screening. He was treated with surgery and remains cancer-free to this day. This same time of action is needed during the COVID-19 pandemic. Public figures should follow Ambassador Reverend Young's example and promote the need for early cancer diagnosis, as cancer when caught early is curable due to advance in treatment technology. As an illustration, early stage non-small cell lung cancer has an excellent rate of local control and minimal complications among older and frail patients with stereotactic body radiotherapy who are not candidates for surgery (108). The public message should continue to allay the fear of COVID-19, be positive about the effectiveness of the vaccine, and target ED patients and older people to seek early diagnosis and cancer treatment. Most ED patients have poor knowledge of cancer symptoms and/or face barriers to access cancer screening (109, 110). Lack of education about precision medicine, unmet psychosocial needs, and financial burdens are frequently cited by ED cancer patients as barriers to accessing quality treatment (110). Thus, social media interventions if conducted properly, may be effective in reaching that specific demographic for education and reassurance that chronological age is not an impediment for cancer treatment. A meta-analysis of social media intervention reported that use of a social media platform may be an effective way to improve basic cancer knowledge, increase cancer screening rates, and alleviate psychological distress through social support (111). As an illustration, pictures of sun-damaged skin and testimony from cancer survivors are powerful ways to educate a large public audience about the risk of skin cancer and the benefit of sunscreen (112). However, it is important to have a social influencer from the same ethnic, cultural, and age group who speaks out in simple terms in order to modify the behavior of those targeted (113). Participation of individuals from diverse ethnic groups and cultures in social media such as YouTube or Facebook may be more effective because of the

sense of connection between the social influencer and their followers. There are many social media sites available, but according to the Pew Institute survey, YouTube and Facebook are the ones most predominantly used by individuals aged 65 or older (<https://www.pewresearch.org>). The current trend is very encouraging: many celebrities have opened up about their cancer diagnosis on World Cancer Day 2022, such as Karim Abdul Jabar who had chronic leukemia in 2008 and recently at the age of 73 was diagnosed with prostate cancer. Actress Jane Fonda also communicated her diagnosis of non-Hodgkin's lymphoma through Instagram at the age of 84 and has begun her chemotherapy. Her message was very positive and reflected confidence about a good outcome. We hope that more older women will be encouraged by her example to seek medical care early if cancer is suspected. The role of faith-based social influencers was illustrated in a study which encouraged ED patients to seek cancer screening. Out of 778 ED patients who were not aware of cancer risks and the needs for early cancer screening, over a third had discussed cancer screening with their primary care providers following enrollment (114). Collaboration between health communication professionals and faith-based leaders was critical in educating those patients to seek cancer screening, with potentially life-saving consequences. As an international research network dedicated to older cancer patients, minorities, and women who are frequently excluded from clinical trials, we also hope that social media will be used in the future to attract older cancer patients to participate in clinical trials. Their enrollment in prospective studies will be crucial to develop guidelines to manage this vulnerable population.

Special consideration for hypofractionated radiotherapy for older cancer patients after the pandemic

During the pandemic, many professional groups have advocated the use of hypofractionated radiotherapy to shorten the treatment course of cancer patients and to reduce the risk of exposure to the SARS-CoV-2 virus (115, 116). Given the reduced mobility of older cancer patients, preexisting comorbidities, and/or frailty, this delivery of higher biological doses of radiation within a shorter treatment time may be particularly advantageous. The reduced need for daily transportation without sacrificing treatment effectiveness is an extra incentive for ED patients. As an illustration, a once a week treatment for six weeks has been reported to be well tolerated among 486 older breast cancer patients following surgery with excellent local control and survival (117). Thus, hypofractionated radiotherapy alone or associated with systemic therapy should be investigated in future prospective studies for older cancer patients (118).

Perspective on the impact of COVID-19 on cancer mortality and future pandemics

It is clear that COVID-19 may increase the mortality rate of cancer patients regardless of age, due to delayed diagnosis and/or treatment. Many algorithms have been proposed to estimate the mortality risk

following the pandemic which is currently far from over (119, 120). On the other hand, the pandemic also highlights the plight of older cancer patients who are frequently excluded from clinical trials (121). It is a paradox that although cancer prevalence increases with age, the number of older patients recruited in cancer clinical trials is low. As an illustration, in a review of 356 cancer trials, 67.7% either impose a strict upper age limit or a criterion on performance status which would reliably exclude older adults (122). Thus, public awareness and social media exposure may have a positive impact on clinical investigators, influencing them to review and reconsider those strict criteria for older cancer patients recruitment into clinical trials. Support and education through social media about the challenges facing older cancer patients may lead to innovative solutions to help them enroll in clinical trials, as older cancer patients may be socially isolated and less computer savvy than the younger generations (123, 124). In addition thanks in large part to the pandemic, the use of telemedicine has been accepted by the public, government, and the physician community as a convenient and potentially cost-saving measure to deliver quality care at a distance (125). Thus, on the positive side, COVID-19 has provided lessons on how to prepare and protect the most vulnerable segment of our society, older cancer patients, from future pandemics.

Conclusions

Older cancer patients have suffered disproportionately during the pandemic. Their fear of death due to viral infection has led to a delay in early cancer diagnosis and treatment. We propose telemedicine combined with spiritual therapy and a strong message through social media, as a way to allay the fear of these patients. In addition, we propose the development of treatment strategies that take into consideration ethnicity and culture for personalized treatment.

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

All authors collected the data, discuss the data analysis, and review the final draft. 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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Oral health behavior and oral health service utilization among cancer patients in China: A multicenter cross-sectional study

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Purpose: Oral health plays an important role in overall health. But there is scarce information available on oral health behavior and oral health service utilization among cancer patients. This study aimed to evaluate oral health behavior and oral health service utilization among different population groups of cancer patients in China.

Methods: A multicenter cross-sectional study in three tertiary hospitals was conducted to explore the oral health behaviors and oral health service utilization of 162 cancer patients in China.

Results: We investigated a total of 162 cancer patients, 81 from urban and rural areas, respectively. The participant's ages ranged from 18 and 82 years, mean age was 44.62 years (SD = 15.72). Overall, cancer patients have poor oral health behaviors and limited oral health service utilization. There were statistically significant differences ($p < 0.05$) between urban and rural cancer patients in terms of oral health behaviors, including brushing methods, the use of fluoride toothpaste, the use of dental floss, dental caries, and bleeding gums while brushing teeth. As for oral health service utilization, there were significant differences ($p < 0.05$) between urban and rural cancer patients on regular dental cleaning, the reasons for visiting a dental clinic, and whether they took the initiative to learn about oral health.

Conclusion: The study findings suggest that cancer patients had poor oral health behaviors and limited oral health service utilization, and rural patients perform poorer than their urban counterparts. Oral health education should be provided to cancer patients to improve their oral health behaviors and oral health service utilization.

KEYWORDS

oral health behaviors, oral health service utilization, oral health, cancer patient, cross-sectional study

1 Background

Cancer is one of the major challenges facing public health and healthcare systems globally, which poses a heavy burden (1). In 2018, a total number of 18 million new cases have been diagnosed and 8.97 million deaths were attributed to cancer worldwide (1), and cancer is the leading cause of death in China (2).

As great progress has been made in the diagnosis and treatment of cancer, the cancer survival rate has increased dramatically (3), and improving the quality of life remains a unique challenge for these cancer survivors (4). Besides, the decrease in systemic immunity due to disease and treatment modalities such as surgery, radiotherapy, and chemotherapy can have profound effects on the whole and oral health (5), patients are often susceptible to periodontal diseases including periodontitis, loose teeth, tooth decay, mucositis, loss of taste, and bad breath (6). Studies have shown that the incidence of oral mucositis in cancer patients during treatment ranges from 20% to 90% (7, 8), and 37% of head and neck cancer patients experienced dental caries following radiotherapy (9). According to previous studies in other countries, the oral problems of cancer patients are not optimistic, the prevalence of oral health problems including bleeding gums, toothache, mouth ulcers experienced by cancer patients was up to 86.1% (10). More than 36% of survivors had periodontal disease and 15.9% needed dentures, which was higher than the general public, according to data from cancer survivors from Korea (11).

In addition, some studies have shown that poor oral health affects survival in head and neck cancer (12), and poor oral health may impose a financial burden on patients (10). The maintenance of good oral health care is essential for nutrition, recovery, and well-being in cancer patients (13). The impact of oral health on the quality of life of cancer patients has received increasing attention in recent years (14), and it has been demonstrated in numerous studies that oral health is influenced by oral health behaviors and the use of oral health care services (11, 15, 16). To achieve and maintain good oral hygiene, tooth brushing, flossing, and the use of fluoride toothpaste are recommended (17).

However, existing studies show that the oral health behavior of cancer patients is not optimistic (10, 11). A Korean nationwide survey showed that the percentages of cancer patients reporting flossing, mouthwash, interdental brushes, and electric toothbrushes were 17%, 20%, 15.9%, and 5.5%, respectively, and 30.8% of patients reported having an oral examination (11). The overall percentages of Chinese adults who exhibited dental flossing, mouth rinsing, and scaling were 2.6%, 10.3%, and 2.6%, respectively, and only 6.4% of them sought a dentist in the case of gingival bleeding (18). Furthermore, according to the 4th National Oral Health Survey of China (19). The prevalence of the utilization of oral health services in the past 12 months in the subject groups - 3 to 5 years, 12 to 15 years, and 35 to 74 years was 14.6%, 23.6%, and 20.1%, respectively, which is lower than the percent of 26.4% of adult Nigerians (20), and much lower than the percent of 56.2%–65.1% of American adults (21).

At present, studies on oral health mainly focus on children and the elderly in China (22, 23), while cancer patients, as a population with a high prevalence of oral diseases, deserve more attention. This study aims to investigate the oral health behaviors and oral health service utilization of cancer patients.

2 Methods

2.1 Study design

A multicentral cross-sectional study design was conducted from March 2022 to July 2022 with 162 patients aged from 18 to 82 years old that attended Xiangya Hospital of Central South University, Xiangya Second Hospital, and Xiangya Third Hospital of Central South University, Hunan, China. The three tertiary hospitals in Hunan province with an oncology department, provide comprehensive cancer treatment to thousands of patients each year. Written informed consent was obtained from the participants. The inclusion criteria, specifically, included both male and female adult cancer survivors, aged ≥ 18 years, who had no evident cognitive impairment and agreed to enroll in the study, and were able to judge independently and fill out the questionnaire. Patients with mental disorders or other serious illnesses and those who were unable to cooperate with the completion of the questionnaire were excluded.

2.2 Sampling

The sample size was estimated based on a 95% confidence level and a precision of 5%.

Since this survey is about oral health behaviors and oral health care utilization of cancer patients, and there is no domestic survey for cancer patients, we refer to the national survey data for adults (18). The overall percentages of dental flossing, mouth rinsing, scaling and dental visiting owing to gingival bleeding were 2.6%, 10.3%, 2.6%, and 6.4%, respectively. According to the principle of maximum sample size, the minimum required estimated sample for this study was calculated as 10.3%. Using the formula $n = \frac{u^2 p(1-p)}{\delta^2}$ (2), the effective response rate is calculated according to 90%, then a total sample of 157 participants was recommended for this study.

2.3 Data collection

2.3.1 Socio-demographics questionnaire

A self-reported questionnaire was used to collect information on the patient's sociodemographic characteristics, such as age, gender, place of residence, marital status, education level, monthly household income, occupational status, smoking status, alcohol consumption status, and monthly household income. We also collected their clinical characteristics information including types of diseases and the length of diagnosis, which were extracted from the electronic medical record system.

2.3.2 Oral health behavior

After reviewing literature and group discussions (24, 25), we developed an 11-item oral health behavior questionnaire, including daily brushing frequency, brushing method, brushing time, frequency of toothbrush replacement, rinsing the mouth after meals, using mouthwash, flossing, using fluoride toothpaste, whether there is caries, whether gums bleed when brushing teeth, and measures to deal with bleeding gums or swollen and painful gums. After a pre-

survey of 20 patients, the questionnaire was found to be simple and easy to understand, and it took 5-8 minutes to complete.

2.3.3 Oral health service utilization

The oral health service utilization of participants was self-reported as whether they visited the dentist in the past year (yes or no), whether regular oral examinations are performed (yes or no), whether to have regular dental cleaning (yes or no), the reasons for visiting dentist (toothache is unbearable and medication is not effective, tooth pain is still tolerable, tooth decay is found, regular checkup even without discomfort), and whether they take the initiative to learn about oral health (never, occasionally, often).

2.4 Ethical approval and informed consent

All respondents gave informed consent before conducting the interview. All methods were carried out by relevant guidelines and regulations (Declaration of Helsinki). The study protocol was approved by the College of Nursing, Central South University, Nursing and Behavioral Medicine Research Ethics Review Committee (E202295).

2.5 Statistical analysis

The data were analyzed using SPSS statistical software version 24.0 (SPSS, Central south university, China). Descriptive data for categorical variables were reported as frequency counts and percentages (%). Differences between groups were calculated using the chi-squared test. All tests of significance were carried out at a p -value <0.05. Data were presented in tables and narratives as shown in the result section.

3 Results

3.1 Subjects

In total, 200 questionnaires were distributed and 168 copies were collected. After checking and excluding 6 cases of invalid questionnaires, 162 valid questionnaires were recovered, with a valid response rate of 81.0%.

The characteristics of the participants from urban and rural areas are shown in Table 1, patients living in urban and rural areas are equally divided (81/81). Briefly, the average age of the participants was 44.62 years (SD = 15.72), more than half of them

TABLE 1 Demographic characteristics of cancer patients.

