

Cancer of Unknown Primary Origin: Incidence Trend and Athological Features, Iraq, 2005-2019

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ABSTRACT:

BACKGROUND:

Cancer of unknown primary origin is an obscure group of diagnoses in which the primary anatomical site of tumor origin is not specified.

OBJECTIVE: This study aimed to determine the trend of cancer of unknown primary origin in Iraq in the period from 2005 to 2019 at the national and governorate level and its pathological characteristics.

METHODS:

The data was compiled from the cancer registry of Iraq for the period 2005-2019 and from Al Amal Cancer Hospital for the period 2010-2019. Data included information on gender, age, geographical distribution, site of metastasis, and histology types.

RESULTS:

A total of 9,593 cases of CUP were registered in the cancer registry for the period 2005-2019. The total number of registered patients in Al Amal Cancer Hospital between 2010- 2019 was 1,698. The incidence of cancer of unknown primary origin demonstrated a convergence during 2005-2019 with an average of 1.88/100,000. There was a slight increase in incidence through 2006 (2.6/100,000) and 2007 (2.4/100,000) for both sexes. The majority of reported cases were in the age group 56-65 (31.5%) and males constituted 53.9% of all the cases. The commonest metastatic sites were lymph nodes (18%) and the liver (16%). Adenocarcinoma constituted 55.9% of cases.

CONCLUSION:

Iraq is considered a country with a low incidence of cancer of unknown primary origin. The diagnosis and treatment of cancer of unknown primary origin are challenging due to its late presentation, difficulty in diagnosis and the treatment choices offered are limited and non-selective.

KEYWORDS: cancer of unknown primary origin, incidence, trend, Iraq.

INTRODUCTION:

Cancer of unknown primary (CUP) origin is defined as a malignant neoplasm without specification of the site [1]. It is characterized as a histologically confirmed metastatic tumor detected when the site of primary origin cannot be determined based on clinical history, complete physical examination, routine laboratory tests, imaging and radio-metabolic techniques, and careful review of histological specimens [2].

Worldwide, CUP is the sixth to eighth most common cancer, accounting for 2.3% to 5% of newly diagnosed malignancies and the third to the fourth most common cause of death due to cancer-related disease. It is among the top ten cancers in both sexes in terms of incidence and mortality [3,4]. The annual age-adjusted incidence patients among all cancer cases was 3% [6]. Cancers of unknown primary (CUPs) represent up to 150,000 new cases diagnosed each year in the United States and the European Union,

per 100,000 population in the Netherlands is 5.3-6.7 cases [5]. In the UK, the proportion of CUP but the number may increase to 400,000 [7,8]. The American Cancer Society estimates that about 30,270 cases of CUP diagnosed in 2020 in the United States. This number represents about 2% of all cancers [9]. Within the past few years, the rate of CUP has declined by improvement in technology of detecting the primary tumor site, thus reducing the unknown primaries [3].

In Saudi Arabia, CUP incidence accounted for only 1.8% of all cancer cases over 35 years from 1975 to 2010 and the median age at diagnosis was 56 ± 16 years with a male to female ratio of 1.2:1. The liver was the most common site of metastasis, followed by the neck and peritoneum [10]. The prognosis of CUP is rather poor with the median survival of three to six months in the previous studies, but according to recent studies, the average survival time is about 9 to 12 months after diagnosis.

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This can vary widely depending on many factors, including the cancer cell type, site, metastasis, general condition of the patient, the treatments received, and the response to therapy.^[9,11] The nature or biology of CUP is poorly understood despite the ongoing molecular and translational research work.^[12]

The clinical presentation of CUP is extremely heterogeneous. About 15%–20% belong to clinicopathological subsets with a more favorable prognosis and similar to those with relevant known primary tumors. On the other hand, the majority of CUP patients (80%–85%) do not belong to specific subsets with modest sensitivity to therapy.^[13]

Aggressive behavior with the involvement of three or more organs, a short history of signs and symptoms, unpredictable metastatic patterns are among the fundamental characteristics of CUP.^[14] The site of primary origin can be found during a lifetime or autopsy. Autopsy data suggest that the lung, liver, pancreas, and gastrointestinal tract are common sites for primary tumors.^[15] Besides the clinical data, immunohistochemistry studies, blood tests, radiological techniques, and endoscopic procedures, can help to demonstrate the primary site.^[16]

In Iraq, cancer has become a major public health problem and its burden continues to grow without having the embraced environment that can help in the prevention of different non-communicable diseases including cancer. It is crucial to set studies to identify profiles and trends of different cancers that can help health policymakers to forecast the necessary resources for cancer prevention and management. Therefore, this study aimed to determine the trend in the incidence of CUP in Iraq during 2005-2019 at the national and governorate level and to determine its pathological characteristics.

METHODS:

The necessary data were collected from two main sources: the Iraq Cancer Registry, Cancer Board, Ministry of Health, and AL-Amal Hospital for Cancer Management. All registered cases of CUP during the period 2005-2019 were retrieved from the cancer registry. The Iraqi Cancer Registry registers all cancer cases attending the public and private health facilities in Iraq. A data collection form was developed to collect the following information: registered cases of CUP reported in 15 years from 2005 to 2019, gender, age, and geographical distribution by governorates. The incidence of CUP

including crude incidence and sex-specific incidence rates was calculated. The population data of Iraq was obtained from the Central Statistics Office, Iraq Ministry of Planning. The age-specific incidence rate was calculated from 2006-2019. This rate was not calculated for the year 2005, since the age grouping was different in this year.