Variables	Urban n (%)	Rural n (%)	Total n (%)	Chi-square	<i>P</i> value
Gender				15.584	<0.001
Male	32 (39.5)	57 (70.4)	89 (54.9)		
Female	49 (60.5)	24 (29.6)	73 (45.1)		
Ethnicity				3.287	0.070
Han Chinese	80 (98.8)	74 (91.4)	154 (95.1)		
Ethnic Minority	1 (1.2)	7 (8.6)	8 (4.9)		
Age group(years)				2.241	0.326
18~25	17 (21.0)	10 (12.3)	27 (16.7)		
26~55	41 (50.6)	44 (54.3)	85 (52.5)		
≥56	23 (28.4)	27 (33.3)	50 (30.9)		
Education level				44.738	<0.001
Primary	5 (6.2)	21 (25.9)	26 (16.0)		
Junior Secondary	15 (18.5)	35 (43.2)	50 (30.9)		
Senior Secondary	15 (18.5)	17 (21.0)	32 (19.8)		
College	21 (25.9)	4 (4.9)	25 (15.4)		
Bachelor's and above	25 (30.9)	4 (4.9)	29 (17.9)		
Smoking				2.045	0.153
No	51 (63.0)	42 (51.9)	93 (57.4)		
Yes	30 (37.0)	39 (48.1)	69 (42.6)		
Alcohol				0.107	0.743

(Continued)

TABLE 1 Continued

Variables	Urban n (%)	Rural n (%)	Total n (%)	Chi-square	<i>P</i> value
No	51 (63.0)	53 (65.4)	104 (64.2)		
Yes	30 (37.0)	28 (34.6)	58 (35.8)		
Occupational status				27.338	<0.001
Full-time	32 (39.5)	12 (14.8)	44 (27.2)		
Unemployed	8 (9.9)	29 (35.8)	37 (22.8)		
Retired	15 (18.5)	5 (6.2)	20 (12.3)		
Other	26 (32.1)	35 (43.2)	61 (37.7)		
Marital Status				1.754	0.416
Married	56 (69.1)	63 (77.8)	119 (73.5)		
Unmarried	21 (25.9)	16 (19.8)	37 (22.8)		
Divorced or widowed	4 (4.9)	2 (2.5)	6 (3.7)		
Sleeping status				3.002	0.223
Good	36 (44.4)	27 (33.3)	63 (38.9)		
Fair	35 (43.2)	46 (56.8)	81 (50.0)		
Poor	10 (12.3)	8 (9.9)	18 (11.1)		
Monthly household income (RMB)				34.399	<0.001
≤2000	11 (13.6)	41 (50.6)	52 (32.1)		
2000~5000	21 (25.9)	23 (28.4)	44 (27.4)		
5000~10000	35 (43.2)	15 (18.5)	50 (30.9)		
≥10,000	14 (17.3)	2 (2.5)	16 (9.9)		
Economic pressure				39.534	<0.001
None	18 (22.2)	2 (2.5)	20 (12.3)		
Lighter	17 (21.0)	5 (6.2)	22 (13.6)		
Fair	28 (34.6)	21 (25.9)	49 (30.2)		
Heavy	14 (17.3)	30 (37.0)	44 (27.2)		
Cancer type				7.065	0.422
Lung cancer	6 (7.4)	12 (14.8)	18 (11.1)		
Breast cancer	3 (3.7)	4 (4.9)	7 (4.3)		
Nasopharyngeal Cancer	8 (9.9)	9 (11.1)	17 (10.5)		
Oral Cancer	10 (12.3)	15 (18.5)	25 (15.4)		
Bone Tumor	21 (25.9)	22 (27.2)	43 (26.5)		
Glioma	12 (14.8)	7 (8.6)	19 (11.7)		
Lymphoma	8 (9.9)	4 (4.9)	12 (7.4)		
Other	13 (16.0)	8 (9.9)	21 (13.0)		
Time since diagnosis(years)				0.259	0.879
≤1	53 (65.4)	54 (66.7)	107 (66.0)		
1~5	18 (22.2)	19 (23.5)	37 (22.8)		
≥5	10 (12.3)	8 (9.9)	18 (11.1)		

The significance level was set at 0.05. All statistically significant ones have been marked in bold.

were male (54.9%), and 53.1% of the participants had obtained senior high education; 73.5% were married, and only 27.2% were employed. The study sample predominantly comprised patients suffering from bone tumor (26.5%) and oral cancer (18.5%). In addition, 66% of cancer patients enrolled in the study were newly diagnosed within 1 year. Ethnicity, smoking, alcohol, marital status, sleeping status, cancer type, and time since diagnosis was similar between urban and rural cancer patients. However, there were significant differences ($p < 0.05$) between gender, education level, occupational status, monthly household income, and economic pressure between the two groups. Compared to urban areas, rural areas have more men than women. Generally, patients in rural areas tend to be less educated, unemployed, and have lower monthly incomes, as well as facing more financial struggles.

Table 2 shows the oral health behaviors among urban and rural cancer patients. Statistically significant differences were found between rural and urban cancer patients in brushing methods, dental flossing, fluoride toothpaste, and self-reported dental caries ($p < 0.05$). The majority of respondents (75.3%) brush their teeth twice or more daily, and more than half of patients (59.3%) brush with no fixed method. Up to 74.7% of patients do not floss, with more participants in rural areas than in cities. Over half of the patients (59.3%) are not aware of fluoride toothpaste. About one-third (30.9%) of the participants self-reported having dental caries, 32.1% of the respondents indicated that they were not sure if they had dental caries, and 37% of the patients self-reported having no dental caries.

Table 3 below shows the oral health service utilization between urban and rural cancer patients. There were statistically significant

TABLE 2 Oral health behaviors between urban and rural cancer patients.

Variables	Urban n (%)	Rural n (%)	Total n (%)	Chi-square	P value
Daily brushing frequency				2.124	0.547
0	1 (1.2)	4 (4.9)	5 (3.1)		
1 time	17 (21.0)	18 (22.2)	35 (21.6)		
2 times	54 (66.7)	49 (60.5)	103 (63.6)		
More	9 (11.1)	10 (12.3)	19 (11.7)		
Brushing method				12.722	0.005
Brush horizontally	9 (11.1)	27 (33.3)	36 (22.2)		
Brush vertically	20 (24.7)	11 (13.6)	31 (19.1)		
Brush in a circle	11 (13.6)	11 (13.6)	22 (13.6)		
No fixed method	41 (50.6)	32 (39.5)	73 (45.1)		
Brushing time				1.222	0.543
1 minute or less	10 (12.3)	15 (18.5)	25 (15.4)		
2 minutes	41 (50.6)	37 (45.7)	78 (48.1)		
≥ 2 minutes	30 (37.0)	29 (35.8)	59 (36.4)		
Frequency of toothbrush replacement				2.109	0.550
Never	9 (11.1)	12 (14.8)	21 (13.0)		
Semi-annually	14 (17.3)	16 (19.8)	30 (18.5)		
2~3 months	46 (56.8)	37 (45.7)	83 (51.2)		
1 month	12 (14.8)	16 (19.8)	28 (17.3)		
Rinsing the mouth after meals				6.004	0.111
Never	33 (40.7)	46 (56.8)	79 (48.8)		
1 time per day	16 (19.8)	13 (16.0)	29 (17.9)		
2 times a day	16 (19.8)	7 (8.6)	23 (14.2)		
≥3 times a day	16 (19.8)	15 (18.5)	31 (19.1)		
Use mouthwash				0.121	0.727
No	57 (70.4)	59 (72.8)	116 (71.6)		

(Continued)

TABLE 2 Continued

Variables	Urban n (%)	Rural n (%)	Total n (%)	Chi-square	P value
Yes	24 (29.6)	22 (27.2)	46 (28.4)		
Flossing				7.347	0.007
No	53 (65.4)	68 (84.0)	121 (74.7)		
Yes	28 (34.6)	13 (16.0)	41 (25.3)		
Use fluoride toothpaste				12.254	0.002
Yes	22 (27.2)	22 (27.2)	44 (27.2)		
No	11 (13.6)	29 (35.8)	40 (24.7)		
Don't know	48 (59.3)	30 (37.0)	78 (48.1)		
Whether there is caries				7.356	0.025
Yes	27 (33.3)	23 (28.4)	50 (30.9)		
No	22 (27.2)	38 (46.9)	60 (37.0)		
I don't know	32 (39.5)	20 (24.7)	52 (32.1)		
Gums bleed when brushing teeth				1.229	0.268
No	39 (48.1)	32 (39.5)	71 (43.8)		
Yes	42 (51.9)	49 (60.5)	91 (56.2)		
When brushing bleeding or gums are swollen and painful				5.729	0.126
No treatment needed	43 (53.1)	55 (67.9)	98 (60.5)		
Go back to the dentist when you have time	17 (21.0)	14 (17.3)	31 (19.1)		
Seek immediate medical care	10 (12.3)	3 (3.7)	13 (8.0)		
Take medication or other	11 (13.6)	9 (11.1)	20 (12.3)		

The significance level was set at 0.05. All statistically significant ones have been marked in bold.

differences ($p < 0.05$) between urban and rural cancer patients in reasons for regular dental cleaning, dental visiting, and taking the initiative to learn about oral health.

A majority of patients (80.9%) didn't visit the dentist in the past year, patients who didn't have a regular oral examination and dental cleanings each accounted for 78.4%, and most of the reasons for visiting the dentist were toothache (66.7%), only 20% of patients reported regular dental cleanings, the percentage of a dental cleaning in urban areas and rural areas are 28.4% and 14.8%, respectively. More than half (60.5%) of patients self-reported that they occasionally took the initiative to learn about oral health.

Table 4 shows the results of binary and multivariate logistic regression analyses of outcomes variables (i.e., oral health behaviors and oral health service utilization) across urban and rural cancer patients controlling for demographics. For the binary outcome variables, a binary logistic regression analysis was performed; otherwise, a multivariate logistic regression analysis was performed. Regarding the method of brushing teeth, there is an urban-rural disparity ($p=0.01$) with 50.6% of urban patients reporting no fixed method of brushing teeth compared to 39.5% for rural patients. As for flossing, there is an urban-rural disparity ($p=0.08$) with 34.6% of urban patients reporting flossing compared to 16.0% for rural patients. When it comes to fluoride toothpaste,

there is an urban-rural disparity ($p=0.042$) with 39.5% of urban patients reporting not sure whether it is fluoride toothpaste compared to 24.7% for rural patients. An urban-rural disparity also emerged for dental caries. More rural patients than urban patients reported no dental caries. Concerning dental cleaning, 28.4% of urban patients reported regular dental scaling compared to 14.8% of rural patients.

4 Discussion

This study examined oral health behavior and oral health utilization among cancer patients in China. Despite nationally stated goals to reduce oral health disparities, our study confirms a persistent gap between urban and rural cancer patients. We found that rural cancer patients were more likely to deliver poor oral health behaviors and have limited oral health utilization compared to rural cancer patients. These findings suggest the need for better strategies to improve oral health for both urban and rural cancer patients.

Numerous studies have shown that proper brushing, appropriate use of dental care products, and regular dental checkups are the main ways to maintain oral health (24, 26). The

TABLE 3 Oral health service utilization between urban and rural cancer patients.

Variables	Urban n (%)	Rural n (%)	Total n (%)	Chi-square	P value
Visited the dentist in the past 12 months				0.359	0.549
No	64 (79.0)	67 (82.7)	131 (80.9)		
Yes	17 (21.0)	14 (17.3)	31 (19.1)		
Regular oral examination				1.786	0.181
No	60 (74.1)	67 (82.7)	127 (78.4)		
Yes	21 (25.9)	14 (17.3)	35 (21.6)		
Regular dental cleaning				4.410	0.036
No	58 (71.6)	69 (85.2)	127 (78.4)		
Yes	23 (28.4)	12 (14.8)	35 (21.6)		
Reasons for visiting the dentist				10.206	0.037
Never	14 (17.3)	26 (32.1)	40 (24.7)		
Toothache is unbearable and medication is not effective	28 (34.6)	27 (33.3)	55 (34.0)		
Tooth pain is still tolerable	26 (32.1)	22 (27.2)	48 (29.6)		
Tooth decay is found	5 (6.2)	5 (6.2)	10 (6.2)		
Regular checkups even without discomfort	8 (9.9)	1 (1.2)	9 (5.6)		
Take the initiative to learn about oral health				12.702	0.002
Never	24 (29.6)	45 (55.6)	69 (42.6)		
Occasionally	49 (60.5)	34 (42.0)	83 (51.2)		
Often	8 (9.9)	2 (2.5)	10 (6.2)		

The significance level was set at 0.05. All statistically significant ones have been marked in bold.

results of this study showed that 74.6% of cancer patients brushed their teeth twice a day or more, which is much than the ratio of 36.1% of middle-aged people revealed in the fourth national survey of China (16), and higher than the percent of 66.2% of Peruvian adults (24), but less than the percent of 83.7% of a survey in Korea cancer patients (11). Although most oncology patients can brush their teeth twice a day or more, it is worth noting that there were large differences in brushing methods, with 24.6% choosing horizontal brushing, 16.4% choosing vertical brushing, only 13.4% choosing rotary brushing, and nearly half (45.5%) not having a fixed brushing method. Correct and proper brushing method helps to control plaque to maintain good oral hygiene, thus largely preventing or controlling caries and periodontal disease (27). The modified Bass brushing method or the vertical brush rotation method is recommended by dental specialists (28, 29). In addition, those who could brush for two minutes or more each time accounted for 84.4%. Most patients (51.2%) change their toothbrushes every two to three months, 18.5% of patients changed their toothbrushes every six months, while there were 13% of the patients never changed their toothbrushes, the results were similar to a previous survey of Pakistani medical students (30).

The “Chinese Residents’ Guide to Oral Health Behavior” manual for health care professionals recommends the use of

comprehensive oral cleaning behaviors including brushing, rinsing, and flossing to maximize plaque removal and control plaque growth [15]. The awareness and utilization of oral health care products, except for the most basic toothbrush and toothpaste, the behaviors of rinsing the mouth, using mouthwash, flossing, and using fluoride toothpaste are limited. Nearly half of the patients (48.8%) never rinse their mouth after meals, and only 28.4% of patients choose to rinse with mouthwash, which was much lower than the ratio of 47% of the Swedish adult population (31). Studies have shown that a mouth rinse administered intraorally causes salivary and mouth rinse properties to change, and the changes in those factors can affect preventive and therapeutic effects, as well as oral health (32). Researchers have shown that dentist recommendations play an important role in mouthwash use, so dental professionals should play a greater role in advising patients who need to use mouthwash to pick the most appropriate product (31).

Flossing is the use of threads made from synthetic fibers to clean plaque and food debris from the adjacent surfaces of teeth and interdental spaces, but our study showed that only 25.3% of patients flossed, and there was an urban-rural difference, with a much lower percentage of patients from rural areas flossing than those from urban areas. Previous studies have shown that flossing is influenced by flossing self-efficacy (33, 34), so patients should be encouraged to

TABLE 4 Binary and multivariate logistic regression analyses of oral health behaviors and oral health service utilization across urban and rural cancer patients controlling for demographics.

Independent variable		β	SE	β'	P	EXP (B)	OR value	
							Upper limit	Lower limit
Brushing method	Brush vertically	1.312	0.708	3.433	0.064	3.715	0.927	14.890
	Brush in a circle	1.479	0.766	3.728	0.054	4.391	0.978	19.713
	No fixed method	1.534	0.598	6.572	0.010	4.634	1.435	14.968
Flossing		1.016	0.382	7.067	0.008	2.763	1.306	5.847
Fluoride toothpaste	No	-0.278	0.604	0.211	0.646	0.758	0.232	2.475
	I don't know	1.050	0.517	4.126	0.042	2.858	1.038	7.874
Dental caries	No	-1.068	0.529	4.073	0.044	0.344	0.122	0.970
	I don't know	0.353	0.531	0.442	0.506	1.423	0.503	4.029
Dental Cleaning		0.824	0.398	4.285	0.038	2.280	1.045	4.976
Dental visiting	Toothache is unbearable and medication is not effective	-0.510	0.575	0.785	0.376	0.601	0.195	1.855
	Tooth pain is still tolerable	-0.685	0.603	1.293	0.255	0.504	0.155	1.642
	Tooth decay is found	0.838	0.867	0.934	0.334	2.311	0.422	12.643
	Regular checkups even without discomfort	2.108	1.237	2.904	0.088	8.232	0.729	92.971
Take the initiative to learn about oral health	Occasionally	-0.095	0.442	0.046	0.830	0.909	0.383	2.161
	Often	0.909	0.989	0.846	0.358	2.483	0.357	17.248

The significance level was set at 0.05. All statistically significant ones have been marked in bold.

floss and strategies to overcome barriers should be discussed by dental professionals.

Although it is recognized that fluoride toothpaste can greatly reduce the incidence of dental caries (35), it is surprising that nearly half of the patients (48.1%) did not know whether the toothpaste used as fluoride toothpaste or not, and unexpectedly, it is also surprising that the urban patients were less aware of fluoride toothpaste than the rural patients. About one-third (30.9%) of the participants self-reported having dental caries, 32.1% of the respondents indicated that they were not sure if they had dental caries, and another 37% of the patients self-reported having no dental caries. However, the Fourth National Oral Health Survey (2015-2016) in mainland China (36) showed that the periodontitis rates of adults were 52.8%~69.3%, and the prevalence of dental caries among Chinese preschool children was as high as 62.5% (37), and a systematic review shows that the caries rate has been gradually increasing in recent years, from 36.4% in the 1980s to 53.1% in 2010s (38). However, despite the high incidence of dental caries and periodontal disease, only a minority of residents seek treatment, which remains a problem that needs to be addressed (39). Since the use of fluoride toothpaste is one of the important ways to prevent caries (35), it is still necessary to increase the awareness and usage of fluoride toothpaste.

More than half of the patients (56.2%) experienced gums bleeding when brushing their teeth. The prevalence of self-

reported gingival bleeding is consistent with previous studies, with a survey of adults in Hong Kong (15) showing a prevalence of 62.2% and a survey of adolescents aged 12-15 years in Jiangxi showing an incidence of 66.5% (40). However, most patients (60.5%) believe that bleeding gums or swollen gums do not need to be treated, nearly one-fifth (19.1%) of the patients chose to delay medical treatment, and 12.3% of them chose to take their medication or other, only 8% of patients would seek immediate medical care. Although there is no statistical difference, we can see that the incidence of gingival bleeding during tooth brushing is higher in rural patients than in urban patients. The difference may originate from their lack of knowledge about oral health, so they didn't realize that gum bleeding may be a symptom of other systemic diseases. Bleeding gums are an early sign of periodontal disease, and its association with periodontal health has been studied extensively in the literature (41). Patients with bleeding gums should receive advice and encouragement from professionals, especially if they have a visible periodontitis infection, poor dental awareness or behaviors, and a poor lifestyle. This will allow them to take action and improve their gum health.

Regarding the utilization of oral health care services, our survey showed that only 19.1% of patients visited the dentist in the past 12 months, which is consistent with the percentage of 20.1% of the 4th National Oral Health Survey of China (19), and 80.9% of patients did not visit the dentist in the past 12 months, which is higher than that of

69.2% of cancer patients in Korea (11). Overall, the patients who didn't have regular oral examinations and dental cleanings each accounted for 78.4%. Although participants from urban areas performed better on dental scaling behavior than those from rural areas, none of them achieved the desired level. This reason may stem from differences in economic and medical resources between rural and urban areas, and the survey in this study also showed that participants in rural areas generally had lower economic income and education, who did not place enough emphasis on oral health had a significant lack of understanding of oral health. A prospective longitudinal study showed that regular dental cleanings prevented tooth loss in older adults (42) and that early and consecutive dental scaling prevents the development of Parkinson's disease (43). Nevertheless, a study in Brazil (44) showed that the implementation of a national dental scaling policy could indeed increase the rate of scaling among the population but would exacerbate the disparity in socioeconomic inequalities in dental scaling, and therefore universal dental coverage should be considered.

As for the reasons for visiting a dentist, only 5.6% had regular checkups without discomfort, which is lower than the percentage of 19% of a survey of older Chinese and much lower than the percentage of 71.6%~77% of adults in America (21), and there is an urban-rural disparity (45). This may be explained by the fact that dental care is mostly excluded from healthcare coverage in China (45), which means more financial stress for oral health, and compared to oral health, cancer patients are more concerned about the effect of cancer treatment modalities and its effects (46). In addition, perhaps patients have little knowledge of oral health care and a low willingness to take care of oral health, which affects oral health practices (47). Regular dental visits and routine prevention may offer more opportunities for oral health education and reinforcement, which may improve oral health. Since rural cancer patients visit the dentist less, this highlights the importance for dentists to view each visit as a teachable opportunity to promote positive oral health behaviors and improve their knowledge about oral health.

Our survey showed that the majority of patients went to the dentist because of oral discomfort (59.8%), especially swollen and sore gums (59.6%), which is consistent with a survey of adults in Peru (25), but much higher than the ratio of 23%~28.4% of American adults (21). Only 5.6% of patients were able to have regular oral examinations, even without uncomfortable symptoms, which indicated that most of them chose to respond negatively to oral problems and might seek treatment in uncomfortable situations. The survey results suggested that oral health education for cancer patients should focus on guidance on developing good habits of regular dental visiting, and actively seeking medical treatment.

In terms of taking the initiative to learn about oral health-related knowledge, 42.6% of patients never learned, 51.2% learned occasionally, and only 6.2% thought they took the initiative to learn it frequently, indicating that, to some extent, the awareness and behavior of oral health care of cancer patients in China are poor, and do not pay enough attention to oral health. Since it plays an important role in oral health, it is imperative to enhance their knowledge of oral health.

Overall, this study indicates that oral health behaviors among cancer patients, especially those living in rural areas, need to be

improved, besides, basic oral hygiene habits, knowledge and use of oral health care products, utilization of oral health care services, and awareness of oral health knowledge still need to be enhanced.

5 Limitations

This study is not without limitations. Firstly, due to the cross-sectional nature of the study, cause and consequence cannot be distinguished. Besides, self-rated oral health questionnaires may be affected by recall bias, and the study used a convenience sample of three large general hospitals in Hunan, all of them running under the same management umbrella. The results might have been different if the other organizations had been involved in the study. Furthermore, the study was conducted in the oncology wards without including cancer survivors in the home recovery period, so conclusions should be taken with caution. Moreover, it is worth noting that some oncology patients, especially those with head and neck tumors, rinse their mouths or brush their teeth during radiotherapy under medical prescription, which may be different from their oral health habits previously, or due to the impact of some specific oncology treatment modalities on oral complications such as oral mucositis, oral pain, and dry mouth, among them especially in head and neck radiotherapy patients and other oncology chemotherapy patients, which may affect their daily oral health behaviors. Finally, many factors affect individual health behaviors, and the association and difference between oral health awareness and practical behaviors should be considered, and this study did not investigate the overall health status of patients.

6 Conclusion

This study found that cancer patients, both urban and rural patients have poor oral health behaviors and limited oral health service utilization. In some aspects, patients in rural areas performed worse oral health behaviors. Furthermore, many patients never visited the dentist, only a minority of patients have regular dental cleanings or oral exams. Therefore, oral health education should be provided to cancer patients and their caregivers, and oral health assistance and oral assessment should be provided to patients with poor oral health awareness and oral health status to improve their oral health awareness and behavior.

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 the study protocol was approved by the College of

Nursing, Central South University, Nursing and Behavioral Medicine Research Ethics Review Committee (E202295). The patients/participants provided their written informed consent to participate in this study.

Author contributions

RA and WC were responsible for the conception and design of the study. RA, ZW, and ML performed the data collection. RA and ML carried out the analysis of the data and the interpretation of the results. RA drafted the manuscript, with Muhammad Sohaib and WC providing critical revisions. All authors contributed significantly, and read and approved the final manuscript.

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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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Why is advance care planning underused in oncology settings? A systematic overview of reviews to identify the benefits, barriers, enablers, and interventions to improve uptake

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Background: Advance care planning (ACP) centres on supporting people to define and discuss their individual goals and preferences for future medical care, and to record and review these as appropriate. Despite recommendations from guidelines, rates of documentation for people with cancer are considerably low.

Aim: To systematically clarify and consolidate the evidence base of ACP in cancer care by exploring how it is defined; identifying benefits, and known barriers and enablers across patient, clinical and healthcare services levels; as well as interventions that improve advance care planning and are their effectiveness.

Methods: A systematic overview of reviews was conducted and was prospectively registered on PROSPERO. PubMed, Medline, PsycInfo, CINAHL, and EMBASE were searched for review related to ACP in cancer. Content analysis and narrative synthesis were used for data analysis. The Theoretical Domains Framework (TDF) was used to code barriers and enablers of ACP as well as the implied barriers targeted by each of the interventions.

Results: Eighteen reviews met the inclusion criteria. Definitions were inconsistent across reviews that defined ACP (n=16). Proposed benefits identified in 15/18 reviews were rarely empirically supported. Interventions reported in seven reviews tended to target the patient, even though more barriers were associated with healthcare providers (n=40 versus n=60, respectively).

Conclusion: To improve ACP uptake in oncology settings; the definition should include key categories that clarify the utility and benefits. Interventions need to

target healthcare providers and empirically identified barriers to be most effective in improving uptake.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?](https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288825), identifier CRD42021288825.

KEYWORDS

advance care planning (ACP), barriers and enablers, healthcare provider (HCP), improving uptake, patient-centered care, theoretical domains framework

Introduction

A recent international consensus definition for advance care planning (ACP) states that ACP is “the ability to enable individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and healthcare providers, and to record and review these preferences if appropriate” (1). Ultimately the goal of ACP is to align the treatment a person receives with their preferences for care (2). Despite practice guidelines recommending ACP for people with cancer, results from the Australia National Advance Care Directive Prevalence study (2017) suggested that only 27% of people with cancer had documented their ACP preferences in an advance care directive (3). This finding is consistent with low rates of ACP discussion and documentation reported internationally (4–6).

In Australia, the terms used in advance care planning differ by state. Nationally, the term ‘substitute decision maker’ is used to denote the person who makes medical decisions if a person loses medical decision-making capacity. ‘Advance care directive’ is the umbrella term for documents expressing the person’s preferences for future health care in the event that they lose medical decision-making capacity. Internationally there is considerable variation in terminology used for ACP. However, the principles of appointing a surrogate decision maker, having conversations about preferences and values, and recording a written advance care directive are generally applicable. In the USA, physician orders such as Do Not Attempt Resuscitation (DNAR) are included in ACP documentation (1). In Europe, concepts and laws regarding ACP differ, with some countries having legally binding frameworks and others not (1). Some examples from English-speaking countries and Europe are presented in [Supplementary File 1 \(Advance care planning terms of reference\)](#). Often, laws regarding ACP are made at a state or provincial, rather than at a national, level. The lack of consistency in terms and definitions used can be confusing for patients and health providers.

Literature proposes a range of benefits of ACP across various populations. However, it is uncertain from the literature on cancer patients if proposed benefits of ACP have been empirically identified. Studies have found that the values and needs of cancer patients in response to ACP are different to other patient populations (7). For example, patients with cancer placed greater emphasis on decisions on their preferences for site or care rather

than intervention-based treatment decisions (7). Also unknown from the literature is whether interventions to support uptake of ACP are targeting the most frequently reported barriers and enablers of ACP, and if so are they effective in improving uptake.

With several published reviews identifying barriers to ACP (8–10) and interventions to support uptake of ACP (11, 12), the aim of this overview of reviews is to clarify and consolidate the evidence base in oncology settings to inform recommendations for improving uptake of ACP. This overview took a systematic approach to searching, appraising, and synthesizing the review literature to address the following research questions (13):

1. How has advance care planning (ACP) been defined and what are the included elements?
2. What are the proposed and empirically supported benefits of ACP in oncology settings?
3. What are the known barriers and enablers of ACP uptake across patient, clinician, healthcare service, and systems levels?
4. Which interventions to improve ACP uptake have been reported, do they target the identified barriers and enablers, and how effective are they?

Methods

This systematic overview of reviews used a standardized protocol prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (14). The protocol was registered with Prospero; registration number: CRD42021288825 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021288825).

Search strategy

The search was conducted by one author (LG) using databases PubMed, Medline, PsycInfo, CINAHL, and EMBASE. Papers were restricted to reviews published in English, within a 10-year publication date range from 2011 to August 4, 2021. The search strategy was designed in collaboration with an expert librarian and

critically discussed by the research team, capturing terms and synonyms relating to three domains: “advance care plan”, “cancer” and “review”. A full list of search terms is provided in [Supplementary File 2](#).

Inclusion and exclusion criteria

A review was included in this systematic overview of reviews if it fulfilled all the following inclusion criteria: (1) published in a peer-reviewed journal; (2) English language; (3) reported only on the populations of interest: adult cancer patients of any gender, healthcare providers responsible for facilitating ACP with adult cancer patients, or family or caregivers of adult cancer patients; and (4) reported on ACP using any definition from the perspectives of patients, healthcare professionals, or staff at hospital service or system levels. We excluded an article if it: (1) reported on a pediatric cancer population; (2) focused on community settings; or (3) did not address at least one of the research questions.

Screening and selection of the literature

All identified reviews were uploaded to EndNote (15) and imported into Covidence (16) to manage citations and remove duplicates. Following de-duplication, two authors (LG and SF) screened identified articles to determine eligibility for inclusion. Screening occurred in two steps: an initial screen of titles and abstracts against the eligibility criteria, and a further step of retrieving the full paper if eligibility could not be confirmed from the abstract. Screening involved judging each review as either: eligible, not eligible, or potentially eligible. Conflicts were resolved initially through discussion (LG and SF) and presented to the research team for final resolution. All differences of opinion were resolved by consensus.

Data extraction and analysis

Data extraction templates were designed to enable extraction of all data addressing the research questions and to facilitate consistency of extraction across studies and reviewers. For all reviews that met the inclusion criteria, data extraction was conducted by one author (LG), with 20% of the reviews crosschecked by a second author (SF).

Content analysis (17, 18) and narrative synthesis (19) were used to organise and summarise ACP definitions (research question 1), and the proposed and empirically supported benefits of ACP (research question 2). Proposed benefits were those that formed part of the rationale of an included review, and empirically identified benefits, were those that reported measured outcomes of ACP. These analyses were conducted by one author (LG) and reviewed by a second author (AH or KG).

Reported barriers and enablers of requesting and recording ACP details from a healthcare professional perspective, or deciding

and communicating ACP details from a patient perspective were coded into the Theoretical Domains Framework (TDF) (20) (research question 3). This framework was developed to synthesise 33 theories of behaviour, to provide a theory-informed basis for identifying barriers and enablers of behaviour (21, 22). The thematic analysis was conducted by one author (LG) and reviewed by a second author (JF). Identified themes were assessed against previously published ‘importance criteria’ to determine the likely importance and role of each domain in influencing behaviours related to ACP (23). These criteria were: frequency (number of reviews that identified each domain; elaboration (number of content themes identified in each domain); and ‘expressed importance’ (statement from the authors expressing importance in relation to ACP uptake).

Content analysis (17, 18) was used to organize and summarise the details of the interventions such as the various forms of delivery and intervention content. The implied barriers targeted by each of these interventions were coded to the Theoretical Domains Framework domains. For example, educational interventions imply that lack of knowledge is a barrier, whereas communication skills training implies that lack of skills or lack of confidence to discuss ACP are barriers, even if these assumptions are not explicit. This analysis was conducted by one author (LG) and reviewed by another author (JF). We also report on evidence of effectiveness of these interventions for improving documentation of ACP (research question 4).

Quality assessment

The Joanna Briggs Institute (JBI) critical appraisal assessment checklist for systematic reviews was used to assess the methodological quality of the systematic and scoping reviews included in this overview of reviews. This checklist consists of 10 items that address methodological characteristics of a review article including: appropriateness of search strategies, potential sources of bias, and prospects for future research and policy-making (24). Each item is scored as 1 (*met*) or 0 (*not met, unclear, or not applicable*) with item scores summed to calculate an overall score. Studies scoring 0–4, 5–7 and 8–10 points were categorized as low, medium, and high quality, respectively, as described by Hossain et al. (25).

The methodological quality of narrative reviews included in this overview was assessed using the Scale for the Quality Assessment of Narrative Review Articles (SANRA) tool. The SANRA is a 6-item scale whereby each item is scored as 0 (*low quality*) to 2 (*high quality*), with item scores then summed; hence, the range of overall quality scores is 0–12. (Reviews scoring ≥ 9 are classified as high quality) (26).

All quality assessments were conducted by one reviewer (LG), with a second reviewer (SF) independently assessing a random selection of 20%. Minor differences in assessment were identified and discussed to reach consensus, or discussed with a third author (KG or MT). Reviews were not excluded based on quality assessment scores but any findings from reviews that received low scores were noted.

Results

Search results

A total of 478 records from MEDLINE (n=56), PubMed (n=208), PsycInfo (n=27), CINAHL (n=92) EMBASE (n=95) were identified across all searches. Of these, 210 duplicates were removed. Following review of titles and abstracts, 29 records met the eligibility criteria and were retained for full text review. A further 11 records were excluded at initial full-text review, resulting in 18 records (12, 27–43) being included in the analysis (Figure 1).

Characteristics of included reviews and quality appraisal

The included reviews consisted of systematic reviews (n=6), scoping reviews (n=3) and narrative reviews (n=9), published from 2011 to August 4, 2021, with more than half of these in the period 2018–2020. The majority used mixed-methods with only four using purely quantitative methods. The reviews mostly included both patients and healthcare providers (n=10), with seven reviews involving patients only and one review of healthcare providers only.

All systematic reviews included in this overview were appraised as high quality. The three scoping reviews, also assessed using the JBI checklist, were appraised as low (n=1), medium (n=1), and high quality (n=1). The main criteria leading to low scores included unclear search strategy, poorly defined or missing inclusion criteria, and no appraisal of included studies, which is likely due to a lack of standardized reporting for scoping reviews whereby these details are often omitted (44).

SANRA scores for narrative reviews ranged from 5–10 points, with a median score of 9 points. Although there are no predefined quality categories for this scale, experience suggests a score ≤ 4 is indicative of poor quality (26). Study characteristics and quality assessment scores are summarized in Table 1.

How has ACP been defined?

ACP was defined in 16 of the 18 reviews (12, 27–31, 33–39, 41–43). The systematic (32) and narrative review (40) without a definition of ACP both scored the lowest on the JBI and SANRA quality assessment tools, respectively.

Figure 2 presents the content categories and sub-categories used to define ACP across all reviews, listed chronologically. Overall, it appears that a consistent definition of ACP has not developed over time. The most common combination of categories and subcategories used in defining ACP were as follows: ‘the purpose of ACP is—to make decisions’; ‘patients should have conversations with—family and healthcare providers’; ‘conversations should cover—care options’; and ‘ACP should result in documentation—in the form of a legal document’. Notably, prior to 2017, the timing of ACP development was not included in any definition, and once present, not consistently described; although in the context of oncology settings, reviews included both terminal and non-terminal cancer patients (terminal patients only, n=6; non-terminal patients, n=4; and unclear, n=8).

Proposed and identified benefits of ACP

Content analysis identified three categories of proposed and empirically supported benefits of ACP: patient benefits, family benefits, and healthcare service benefits, presented in Table 2.

A misalignment was found between the proposed and empirically supported benefits of ACP, with many proposed benefits for patients, families, and healthcare providers not empirically supported within the same review. In terms of patient benefits, only ‘quality care’, ‘patient information’ and ‘care alignment’ had both proposed and empirically supported benefits (27, 28, 31, 41). For families, only ‘satisfaction with care’ was proposed as a benefit and empirically supported in the same review (28). Assessment of health care service benefits identified reduced hospitalization, reduced aggressive care, and reduced cost of care, as both proposed and empirically supported (28, 30, 39).

Barriers and enablers of requesting, recording, deciding, and or communicating ACP

A deductive analysis identified barriers and enablers of ACP across 12 of the 14 Theoretical Domains Framework domains from 15/18 reviews (12, 27–29, 32–35, 37–43). Table 3 presents frequencies of the barriers and enablers by Theoretical Domains Framework domain, and content themes identified within each domain from the patient, healthcare provider, and healthcare service perspectives. More barriers of ACP were associated with healthcare providers (n=60) in comparison to patients (n=40) and healthcare services (n=3). Enablers of ACP were more frequently identified for patients (n=17) compared to healthcare providers (n=15) and healthcare services (n=3).

As described in the method, we assessed importance in relation to three previously published criteria: domain frequency, level of elaboration within each domain, and authors’ explicit statements about importance (22, 23). Of 14 possible domains, the most frequently coded across the 15 reviews were: knowledge (66%); environmental context and resources (66%); emotion (66%); skills (60%); social/professional role and identity (53%); beliefs about consequences (46%); and social influences (40%). High levels of elaboration were found in the most frequently coded domains, except for those where minimal themes are to be expected: for example, skills whereby communication and training were predominant.

Evidence of importance was further supported by the authors of reviews articulating specific barriers or enablers as important in influencing ACP; for example, “*Health professionals’ knowledge of and attitudes towards ACP was also consistently found to be an important factor in their willingness to initiate or participate in ACP*” (27). Importance was also inferred in statements that articulated the patient’s voice; for example, “*Patients generally preferred to do ACP with the physician who knows them best, preferred that their physicians initiated discussion regarding ACP, and were more likely to participate in ACP or draw up an advance directive (AD) if they had discussed this with their oncologist*” (27).

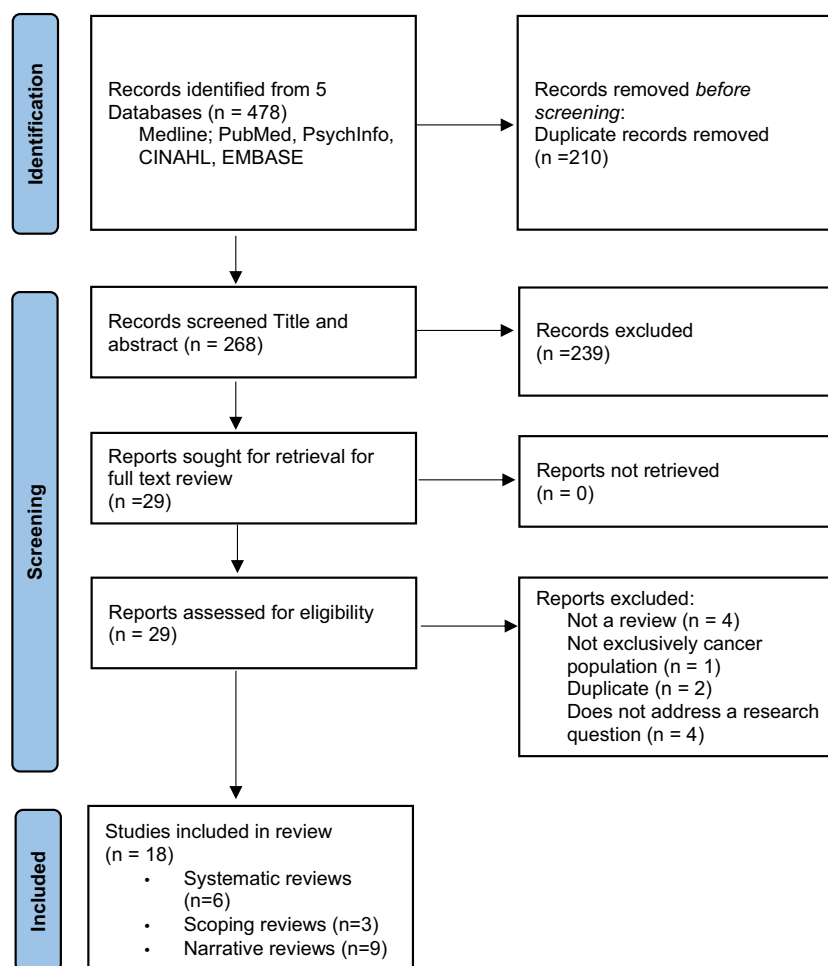


FIGURE 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Statements of expressed importance were identified in seven reviews (27, 29, 32, 35, 39, 42, 43) and these aligned with the seven most frequently coded domains with the greatest level of elaboration: knowledge (n=5); skills (n=4); environmental context and resources (n=4); social influences (n=3); beliefs about consequences (n=2); social/professional role and identity (n=2); and emotion (n=1). High frequency content themes within these domains also aligned with expressed statements of importance. Details on domains of importance and example quotations are presented in Table 4. Supplementary File 3 presents a narrative description and sample quotations for all themes across Theoretical Domains Framework domains.

ACP Interventions – the barriers they address and effectiveness

Nine of the 18 reviews identified interventions that aim to improve ACP uptake at various phases and target either the patient, healthcare provider, or healthcare service levels (12, 28, 29, 31, 32, 38–40, 43). In Figure 3, interventions have been mapped to the phases of ACP as presented by the Australian National Framework

for advance care planning documents (45), with the addition of a preparatory phase, labelled Phase 1a. This figure also depicts the intervention target and interactions associated with delivering the intervention.

Interventions targeting the patient

Seven reviews reported interventions that targeted the patient (12, 28, 29, 38–40, 43). Reporting of intervention effectiveness varied. Patient education tools were effective in increasing ACP documentation. Interventions that involved websites, patient prompts and/or patient tools to improve communication resulted in increased discussions of end-of-life issues and patients asking more questions (12, 29, 39, 43). Video-decision aid interventions increased knowledge scores and patients were less likely to opt for life-sustaining care (12, 28, 38–40). Consultation-based interventions did not report any effectiveness in improving ACP (12).

Multimodal interventions did not result in changes to ACP documentation, healthcare utilization, patient quality-of-life, consultation length, or communication self-efficacy. However, patients' willingness to discuss end-of-life care, patient-physician

TABLE 1 Characteristics of included reviews and advance care planning (ACP) definition.

Study	Type of Review	Method of synthesis/ analysis	No., and timeframe of data-bases searched	No., types of publication., timeframe of primary studies	Country of the primary studies	Sample Characteristics. (patients and/ healthcare providers; terminal/ non-terminal, settings)	Quality assessment * JBI critical appraisal; SANRA appraisal	Definition of ACP
Argarwal et al. (38)	Narrative Review	Narrative	Not Reported	Not reported; quantitative and qualitative; 1996-2017	Not reported	Patients and healthcare providers; unclear if terminal or non-terminal; inpatient and outpatient settings	SANRA Score 10	<i>“the multifaceted process by which patients make decisions regarding their future medical care. Oncologists and palliative care specialists have shared responsibility to candidly discuss prognosis and recommend end-of-life care options at appropriate times in a cancer patient’s disease trajectory. The primary objective ... to enable patients to cogitate about their goals at the end of life, and in turn, make informed health care related choices that are congruent with and fulfil these wishes.”</i>
Argarwal et al. (43)	Narrative Review	Narrative	1 database; Not reported	Not reported; quantitative and qualitative; 1991-2017	Not reported	Patients and healthcare providers; unclear if terminal or non-terminal; patient settings unclear	SANRA Score 9	<i>“an essential process by which patients with serious illnesses are empowered to articulate their personal values, preferences, and goals to make decisions for their future care... having conversations between patients, providers, and families, it should ultimately lead to documentation of patients’ wishes, beliefs, and values by way of completing an advance directive while the patient still has decisional capacity.”</i>
Bestvina et al. (39)	Narrative Review	Narrative	1 database; 2006-2013	26; quantitative; 2007-2017	Australia, USA, Europe,	Patients and healthcare providers; non terminal; outpatient settings	SANRA Score 8	<i>“process whereby a patient, in consultation with health care providers, family members, and important others, makes decisions about his or her future health care.”</i>
Buiar et al. (32)	Scoping Review	Narrative	1 database; 1979-2019	Not reported; quantitative and qualitative; 1987-2018	Not reported	Patient and healthcare providers; unclear if terminal or non-terminal; both inpatient and outpatient settings	Low-quality (JBI)	None provided.
Cohen et al. (35)	Narrative Review	Narrative	Not reported	Not reported; quantitative and qualitative; 2002-2011	USA	Patients and healthcare providers; unclear if terminal or non-terminal; inpatient settings	SANRA Score 10	<i>“a process that allows people to make decisions in advance regarding their medical treatment at the end of life (EOL)... includes clear discussions about prognosis, information about ADs, explanation of the do-not-resuscitate (DNR) option, information about palliative care options (e.g., hospice), and discussion about where patients would prefer to die. ADs are legal documents representing those decisions and can be statements written by patients about how they want their medical decisions made (i.e., living will) or whom they would like to make decisions if they are no longer able to make them themselves (i.e., power of attorney or healthcare proxy), or a combination of both (i.e., Five Wishes document).”</i>
Dirven et al. (37)	Narrative Review	Narrative	Not Reported	Not reported;	Not reported	Patients only; terminal;	SANRA Score 7	<i>“a process in which patients, in consultation with their families and</i>

(Continued)

TABLE 1 Continued

Study	Type of Review	Method of synthesis/ analysis	No., and timeframe of data-bases searched	No., types of publication., timeframe of primary studies	Country of the primary studies	Sample Characteristics. (patients and/ healthcare providers; terminal/ non-terminal, settings)	Quality assessment * JBI critical appraisal; SANRA appraisal	Definition of ACP
				quantitative and qualitative; 1996-2014		inpatient settings		<i>physicians, make decisions regarding future goals of the EOL care. These discussions may result in the completion of an advance directive."</i>
Johnson et al. (27)	Systematic Review	Thematic	5 databases; from inception to November 2014	40; quantitative and qualitative; 1996-2014	USA, UK, Europe, Australia, Taiwan and Canada	Patients and healthcare providers; unclear if terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>"formalised discussion between patients and healthcare providers which may include family members or friends, with possible outcome of formal documentation of EOL care wishes."</i>
Karlin et al. (40)	Narrative Review	Narrative	1 database; Not reported	Not reported; quantitative and qualitative; 1991-2017	Not reported	Patients only; terminal; patient settings unclear	SANRA Score 5	None provided
Khan et al. (36)	Narrative Review	Narrative	1 database; Not Reported	Not reported; quantitative and qualitative; 1990-2013	Not reported	Patients only; terminal; patient settings unclear	SANRA Score 9	<i>"Discussing and documenting patients' preferences for their end-of life care through advance care planning is a key component of palliative care."</i>
Kuusisto et al., (33)	Scoping Review	Content Analysis	4 databases; None applied	12; quantitative and qualitative; 2010-2019	USA, Europe, Asia and Australia	Healthcare providers only; non terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>"a multifaceted, family-centred and social process by which patients make decisions regarding their future medical care. The primary goal is to enable patients to consider their goals at the end of life so that they will receive the care they desire ... their preferences can be taken into account even if they are unable to make their own decisions. The starting point... should be patients' right to self-determination ... Documentation of ... conversations and/or completion of legal documents ... is recommended ... refers to both oral discussion (advance care planning) and written document (advance care plan)."</i>
Levoy et al. (12)	Systematic Review	Realist approach	5 databases; 1990-2018	25; quantitative; 2007-2018	USA, Australia, UK, Switzerland, China,	Patients only; non terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>"an essential aspect of providing patient-centred care to those with an advanced serious illness, such as cancer....has three main components: completing a living will, designating a health care surrogate, and participating in end-of-life (EOL) discussions....is not a one-time event, but rather a process that evolves over the patient's illness trajectory to match care to the patient's goals and values....should be initiated early in the illness trajectory and routinely reviewed when changes in the patient's condition or transitions of care occur."</i>
Lin et al. (41)	Narrative Review	Narrative	Not Reported	Not reported; quantitative and	Not reported	Patients and healthcare providers; non terminal; in-patient and	SANRA Score 10	<i>"a voluntary process that supports adults at any age or stage of health who possess mental capacity (the ability to make a decision for him- or herself) in understanding and sharing their personal</i>

(Continued)

TABLE 1 Continued

Study	Type of Review	Method of synthesis/ analysis	No., and timeframe of data-bases searched	No., types of publication., timeframe of primary studies	Country of the primary studies	Sample Characteristics. (patients and/ healthcare providers; terminal/ non-terminal, settings)	Quality assessment * JBI critical appraisal; SANRA appraisal	Definition of ACP
				qualitative; 1991-2018		outpatient settings		<i>values, life goals, and preferences regarding future (medical) care. It is an ongoing process of assessment and communication among patients, family members, healthcare professionals and medical surrogates to reach a consensus on medical care for patients, and it consists of written documents such as advance directives/decisions (ADs) or advance statement (AS)... usually used in the context of progressive illness and anticipated deterioration, and it greatly varies from general care planning."</i>
Lin et al. (29)	Systematic Review	Narrative	8 databases; from inception to March 2017	9; quantitative; 2007-2017	USA, UK, Australia	Patients only; terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>"ensuring patients' access to preferred care, by conducting a mutual communication between patients, families and healthcare professionals to achieve consensus on future care."</i>
Marchi et al., (31)	Systematic Review	Thematic	4 databases; from inception to March 2018	7; quantitative and qualitative; 2011-2018	Not reported	Patient and healthcare providers; terminal; settings unclear	High-quality (JBI)	<i>"a decision-making process for future health care for patients undergoing treatment that includes the effective participation of physicians, family members, and other people considered important in this treatment. It aims to ensure that patients' desires are respected when they are no longer able to make decisions.... provides the possibility for patients to be involved in and decide about treatments that he or she wants or does not want at the end of life, in addition to electing a family member or people closer to him or her who can make decisions in a shared manner, ultimately recording their decisions by means of advance directives (ADs) of will or through Physician Orders for Life-Sustaining Treatment (POLST)"</i>
Matsuoka et al. (42)	Narrative Review	Narrative	Not Reported	Not reported; quantitative and qualitative; 1994-2018	Not reported	Patients and healthcare providers; unclear if terminal or non-terminal; patient settings unclear	SANRA Score 6	<i>"the process whereby patients consult with health care professionals, family members and other loved ones to make individual decisions about their future healthcare and medical treatments to prepare for when patients lose competency to express their wishes... enables patients and their families to consider what care and treatments might or might not be acceptable, and to implement care and treatment consistent with their wishes.... primarily focuses on planning for the time when patients are incapable of making a decision, but it can also be applied to patients who retain capacity. Originally... was implemented to complete written documents, such as advance directives (ADs), do-not-resuscitate (DNR) orders and do-not-hospitalize (DNH) orders. Nowadays, the focus... is regarded as not only about the completion of written forms but also on the social process of</i>

(Continued)

TABLE 1 Continued

Study	Type of Review	Method of synthesis/ analysis	No., and timeframe of data-bases searched	No., types of publication., timeframe of primary studies	Country of the primary studies	Sample Characteristics. (patients and/ healthcare providers; terminal/ non-terminal, settings)	Quality assessment * JBI critical appraisal; SANRA appraisal	Definition of ACP
								<i>communication between patients and care providers.”</i>
Song et al. (28)	Systematic Review	Narrative	8 databases; from inception to July 2016	19; quantitative and qualitative; 2000-2016	USA, Italy, Australia, Germany, Austria, Netherlands, Austria and the UK	Patients only; unclear if terminal or non-terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>“the ongoing process that involves decisions made by patients, in consultation with surrogate decision-makers, family and health care providers regarding their values, beliefs, life-sustaining treatment preferences, goals of care (GOC), and palliative care options, should they later become incapable of expressing such wishes....may further include the patient completing an advance directive (AD) which documents his or her wishes and/or appointment of a substitute decision-maker.”</i>
Spelton et al. (34)	Scoping Review	Thematic	4 databases; 2013-2018	11; quantitative and qualitative; 2013-2018	Mostly USA	Patients only; unclear if terminal or non-terminal; both inpatient and outpatient settings	Medium-quality (JBI)	<i>“a patient’s decisions about prospective health care, in consultation with family members and healthcare providers. The aim is to empower patients in anticipation of a decline in their health, ready to be referred to if they become unable to convey their wishes or make decisions about their medical treatment.”</i>
Starr et al. (30)	Systematic Review	Narrative	3 databases; January 2012- January 2019	20; quantitative; 2012-2019	USA	Patient and healthcare providers; terminal; both inpatient and outpatient settings	High-quality (JBI)	<i>“discussions about patient values, prognosis, treatment options, aspects of living and dying, or specific interventions a patient may want if certain future conditions occur... conversation about EOL goals or treatment preferences with a healthcare provider or trained facilitator, documented in medical records or self-reported by patients or surrogates... sometimes includes advance directives (AD), physician orders for life-sustaining treatment (POLST), or do-not-resuscitate (DNR) or do-not-intubate (DNI) orders that suggest discussion about preferences”</i>

*JBI: Joanna Briggs Institute, quality assessment of systematic reviews (19); SANRA: Scale for the Assessment of Narrative Review Articles (21).

communication, and patient knowledge and confidence in decision-making were enhanced (29, 38, 43).

Interventions targeting the healthcare provider

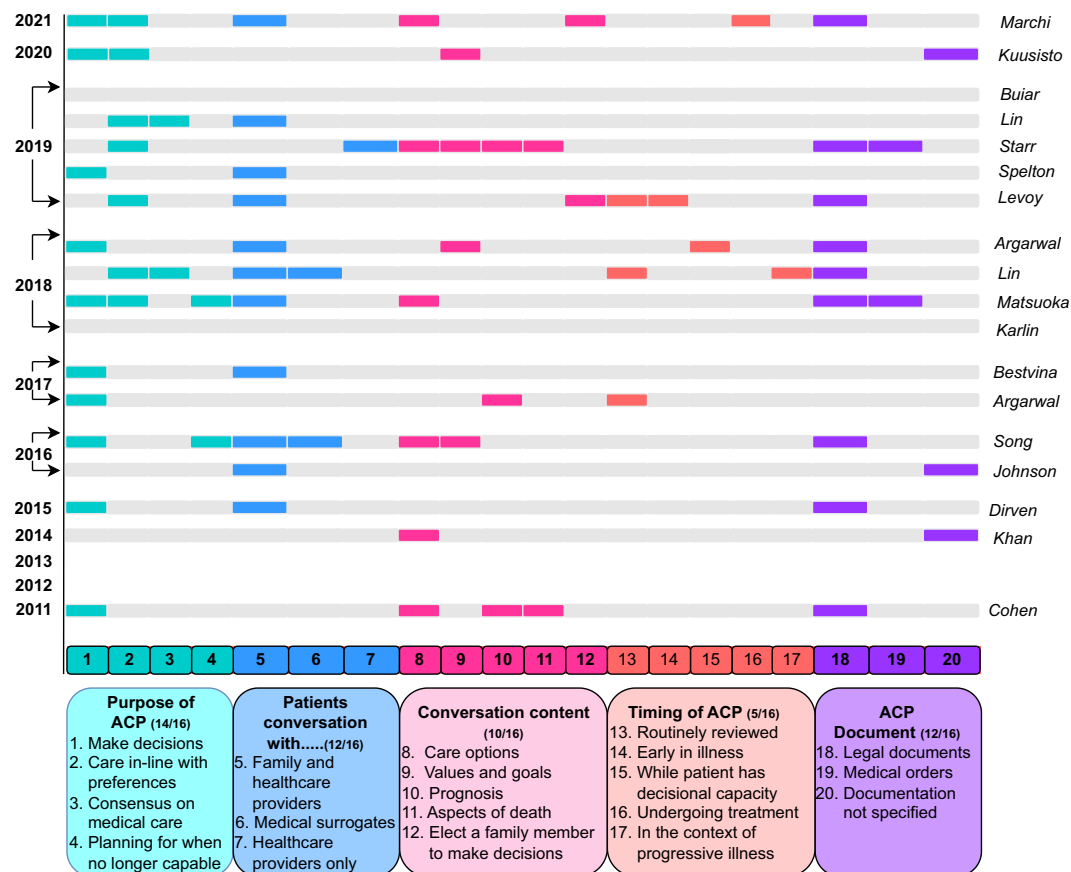
Three reviews reported interventions that targeted the healthcare provider (31, 32, 39). Interventions that used clinician resources reported an increase in ACP discussion (32, 39). Clinician reminders (email reminders to address goals of care) increased ACP documentation from 14.5% to 33.7% (39).

Interventions providing clinician training administered the Serious Illness care program (39), interactive training (31), or

training to improve clinician communication (32). These interventions were associated with an increase in discussions, earlier initiation of ACP discussions, and an increase in clinician confidence in initiating ACP conversations. However, they had little impact on ACP documentation.

Interventions targeting healthcare services

Three interventions targeted healthcare services (32, 39). Intervention effectiveness was not reported; however, an Advance Directive was documented for 33 of 48 patients, with the availability of an EMR note template (39).



* Figure 2 presents the reviews on the y-axis in chronological order of publication. The x-axis represents 20 sub-categories, colour coded to five categories identified in the content analysis of ACP definitions (1: purpose of ACP; 2: patients conversation with...; 3: conversation content; 4: timing of ACP; and 5: ACP documentation), listed below the x-axis. The use of these sub-categories to define ACP is reported with the corresponding coloured segment across each review.

FIGURE 2

Chronological mapping of categories identified in the content analysis of ACP definitions across reviews.

TABLE 2 Summary of proposed and identified benefits of ACP by content categories and frequencies of sub-categories for each.

Proposed benefits (14/18)	Empirically supported benefits (8/18)	Proposed benefits that were then empirically supported in the same review (6/18)
Patient Benefits (13/14): Care aligned with patient preferences (12, 28, 29, 31, 34, 35, 38, 39, 41, 43) Satisfaction (12, 29, 28, 33, 37) Patient empowerment (27, 38, 41, 43) Quality of life (29, 34, 39) Quality care (3/14), and 34, 35, 41) Patient information (27, 35)	Patient Benefits (5/8) Quality care (28, 31, 41) Care aligned with patient preferences (28, 31) Patient information (27) Quality of life (41) ACP not associated with depression (40)	Patient Benefits (4/6) Care aligned with patient preferences (28, 31) Patient Information (27) Quality care (28, 41)
Family Benefits (8/14): Psychological benefits (12, 28, 31, 33, 39) Satisfaction with care (28, 29, 31) Caregiver quality of life (35) Impact on bereavement (34)	Family Benefits (2/8): Psychological benefits (41) Satisfaction with care (28)	Family Benefits (1/6) Satisfaction with care (28)
Healthcare Service Benefits (11/14): Reduced hospitalisations (12, 28, 29, 33, 38, 43) Increased hospice (12, 28, 35, 38, 39, 43) Reduced cost of care (29, 34, 30, 37, 39) Reduced aggressive care/life sustaining intervention (12, 30, 35, 39) Reduced treatment (33, 38, 43) Decreased hospital deaths (33, 43)	Healthcare Service Benefits (7/8): Reduced hospitalisations (28, 30, 31, 36, 41) Increased hospice (30, 31, 40, 41) Reduced aggressive care/life sustaining intervention (39–41) Reduced cost of care (40, 41, 30) Reduced treatment (Marchi, 2020)	Healthcare Service Benefits (3/6) Reduced hospitalisations (28) Reduced aggressive care/life sustaining intervention (39) Reduced cost of care (31)

TABLE 3 Theoretical Domains Framework domains and themes of barriers and enablers across patient, healthcare provider, and healthcare services perspectives.

Theoretical Domains Framework domains and themes	Review References	Frequencies		Patient Perspective		Healthcare Provider Perspective		Healthcare Services Perspective	
		Barriers	Enablers	Barriers	Enablers	Barriers	Enablers	Barriers	Enablers
Knowledge		17	7	9	3	8	4	0	0
• Procedural understanding or lack of knowing when, how, or what to discuss	(30, 35, 38)	2	1	-	-	X	X	-	-
• Clinician certainty of prognosis or lack of	(35, 40)	2	1	-	-	X	X	-	-
• Patient understanding, or lack of understanding of their prognosis	(26, 29, 31, 35, 40)	3	2	X	X	X	X	-	-
• Clinician ignorance as a knowledge deficit	(24)	1	0			X		-	-
• Clinicians understanding of patient preferences of care	(39)	0	1	-	-	-	X	-	-
• Patient lack of knowledge of their disease	(29, 39)	2	0	X	-	-	-	-	-
• Medical knowledge or lack of	(29, 35, 25)	1	1	X	X	-	-	-	-
• Understanding of ACP and its use or non-use	(26, 24, 29–32)	6	1	X	X	X	-	-	-
Environmental context and resources		10	6	2	2	5	1	3	3
• Time constraints associated with outpatient and inpatient settings	(24, 35, 38, 40)	5	1	X	X	X	-	-	-
• System level constraints in accessing information	(26, 29, 30, 32, 39)	3	3	-	-	-	-	X	X
• Privacy – appropriateness of settings to have the conversation	(24, 26, 31)	2	2	X	X	X	X	-	-
Emotion		17	1	8	1	9	0	0	0
• Fear of impacting the therapeutic relationship	(35)	1	0	-	-	X	-	-	-
• Diminishing hope	(24, 32, 35, 37–39)	5	0	-	-	X	-	-	-
• Fear of addressing bad news	(29)	1	0	-	-	X	-	-	-
• Patient stress and anxiety	(24, 29, 31)	3	0	X	-	X	-	-	-
• Patient fear	(24)	1	0	X	-	-	-	-	-
• Patient fear for family members	(24)	1	0	X	-	-	-	-	-
• Perceived physician discomfort in initiating discussions	(24, 32)	3	0	X	-	-	-	-	-
• Acceptance of prognosis and realistic expectations or lack of	(32, 40)	2	1	X	X	X	-	-	-
Skills		8	5	1	2	7	2	0	0
• Training on ACP, or lack thereof (2)	(32, 35–36, 39–40)	5	1	-	-	X	X	-	-
• Lack of training in navigating systems to retrieve ACP information	(30)	1	0	-	-	X	-	-	-

(Continued)

TABLE 3 Continued

Theoretical Domains Framework domains and themes	Review References	Frequencies		Patient Perspective		Healthcare Provider Perspective		Healthcare Services Perspective	
		Barriers	Enablers	Barriers	Enablers	Barriers	Enablers	Barriers	Enablers
• Palliative care skills to aid discussions of ACP preparation/readiness	(40)	0	1	-	-	-	X	-	-
• Clinician communication skills (2)	(24–26, 35, 39)	2	3	X	X	X	X	-	-
<i>Social/professional role and identity</i>		13	3	7	0	6	3	0	0
• Role clarity or lack thereof	(24, 30, 36)	3	0	-	-	X	-	-	-
• Nurses lack of perceived authority in decisions with EoL care	(24)	1	0	-	-	X	-	-	-
• Nurses perception that others (patients/family/doctors) didn't think it was their role	(32)	1	0	-	-	X	-	-	-
• Perception of patient/physician relationship	(24)	1	0	-	-	X	-	-	-
• Multidisciplinary approach	(10, 30, 32)	0	3	-	-	-	X	-	-
• Patients feeling it is not their role to make decisions	(24)	1	0	X	-	-	-	-	-
• Cultural and/or religious beliefs	(31, 34, 38)	6	0	X	-	-	-	-	-
<i>Beliefs about consequences</i>		19	3	5	2	14	1	0	0
• Having the conversation at the wrong time/patient readiness	(29, 38, 40)	2	1	-	X	X	-	-	-
• Discussion would have a negative impact	(24, 29, 37–40)	6	0	-	-	X	-	-	-
• Conversation will damage the patient/physician relationship	(24)	1	0	-	-	X	-	-	-
• Nurses beliefs on repercussions from doctors for initiating ACP conversation	(24, 32)	2	0	-	-	X	-	-	-
• Nurses feeling that patients/families do not want to have the conversation with them	(32)	1	0	-	-	X	-	-	-
• Patient perception that ACP will impact receiving adequate care	(32)	1	0	X	-	-	-	-	-
• Patient unsure if ACP is useful	(32)	1	0	X	-	-	-	-	-
• Patient perception that ACP conversation will upset family members	(24)	1	0	X	-	-	-	-	-
• Past experiences and attitudes towards the health care system	(24, 38)	4	2	X	X	X	X	-	-
<i>Social influences</i>		9	10	6	6	3	4	0	0
• Clinician discussions with other colleagues that share responsibilities of the patient	(24)	0	1	-	-	-	X	-	-
• Consideration of culturally appropriate was to engage in ACP conversation	(38)	0	1	-	-	-	X	-	-

(Continued)

TABLE 3 Continued

Theoretical Domains Framework domains and themes	Review References	Frequencies		Patient Perspective		Healthcare Provider Perspective		Healthcare Services Perspective	
		Barriers	Enablers	Barriers	Enablers	Barriers	Enablers	Barriers	Enablers
• Exclusion from ACP conversations	(29, 31, 35)	3	0	X	-	-	-	-	-
• Family participation in ACP conversation	(24, 39)	1	2	X	X	-	X	-	-
• Institutional culture	(24, 38)	4	0	X	-	X	-	-	-
• Clinician engagement in ACP conversation	(24, 35, 38–39)	2	6	-	X	X	X	-	-
Behavioural regulation		4	0	0	0	3	0	0	0
• No guideline established for the timing of ACP	(30, 35–36)	3	0	-	-	X	-	-	-
Memory, attention and decision processes		4	1	2	1	2	0	0	0
• Not disclosing poor prognosis to patients	(29, 31, 38)	2	0	-	-	X	-	-	-
• Knowing when is the best time to initiate ACP conversations	(29–30)	1	1	-	X	X	-	-	-
• Patients capability to make decisions	(29)	1	0	X	-	-	-	-	-
Intentions		2	0	0	0	2	0	0	0
• Reluctance towards early initiation of ACP	(30, 37)	2	0	-	-	X	-	-	-
Goals		2	0	0	0	2	0	0	0
• Waiting for ACP to be relevant	(24)	2	0	X	-	X	-	-	-
Optimism		1	0	0	0	1	0	0	0
• Not wanting to discuss EoL unless patient is near death	(32)	1	0	-	-	X	-	-	-
Behavioural capabilities	-	0	0	-	-	-	-	-	-
Reinforcement	-	0	0	-	-	-	-	-	-

X denotes domain/themes identified.

Synthesis with theoretical domains framework domains

Table 5 compares the frequencies of Theoretical Domains Framework domains for barriers of ACP with the Theoretical Domains Framework domains for implied barriers targeted by ACP interventions across patient, healthcare provider, and healthcare systems levels. Across levels, there was a misalignment between barriers identified and implied barriers targeted by interventions. Interventions most frequently targeted the patient; however, more barriers for ACP were identified for healthcare providers. There were also implied barriers targeted by ACP interventions that were not identified as barriers to ACP in the included reviews. This occurred for interventions targeting the patient as well as the healthcare provider.

Summary of results

- Five common categories were identified when defining ACP. However, these were not consistently applied across reviews, and there was no emergence of a clear definition of ACP over time.
- The most common combination of categories/subcategories used in defining ACP were: the purpose of ACP is to make decisions; patients should have conversations with family and healthcare providers; conversation should cover care options; and ACP should result in documentation (in the form of a legal document).
- There were more proposed than empirically supported benefits for ACP. There were no proposed or empirically supported benefits for the healthcare provider.

TABLE 4 Theoretical Domains Framework domains of importance in influencing behaviours related to ACP; identified themes and quotations of expressed importance.

Theoretical Domains Framework Domain and level of elaboration	Themes of importance	% frequency of coded theme for domain	Examples of quotations of expressed importance or patient voice	Reviews with statements of expressed importance
Knowledge (8 themes)	Understanding of ACP and its use or non-use	29%	"highlighted the importance of actively educating patients prior to the regular oncology consultation to enhance their 'motivation' and 'competence' to take part in an ACP discussion rather than just providing information on ACP to them" (29)	(27, 29, 32, 42, 43)
			Health professionals' knowledge of ... ACP was also consistently found to be an important factor in their willingness to initiate or participate in ACP" (27)	
	Patient understanding, or lack of understanding of their prognosis	21%	"Meaningful ACP requires good illness understanding and realistic expectations about prognosis so that patients can express their values and make decisions in a timely manner" (43)	
			"main reason patients fail to complete their directives is the difficulty in anticipating their wills based on scenario projections" (32)	
Environmental context and resources (3 themes)	System level constraints	37%	"most importantly a supportive contextual environment (e.g. availability of administrative system, sufficient resources... should be in place to support the implementation" (29)	(27, 29; 32; 42)
	Time constraints	37%	Patient expressed importance "ACP conversations should be initiated with adequate time and place for reflection" (32)	
	Appropriateness of setting	26%	"physicians reported time and privacy as barriers to ACP, they did so because they believed these were fundamental to establishing relationships with patients and families" (27)	
Emotion (8 themes)	Diminishing hope	28%	"Although nurses are well positioned to assist patients in ACP, barriers exist that prevent nurses from supporting patients in this way. The top reasons nurses did not discuss prognosis and hospice referral with their patients were unwillingness of patients or families to accept prognosis.....and nurses' desire to maintain hope for patients and their families" (35)	(35)
	Acceptance of prognosis and realistic expectations	17%		
Skills (4 themes)	Training on ACP or lack thereof	46%	"training in conducting ACP conversations should be offered to health care providers, as providers report feeling inappropriately trained or prepared to have ACP conversations" (39)	(27, 29, 39, 42)
	Clinician communication skills	38%	"communication and coaching skills training for medical staff were identified as essential requirements for successful ACP implementation" (29)	
Social /professional role and identity (7 themes)	Role clarity or lack thereof	19%	Patient expressed importance - "patients generally preferred to do ACP with the physician who knows them best, preferred that their physicians initiated discussion regarding ACP, and were more likely to participate in ACP" (27)	(27, 35)
Beliefs about consequences (9 themes)	Discussion would have a negative impact	30%	Patients expressed importance contradicts this - "important to bear in mind that the majority of patients do not complain about additional depression/anxiety" (32)	(32; 27)
	Past experiences and attitudes towards the healthcare system	27%	"Health professionals' knowledge of and attitudes towards ACP was also consistently found to be an important factor in their willingness to initiate or participate in ACP" (27)	
Social Influences (6 themes)	Clinician engagement in ACP conversation	42%	Patient expressed importance "preferred that their physicians initiated discussion regarding ACP, and were more likely to participate in ACP or draw up an AD if they had discussed this with their oncologist" (27)	(32; 27, 42)

(Continued)

TABLE 4 Continued

Theoretical Domains Framework Domain and level of elaboration	Themes of importance	% frequency of coded theme for domain	Examples of quotations of expressed importance or patient voice	Reviews with statements of expressed importance
	<i>Institutional culture</i>	21%	<i>"The behaviour and choices of patients, their loved ones, and the staff caring for them in relation to EOL are strongly influenced by the institutional culture within which they are operating" (27)</i>	
	<i>Exclusion from ACP conversations</i>	16%	<i>"it is very important to reinforce that the directives should be ideally created by the patient themselves" (32)</i>	
	<i>Family participation in ACP conversations</i>	16%	<i>"Five essential elements of ACP for success (HP) Involvement of family in discussions..." (42)</i>	

- A greater number of barriers for ACP were associated with the healthcare provider than the patient, or healthcare service. Enablers of ACP were greater for the patient than the healthcare provider or service.
- The majority of interventions to improve ACP target the patient rather than healthcare providers. Implied barriers that were targeted by ACP interventions and coded to Theoretical Domains Framework domains did not align with barriers identified in the included reviews as the most important in influencing ACP.
- Theoretical Domains Framework Effectiveness of ACP interventions varied. Interventions targeting identified barriers tended to be more effective.

Discussion

Based on this systematic overview of reviews, consistency is lacking in the literature in relation to defining ACP, its benefits, and its barriers and enablers in oncology settings. While the peer-

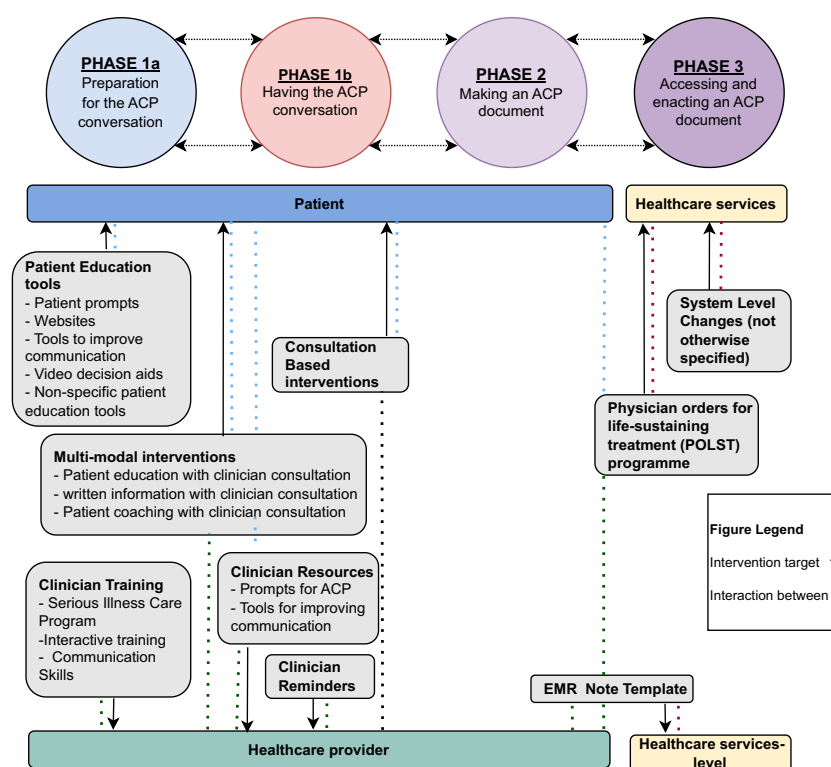


FIGURE 3
Mapping of ACP interventions to the Australian National Framework for ACP phases.

TABLE 5 Frequencies of the Theoretical Domains Framework domains for barriers of ACP and barriers targeted by ACP interventions.

Frequency of domains coded	Theoretical Domains Framework domains for barriers to ACP	Alignment of barrier domains with targeted barrier domains for interventions	Theoretical Domains Framework domains for implied barriers targeted in ACP Interventions	Frequency of domains coded
9	Patient		Patient	12
8	*Knowledge		*Knowledge	6
7	*Emotion		Memory attention and decision processes	5
6	*Social/professional roles and identity		Beliefs about capabilities	4
5	*Social influences		*Social influences	3
2	*Beliefs about consequences		*Beliefs about consequences	3
1	*Environmental context and resources		*Skills	1
1	Memory attention and decision processes		*Social/professional roles and identity	
1	*Skills			
1	Goals			
14	Healthcare provider		Healthcare provider	3
8	*Beliefs about consequences		*Skills	2
7	*Knowledge		Behavioural regulation	1
7	*Emotion		*Knowledge	1
6	*Skills		Beliefs about capabilities	1
5	*Social/professional roles and social			
3	*Environmental context and resources			
3	Behavioural regulation			
2	*Social influences			
1	Memory attention and decision processes			
1	Intentions			
	Optimism			
	Goals			
3	Healthcare services		Healthcare services	3
	*Environmental context and resources		*Environmental context and resources	

*Denotes domains of importance; — represents domains for barriers aligned with implied barriers targeted in ACP interventions; — represents domains for barriers that are not aligned with a corresponding domain for a barrier/implied barrier targeted in an ACP intervention.

reviewed literature lacks a consensus definition, there are key categories and sub-categories that align with the benefits of ACP and overarching values associated with optimal patient care that should be consistently used in its definition. The most frequently used sub-categories to define the purpose of ACP are about making decisions to ensure that the patient receives care in-line with their preferences. Receiving care that is in-line with one's preferences and values is the hallmark of patient-centered care (46) and known to improve care quality and patient satisfaction (47). It is also one of the empirically supported benefits of ACP (28, 41). We suggest that these content categories should be included in the standardized definition of ACP (presented in Figure 4), along with identifying who should participate in the conversation. Evidence suggests the involvement of family and healthcare providers in ACP conversations is an enabler for the patient and healthcare provider for ACP uptake (27, 41–43).

The lack of consensus around the timing of ACP should be addressed within oncology settings, as this is also associated with barriers for healthcare providers not knowing when to initiate the conversation (32, 41, 43). It is important to consider that, within this patient population, the timing of conversations does not necessarily have a negative impact on patients (40) but, rather, consideration of contextual factors is important, such as having the

conversation in an appropriate and private setting important (27, 29, 34). Whilst there is agreement within the literature (12, 28, 30, 31, 35, 37, 41–43) and also in the Australian National Framework of ACP (45), that ACP should result in a legal document, emphasizing the importance of this step, we found no mention of barriers associated with creating this document or any process or person to facilitate this process. Nor did any interventions target this phase of ACP.

Interventions predominantly focused on a preparatory phase of ACP, which we identified as Phase 1a (Figure 3): Preparation for the ACP conversation; currently beyond the scope of the Australian National Framework of ACP, which primarily focusses on three phases ACP; 1) having the conversation; 2) making an ACP document; and 3) accessing and enacting an ACP document (45). Interventions to enhance the uptake of ACP sometimes, but not always, addressed the known barriers and there appeared to be considerable variation in these interventions to improve ACP uptake. They also tended to target the patient rather than healthcare providers, even though the number of barriers associated with healthcare providers were a third greater than those for patients.

Further expanding the 'importance criteria' to a theme level enabled us to identify the mismatch of interventions in targeting

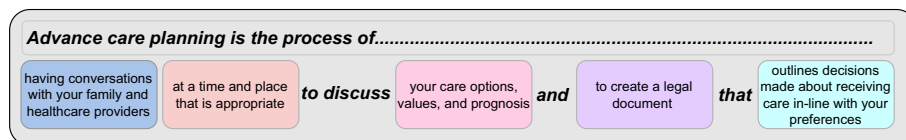


FIGURE 4
Key categories for defining ACP in oncology settings.

empirically identified problems. Interventions that targeted patients did address patient barriers that were coded to important domains, and to some extent were effective in increasing ACP documentation. However, these interventions aimed to improve the knowledge of patients on end-of-life care decisions and gaining medical knowledge, yet the most important knowledge enabler was for patients to have an understanding of their prognosis. Interventions also focused on communication between patients and clinicians. While these interactions are important, the involvement of family members in the process of ACP was an enabler for both patients and healthcare providers. Yet, no interventions focused on educating and actively engaging family members in ACP. This is despite empirically supported psychological benefits and satisfaction with care being linked to the involvement of family members (28, 41).

Few interventions targeted empirically identified problems for healthcare providers, and these were mostly ineffective in increasing ACP documentation. These interventions targeted barriers coded to only two of the seven domains identified as important in influencing ACP uptake for healthcare providers (i.e., skills and knowledge); and were placed in phase 1 of the Australian National Framework of ACP (45). Interventions have failed to address the most frequently reported barriers for healthcare providers, specifically, beliefs that ACP conversations would have a negative impact on patients. This is in spite of patient accounts that this assumption is incorrect and contrary to empirically identified benefits for patients (40).

The pathways from having the ACP conversation to phase 2 of the Australian National Framework of ACP, making an ACP document, were not discussed in the literature reviewed in this overview. The barriers and enablers of making an ACP document have not been explored in the literature, nor addressed in any interventions. Yet, national frameworks identify this as a phase of successful ACP, consistent with many definitions that state ACP should result in some form of documentation. Interventions addressing phase 3 of the framework, accessing and enacting an ACP document, did not report effectiveness in improving ACP. System-level constraints was one of three themes coded to the domain of environmental context and resources and identified as important in influencing ACP uptake.

In summary of the findings discussed above, we recommend that future ACP interventions and research focus on:

- Interventions that target educating family members and actively engaging family in ACP.

- Interventions that encourage the discussion and understanding of prognosis;
- Interventions that challenge clinician beliefs— about understanding the impact and benefits of ACP; and
- The importance of context and availability of resources.

Limitations of this research

While there is the lack of emergence of a clear definition of ACP in the academic literature, governments and non-governmental organisations may employ more complete definitions that were not included in this review; such as the one proposed in the Australian National Framework of ACP (45). The scope of the inclusion criteria for this overview may have also excluded other interventions for ACP that were not trialed only in cancer populations and, therefore, were not included in this analysis. It is possible that additional barriers and enablers of ACP, as well as potentially effective interventions, may also be relevant for cancer populations but have not been identified or included in this review.

In conclusion, this overview of reviews has identified key categories of content that should be included in defining ACP. These address the most frequently used sub-categories and are consistent with empirically supported benefits of ACP. We have also identified that, in many cases, proposed benefits of ACP did not actualize into empirically supported benefits. This was most evident for empirically supported benefits for patients and family members. No benefits of ACP were reported in the literature for healthcare providers. Lastly, interventions tended to target a different population and barriers than the ones the majority of evidence identified as a problem. Implications for this are that, in targeting an imagined problem as opposed to one that has been empirically identified we are unlikely to be effective in changing ACP uptake. Future interventions for ACP should target the domains of importance identified and address key barriers to change the behaviours of healthcare providers and improve ACP uptake.

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

LG conducted the search. Authors LG and SF screened reviews for inclusion and conducted the data extraction. LG, JF, AH and KG participated in the analysis of results. Writing of the original draft manuscript was prepared by LG. 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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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2023.1040589/full#supplementary-material>

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Lung cancer screening beliefs in Armenia

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Introduction: In Armenia, an upper-middle income country, 93% of deaths are from non-communicable diseases and over half of the male population smokes. Armenia has more than double the global lung cancer incidence. Over 80% of lung cancer is diagnosed at stages III or IV. However, there is a significant mortality benefit in detecting early-stage lung cancer via screening with low-dose computed tomography.

Methods: This study employed a rigorously-translated, previously-validated survey based on the Expanded Health Belief Model to understand how Armenian male smokers' beliefs would affect lung cancer screening participation.

Results: Survey responses highlighted key health beliefs that would mediate screening participation. Most respondents felt they were at risk for lung cancer, but over 50% also believed their cancer risk was equivalent to (or less than) non-smokers' risk. Respondents also overwhelmingly agreed a scan could help detect cancer earlier, but fewer agreed early detection could reduce cancer mortality. Important barriers included absence of symptoms and costs of screening and treatment.

Discussion: Overall, the potential to reduce lung cancer-related deaths in Armenia is high, but there are a number of central health beliefs and barriers that would limit screening uptake and effectiveness. Improved health education, careful consideration of socioeconomic screening barriers, and appropriate screening recommendations may be useful in overcoming these beliefs.

KEYWORDS

lung cancer, screening, health beliefs, Armenia, developing countries, smoking, screening barriers, health education (MeSH)

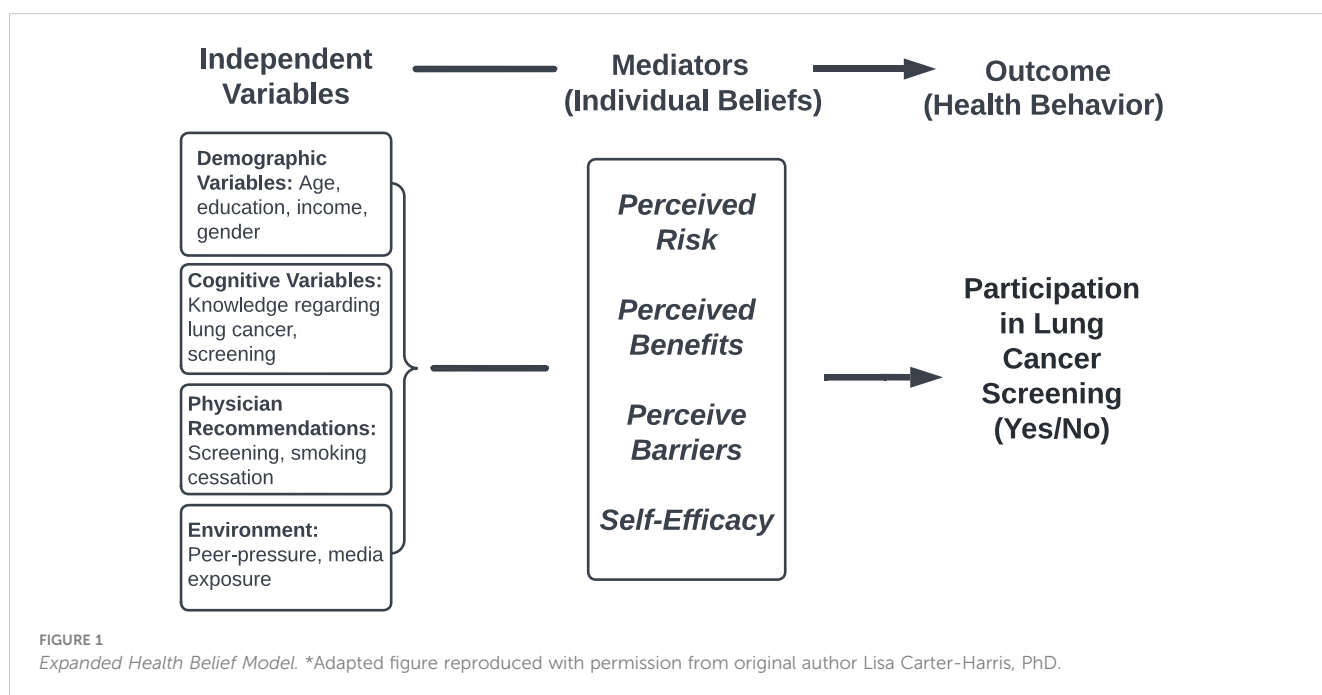
Introduction

Lung cancer is the second most common cancer globally (1) and almost two-thirds of lung cancer deaths occur in low and middle-income countries (LMICs) (2). Within this cohort, upper-middle income countries have the highest rates of lung cancer incidence and mortality (2). Armenia, an upper-middle income country of 3 million in the South Caucasus (3), has more than twice the global age-standardized incidence of lung cancer (4, 5) and the magnitude is only increasing (6). In 2019, Armenian men ages 60–80 had more than a 1 in 20 chance of dying from lung cancer (6). Lung cancer epidemiology already varies significantly by gender, but the contrast is even more stark in Armenia, where mortality is nearly five times higher in men (6). Disparate mortality rates are largely due to gendered tobacco use. Over half of the Armenian male population smokes, compared to 2% of women, and tobacco use is heavy (7, 8).

Primary and secondary non-communicable disease (NCD) prevention should be a priority for Armenia, where 93% of deaths are attributable to NCDs (9). Tobacco cessation is one of the most cost-effective interventions to combat NCDs, including lung cancer (10, 11). Although Armenia signed the World Health Organization (WHO)'s Framework Convention on Tobacco Control in 2004, initial movement was sluggish. More recently, the government mandated health warnings on tobacco packaging (2016), increased tobacco taxes (2019), and banned indoor smoking and public display of tobacco products (2022) (10). However, tobacco cessation services are limited, most advertising is still legal, and teenage tobacco use is increasing (10). Furthermore, Armenia does not have a national lung cancer screening program, yet detection of asymptomatic, early-stage disease requires organized screening protocols (7). Annual low-dose computed tomography (LDCT) in

high-risk individuals (e.g. current and former smokers) is the only screening method proven to successfully identify lung cancer at earlier stages with a 20–26% mortality benefit (12, 13). In Armenia, in the absence of organized screening, over 80% of lung cancer cases are diagnosed at stages III or IV (7) and lung cancer is almost universally fatal (4).

The success of any cancer screening program depends on its uptake. It has been shown in other LMICs that many cultural barriers and health beliefs exist that could potentially limit cancer screening participation, from anxiety around possible diagnosis to fear of treatment and fatalism (14, 15). Consequently, prior to piloting any potential screening programs, it is important to preliminarily understand barriers to uptake in Armenia. One of the most commonly utilized models to evaluate health-promoting behaviors, such as lung cancer screening, is the Expanded Health Belief Model (EHBM), where individual beliefs mediate participation in a health behavior. In this model, individual beliefs are deconstructed into several conceptual elements, specifically perceived risk, perceived barriers, perceived benefits, and self-efficacy (see Figure 1) (16). In this study, a previously-validated lung cancer screening-specific version of the EHBM was translated and employed. Given differential smoking patterns, this study focused on men. The purpose of this study was to assess the attitudes and beliefs of male smokers towards lung cancer screening in Armenia's capital using a pre-validated instrument. Three core research questions guided the data analysis and discussion: 1) What are the perceptions of Armenian male smokers regarding lung cancer screening? 2) Is there any relationship between their perceptions of risk, benefits, barriers, and self-efficacy regarding lung cancer and screening? 3) Do their demographic characteristics impact their beliefs about lung cancer and screening?



Methods

Institutional review board (IRB#21-000784) exemption was obtained from the Office of Human Research Protection Program at the University of California, Los Angeles. Local institutional review board approval was also obtained from the Ethics Committee at Yerevan State Medical University.

Study population

A stratified random sampling approach was used to recruit study participants. Active or former male smokers, aged 40 to 70, were recruited proportionally from the 12 administrative districts of Yerevan, Armenia's capital city. Armenian men were surveyed because they have significantly higher rates of smoking compared to women and are therefore at higher risk for lung cancer (6). The age criteria was determined from the United States Preventive Service Task Force's (USPSTF) lung cancer screening age criteria of 50 to 80 years (11). The age range for recruited participants was lower than existing guidelines to account for the perspectives of those who were nearing screening age. Those with previous lung cancer diagnoses or history of LDCT were excluded from this study. To calculate our sample size target of 384 men, we used a population of 500,000 men in Yerevan with a confidence level of

95%, a margin of error of 5%, and a 50% prevalence based on the proportion of Armenian males who smoke.

Survey design

The survey was adapted from a previously-validated lung cancer health belief scale ($\alpha > 0.7$) utilizing a four-point Likert-type scale to analyze four constructs: 1) perceived risk, 2) perceived benefits, 3) perceived barriers, and 4) self-efficacy (16). The survey was designed and administered through Qualtrics online survey software (Qualtrics, Provo, UT). The survey was translated from English to Armenian and back-translated into English to check for accuracy. Questions were added to the Armenian-language survey to account for local relevance and to gather demographic information. The survey was then administered to native Armenians to ensure face validity. Using the feedback provided, redundant questions due to translation were removed. No prior information or materials regarding lung cancer or lung cancer screening were provided to participants.

Data collection

Data was collected proportionally based on percent of population from each of Yerevan's administrative districts. Study participants were recruited Monday through Sunday from October

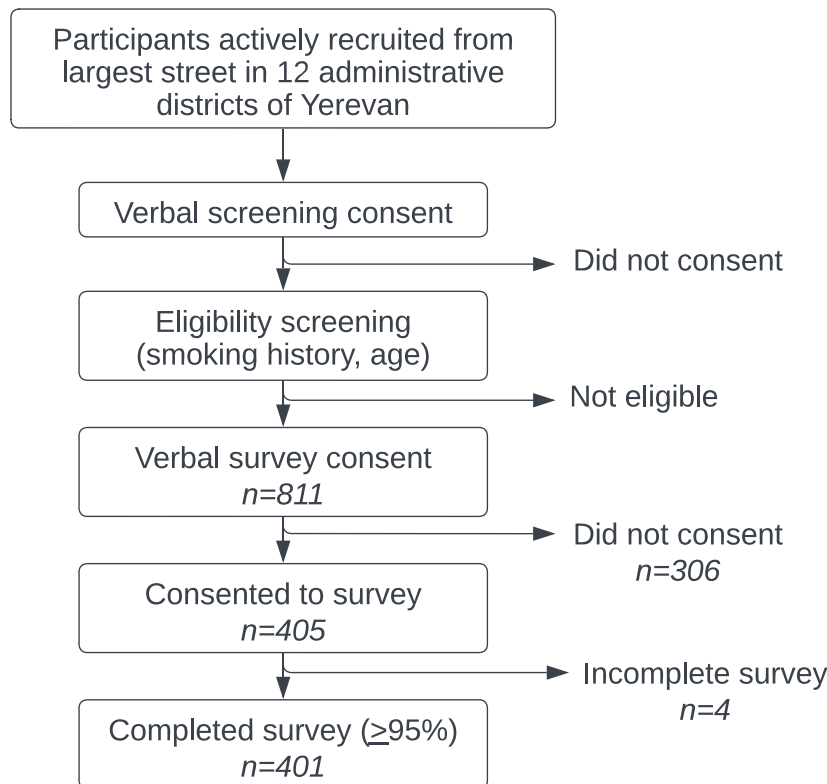


FIGURE 2
Recruitment & sampling methodology.

22, 2021 to January 30, 2022. Potential participants were randomly approached and recruited from the largest street in each of Yerevan's 12 administrative districts (see Figure 2). Trained local surveyors first obtained consent to ask four filter questions to determine study eligibility. There was no mechanism to characterize potential participants who were initially unwilling or ineligible to participate. For eligible participants, verbal informed consent to participate in the full survey was then obtained and documented by surveyors in Qualtrics. Finally, surveyors verbally administered the survey to participants and electronically recorded the deidentified results in a mobile version of Qualtrics' data collection software.

Statistical analysis

The survey data was analyzed using IBM SPSS 26 Statistics software. The statistical analysis included 1) descriptive statistics reporting on frequency analysis, 2) correlational analysis reporting on Spearman's Rho correlation coefficient, and 3) stepwise multiple linear regression analysis. Prior to the analysis, the data was screened for missing values, followed by testing assumptions, including normality, linearity, homoscedasticity, and absence of multicollinearity. Surveys that were at least 95% complete were included in the analysis. For all statistical analyses, the significance criterion was set at $p < 0.05$. Composite mean scores for each construct were calculated and used in correlational and inferential statistical analyses. Correlational analysis included exploring the relationship between different demographic variables and attitudes towards lung cancer screening, specifically the four constructs of perceived risk, perceived benefits, perceived barriers, and self-efficacy. We also examined the correlation between the responses in one construct (e.g., perceived benefits) to responses in each of the other three constructs (e.g., perceived risk, perceived barriers, self-efficacy). A forward stepwise linear regression analysis was used to examine whether participants' demographic characteristics significantly impacted their perceived risk, perceived benefits, perceived barriers, and self-efficacy. The stepwise method in SPSS is a variation of the forward regression method except that every time a predictor is added to the equation, a removal test is made for the least useful predictor (17). Specifically, the predictor variables included self-rated health, marital status, education level, monthly income, age, and pack year (see Table 1 for the categories listed within each predictor variable). The dependent variables included the participants' perceived risks, perceived benefits, perceived barriers, and self-efficacy. The significance level for the variable inclusion in the regression models was set at <0.05 and candidate variables were added until no further variables satisfied the entry criterion ($p < 0.05$).

Results

Demographics

A total of 811 people met eligibility criteria and 405 (49.9%) consented to participate in the full survey. 99.0% ($n=401$) of these

surveys were considered complete ($> 95\%$) and included in the analysis. Full demographic data is available in Table 1. Ages skewed slightly younger but approximately one-third of men were each in their fifth (38.7%), sixth (33.0%) and seventh (28.3%) decades of life.

On average, respondents smoked 22 cigarettes per day, or slightly over one pack per day. There was a significant range in

TABLE 1 Demographic characteristics of respondents.

Characteristic	n (%)
Total Respondents	n= 401
Age	
40-50 yrs	155 (38.7%)
51-60 yrs	132 (33%)
61-70 yrs	114 (28.3%)
Avg Cigarettes per Day *Median (IQR)	22 (10)
Avg Years of Smoking *Mean (SD)	25 (14)
Prior Attempt to Quit	
Yes	159 (39.6%)
No	242 (60.4%)
Marital Status	
Married	294 (73.5%)
Divorced/Separated	29 (7.2%)
Widowed	22 (5.5%)
Single, never married	45 (11.3%)
Other	10 (2.5%)
Highest Educational Level	
Incomplete secondary educa	16 (4.0%)
Complete secondary educat	97 (24.3%)
Vocational	132 (33.0%)
Higher Education	155 (38.8%)
Self-Rated Health	
Excellent	40 (10.2%)
Very Good	61 (15.5%)
Good	131 (33.3%)
Fair	147 (37.4%)
Poor	14 (3.6%)
Monthly Household Income	
Below 100,000 dram	96 (24.4%)
100,000-300,000 dram	193 (49.1%)
300,000-500,000 dram	74 (18.8%)
More than 500,000 dram	30 (7.6%)

responses from 2 to 100 cigarettes per day. Respondents had smoked an average of 25 years and almost 40% had at least one prior quit attempt. Despite over a third (38.7%) being younger than the USPSTF-recommended age for lung cancer screening (50–80 years), already two-thirds (66.3%) of those surveyed reported smoking 20 pack-years or more. Most men were married (73.5%), had completed secondary, vocational or higher education (96.0%), and had a monthly income of 100,000–300,000 dram (49.1%), roughly comparable to the average Armenian monthly nominal wage of approximately 200,000 dram (\$491 USD) (18). Of note, there was a statistically significant negative correlation between age and measures of both income and self-rated health; older respondents, on average, had lower incomes and poorer self-rated health.

Perceived risk

Nearly three-quarters of respondents (71.0%) agreed they were at risk for lung cancer over their lifetime (Figure 3). However, a lower proportion felt the proximity of this risk: 20% fewer agreed that they faced this risk in the next 5 years. A lung cancer diagnosis was felt to carry a high risk of death by 81.3% of respondents. Notably, more than 50% of respondents did not connect tobacco use with increased lung cancer risk: 40.5% of respondents felt that they had “about the same risk” of lung cancer as non-smokers and an additional 10.8% felt that their risk of lung cancer was actually lower than non-smokers. When data on risk perception was further stratified by age group, there were no clear trends.

Perceived benefits

Most understood that a lung scan could help detect cancer earlier (85.7% of respondents agreed or strongly agreed), but almost 30% fewer felt that this would decrease their chances of dying from lung cancer (Figure 4). Less than half of respondents felt a lung scan would help them plan for the future, indicating a sense of diagnostic futility. However, a lung scan – presumably negative – might help their family worry less (69.7%).

Perceived barriers

The most commonly agreed-upon barriers to undergoing a lung scan were absence of symptoms, cost of scan, and paying for treatment (Figure 5). Higher education, which was correlated

with higher income, led to decreased perception of financial barriers for both screening and treatment. Despite almost three-quarters of respondents agreeing they were at risk for lung cancer over their lifetime, the understanding of this risk was nuanced: 75.5% of respondents might put off a lung scan in the absence of symptoms and 47.7% of respondents might put off a lung scan because they did not have any family members with lung cancer. Furthermore, almost one in two respondents (46.9%) indicated a lack of trust in the healthcare system. Respondents generally felt strongly that transportation would not be an impediment to screening.

Self-Efficacy

Most respondents felt at least “somewhat confident” that they could handle the logistics of a lung scan if needed (Figure 6). In particular, they were “confident” or “very confident” that they could find the time (80.8%) and transportation (88.0%) to undergo a scan. However, financial concerns were again highlighted in this category; there was less confidence about covering the cost of a scan with only 26.0% of respondents feeling “very confident.” Respondents were also more apprehensive about obtaining adequate scan information. Age ultimately did not predict mean self-efficacy scores but, for many individual self-efficacy questions, older age correlated with decreased confidence in ability to coordinate scan logistics. Specifically, decreased confidence secondary to anxiety and concern regarding scan results correlated with increasing age. These findings may indicate a more deep-seated trepidation amongst older men regarding lung cancer than evident in the construct of perceived risk, where increasing age did not correlate with perceived risk.

Analysis showed that there were several statistically significant correlations between the target constructs. Specifically, there was a statistically significant positive correlation between perceived benefits and self-efficacy, $r = .25$, $p < .05$ and perceived risk and self-efficacy, $r = .15$, $p < .05$. There was a statistically significant negative correlation between perceived benefits and perceived barriers, $r = -.15$, $p < .05$ and perceived barriers and self-efficacy, $r = -.56$, $p < .05$.

The results from stepwise multiple regression analysis showed that several demographic variables significantly predicted screening attitudes. Specifically, respondents’ perception of the benefits of lung cancer screening was significantly predicted by self-rated health, $R^2 = .01$, $F(1, 373) = 4.52$, $\beta = .12$, $p < .05$. Perceived barriers was significantly predicted by monthly household income and education level, $R^2 = .12$, $F(1, 368) = 24.1$, β (monthly

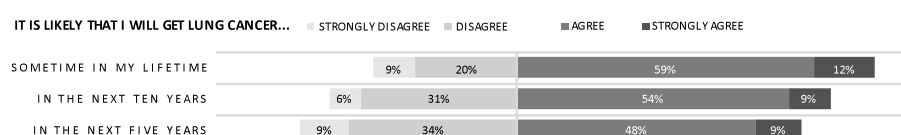


FIGURE 3
Perceived risk.

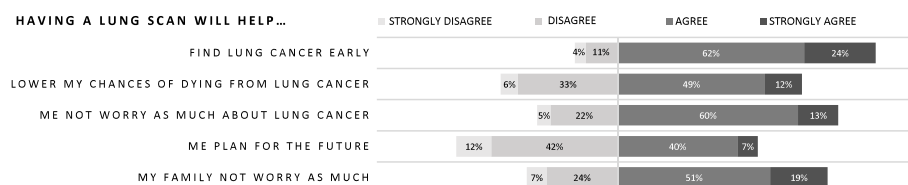


FIGURE 4
Perceived benefits.

household income) = $-.27$, β (education level) = $.15$, $p < .05$. Self-efficacy was significantly predicted by household income and education level, $R^2 = .09$, $F(2, 374) = 18.5$, β (monthly household income) = $-.2$, β (education level) = $.18$, $p < .05$.

Discussion

This study elucidates key health beliefs amongst Armenian male smokers that could both promote and impede lung cancer screening participation. In light of the significant mortality benefit, international organizations, such as the European Union, recommend nations begin planning to implement lung cancer screening using LDCT (19). However, even where screening is available, there has been low uptake. Organized lung cancer screening is part of the United States' national cancer prevention strategy with mandated insurance coverage (20), yet only 5-6% of eligible individuals undergo screening (21, 22). To maximize the mortality benefit of lung cancer screening, it is crucial to understand the potential screening barriers, particularly individual beliefs that predict screening uptake (16).

This survey in particular highlights an urgent need for further tobacco education in Armenia. Over half of respondents felt that they had an equivalent or lower lung cancer risk than non-smokers, demonstrating concerning ignorance of the strong causal relationship between smoking and negative health effects. Smokers have 20 times the risk of lung cancer compared to non-smokers (23) and heavy smoking is prevalent in Armenian men (7). Almost two-thirds of survey respondents had already met the 20-pack year USPSTF screening criterion.

Participants' perceptions and beliefs regarding lung cancer screening indicate that further education about the goal of screening is also needed. Over three-quarters of respondents might put off a lung scan in the absence of symptoms, yet screening serves to identify asymptomatic, early-stage disease. Although most survey respondents agreed that screening facilitates earlier cancer detection, an equivalent proportion did not believe that this could prevent lung cancer death. Screening with LDCT offers an effective mechanism to significantly reduce premature death from lung cancer, largely by stage migration, enabling the majority of cancers to be detected at stage I when the cancer is readily treatable (and typically asymptomatic) (12, 13).

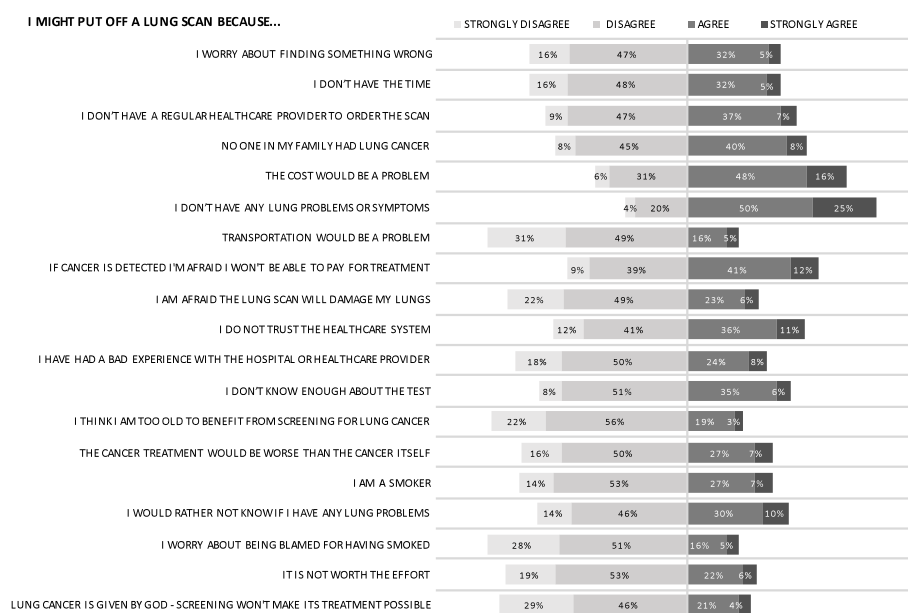
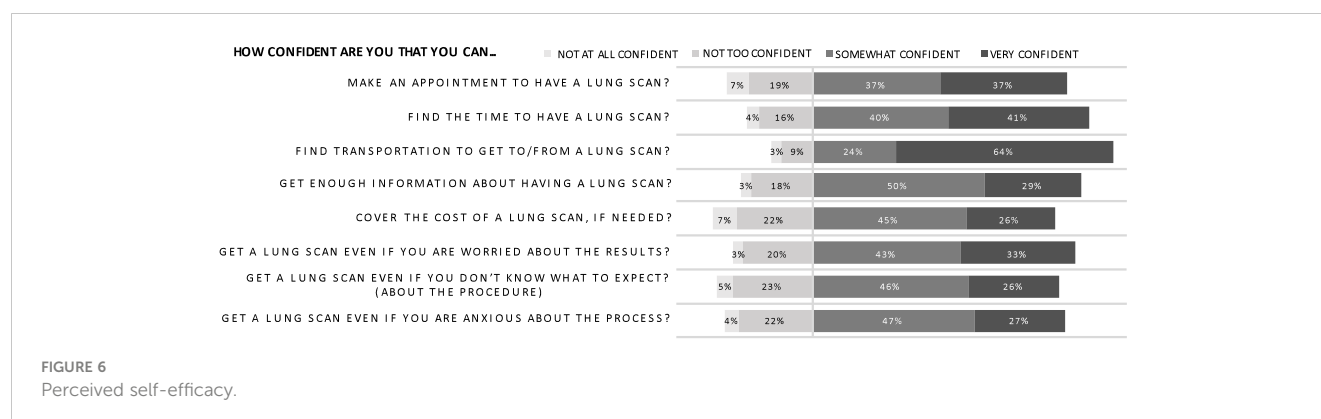


FIGURE 5
Perceived barriers.



Later-stage lung cancer treatment options are limited and usually prohibitively expensive with significant toxicities, particularly in LMICs (24). The cognitive disconnect between early detection and reduction in cancer mortality highlights an opportunity to reverse fatalistic beliefs and to educate Armenians on the curability of early-stage cancer to empower citizens to demand better care.

To some extent, fatalistic attitudes elucidated by the survey probably reflect the current availability and quality of early-stage cancer diagnosis and treatment in Armenia. Inconsistent use of internationally-approved histopathologic protocols often results in confusion and re-biopsy. Only 42% of the WHO's essential chemotherapeutics are registered as essential medications in Armenia with often prohibitive costs. Radiotherapy is centralized in Yerevan and poor utilization of immobilization devices limits therapeutic value and increases adverse effects (7).

Many of the other beliefs expressed in this survey, including concerns about trust and cost, also likely emanate from realities of the Armenian healthcare system. In a telephone survey on the Armenian healthcare system, 79% of Armenians reported they did not trust the government and 45% indicated they were dissatisfied with the healthcare system (25). Almost half of respondents felt equal access was "bad" or "very bad" and nearly one-third of respondents had not used the healthcare system in the last month due to inability to pay (25). The predictive power of education and income on perceptions of screening barriers and self-efficacy in this study further highlights these concerns. In a country where 84% of healthcare expenditures are out-of-pocket (and often catastrophic) despite health system reforms, such findings are unsurprising (25). To avoid exacerbating existing socioeconomic disparities in healthcare access in Armenia, cost, trust and other socioeconomic factors influencing screening behaviors would need to be carefully addressed in any organized screening program.

Next steps

Knowledge should be examined further to guide future education and mass media campaigns. Although this survey hinted at significant knowledge gaps among end-users (patients), it would also be important to characterize the knowledge and attitudes of primary care providers in a country where only 30% of primary care providers addressed the harms of smoking in the

last year (26). The WHO recommends that Armenia increase anti-tobacco media campaigns and access to tobacco cessation resources (10). Implemented together, tobacco cessation and lung cancer screening have positive synergistic effects and even greater magnitudes of cost-saving (27). One large, multicenter randomized controlled trial demonstrated that 40% of screened patients had quit smoking at seven years, compared to 5% in the general population, highlighting screening as a teachable moment and opportunity for intervention (11). Lung cancer screening could be a valuable platform for promoting tobacco cessation in Armenia.

Cost and payment are particularly important considerations in under-resourced settings. Although studies in China and India have shown that LDCT is an equally effective lung cancer screening modality in middle-income countries, no cost-effectiveness analyses for this income bracket have been published to-date despite the elevated burden of disease (8). Cancer cost Armenia about 2% of its gross domestic product in 2017, not including costs of absenteeism and presenteeism, with the vast majority (90%) of that cost due to premature death, not healthcare expenditure (4, 10, 28). Screening with LDCT is known to be cost-effective for high-income countries (8). Even though LDCT is more expensive than other screening modalities, the number needed to screen to prevent one lung cancer death is relatively low (320) compared to other cancers (e.g. 2000 mammograms to prevent one breast cancer death) (12, 29). Other screening programs in LMICs have been successfully funded through price discrimination (i.e. charging those who can pay) and public-private cost sharing (30). In Armenia, the cost of LDCT screening could be further offset by removing non-evidence-based screening exams from the current national screening strategy and by developing tailored screening criteria and intervals (26, 31).

Finally, a complete evaluation of the required resources for both screening and appropriate treatment of lung cancer in Armenia is needed. Armenia has at least seven computerized tomography scanners per 100,000, four thoracic surgery programs, and relatively up-to-date medical oncology, but it is unclear if there is the capacity to safely perform all steps along the continuum of diagnosis to treatment of lung cancer (7). Given the potential harm of screening without proper staging and treatment, further characterization and strengthening of the continuum is needed prior to piloting any organized screening. Formulating a clear and effective national cancer control plan will be an important part of Armenia's effort to tackle the growing burden of lung cancer and other NCDs.

Limitations

This study has several potential limitations. There may have been important unidentified differences between men who initially agreed to undergo the survey and those who declined. The study generalizability is likely limited to urban men. For example, transportation was generally not perceived as a barrier amongst respondents, but the majority of health services are concentrated in Yerevan. Compared to other nations, though, Armenia is relatively small and homogenous with most towns within a three-hour drive. The Nubarashen municipality, a lower-income area of Yerevan representing 1% of Yerevan's population, was not captured in this survey but it is unlikely that the lack of respondents from this municipality significantly affected the data. Regarding the statistical analysis, the use of forward stepwise linear regression has known limitations, including overfitting, bias, and model instability. Model instability, where small variations in the data can lead to the selection of distinct predictor variables and models, is particularly pronounced when predictor variables are highly correlated, although our data was evaluated for multicollinearity upfront. In short, the ability of the aforementioned independent variables to predict the median scores for the outcomes of perceived risk, benefits, barriers, and self-efficacy may be uncertain, and these results may not be generalizable. Finally, in this study, although education and income were evaluated, knowledge, an important factor in health beliefs and screening behavior, was not thoroughly assessed.

Conclusion

This study sought to assess the attitudes and beliefs of male smokers towards lung cancer screening in Armenia using an adapted, previously-validated version of the EHBM. Although many of the respondents' beliefs likely stem from realities of the Armenian healthcare system, this study also uncovered important knowledge gaps and concomitant educational opportunities. While these knowledge gaps warrant further research, this research should not delay robust national education on tobacco use, the nature of asymptomatic disease, and the role of screening.

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 1) Office of Human Research Protection Program at the University of California, Los Angeles (IRB#21-000784) 2) Ethics Committee at Yerevan State Medical University. Written informed

consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

NC: Conceptualization, literature search, interpretation of data, project administration, writing of the original draft. HT: Literature search, interpretation of data, writing of the original draft, visualization (figures), critical revision and editing of the paper. TG: Data curation, validation of all data provided in the paper, data analysis, critical revision and editing of the paper, validation of translation. AL: Study design, validation of translation, supervision and mentorship, critical revision and editing of the paper. JD: Study design, supervision and mentorship. MH: Translation, data collection, critical revision and editing of the paper. SS: Conceptualization, interpretation of data, project administration, supervision and mentorship, critical revision and editing of the 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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