The cancer registry of AL-Amal hospital was used to capture data on clinical and pathological characteristics that are not available in the Iraqi cancer registry. Al-Amal hospital for cancer management is considered the largest cancer facility in the Capital of Baghdad since its establishment in 1969. The available data from the records of CUP cases for the period 2010-2019 were reviewed. A data collection form was developed to retrieve the following information: demographic characteristics (age, gender, address), site of metastasis at presentation, the histopathological diagnosis, and whether the primary site was detected or not.

Data were demonstrated in tables (frequencies and percentages) and graphs. Descriptive analysis of the reported cases of CUP in the Iraqi cancer registry and Al-Amal hospital were done using Excel form and the Statistical Package for Social Sciences (SPSS) version 21.

Official approvals were obtained from the Iraqi Board of Medical Specialization, the Iraqi Cancer Board, and Al-Amal Hospital for Cancer Management.

RESULTS:

A total of 9,593 cases of CUP 4,822 (50.3%) males and 4,771 (49.7%) females were registered between 2005 and 2019. Table 1 demonstrated the incidence of CUP in Iraq, 2005-2019 among males, females, and the total population. Figure 1 demonstrated the trend of this incidence rate per 100,000 population by sex. There is an increase in the incidence of CUP in 2006 and 2007 then followed by a steady decline since then. The average incidence rate of CUP in Iraq was 1.88/100,000 population.

The annual incidence of CUP cases according to gender from 2005 to 2019 showed convergence, in both sexes and the range of incidence for males was $1.16/10^5$ - $2.75/10^5$ with an average of $1.89/10^5$. The trend was not statistically significant in males ($p=0.228$) and females ($p=0.319$). The range of incidence rate was $1.30/10^5$ - $2.49/10^5$ with an average of $1.78/10^5$ population and the trend was not statistically significant ($p=0.890$).

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Table 1: Number and incidence rate of CUP in Iraq, 2005-2019.

Year	No. Male Patients	Incidence per 100,000	No. Female Patients	Incidence per 100,000	Total No. of Patients	Incidence per 100,000
2005	280	1.99	238	1.71	518	1.85
2006	399	2.75	357	2.49	756	2.62
2007	391	2.62	311	2.11	702	2.36
2008	323	2.01	282	1.78	605	1.89
2009	184	1.16	205	1.3	389	1.22
2010	248	1.5	211	1.32	459	1.41
2011	314	1.85	271	1.66	585	1.75
2012	294	1.69	297	1.77	591	1.73
2013	273	1.53	291	1.69	564	1.61
2014	364	1.99	333	1.88	697	1.94
2015	323	1.73	357	1.95	680	1.84
2016	328	1.71	369	1.96	697	1.83
2017	373	1.98	415	2.25	788	2.12
2018	391	2.03	443	2.35	834	2.19
2019	337	1.7	391	2.02	728	1.86
% Change		-14.6%		18.1%		0.5%
P of the trend		0.228		0.319		0.890

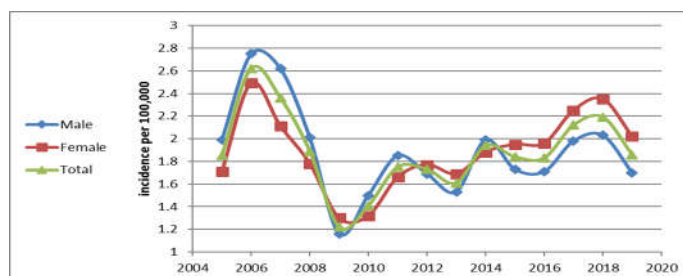


Figure 1: Incidence trend of CUP per 100,000 in Iraq, 2005-2019.

The annual incidence of CUP cases according to age groups in Iraq through 2006-2019 showed an obvious increase in incidence rate after age 40 years throughout the study period and reached the peak at age of 70 years

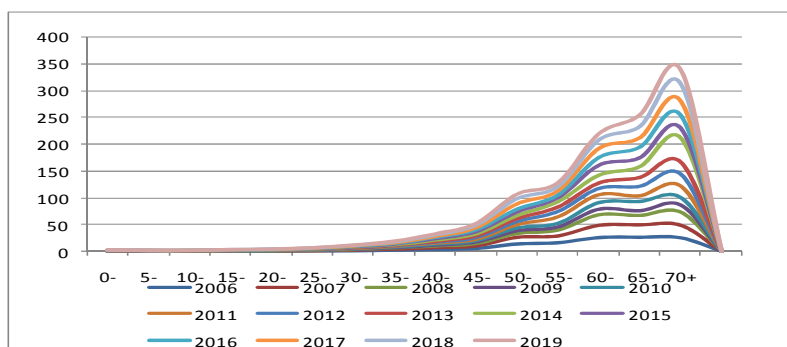


Figure 2: The annual incidence rate of CUP by age groups in Iraq, 2006-2019.

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The highest average incidence was reported in Baghdad (2.5/10⁵ pop) and Babylon (2.1/10⁵ pop) governorates while a low incidence rate was reported in Duhok, Erbil, Kirkuk, Salahuddin,

Anbar, Najaf, Diwaniyah, Thiqr, and Muthanah governorates in a range of 1- 1.5/100,000 population as seen in figure 3.

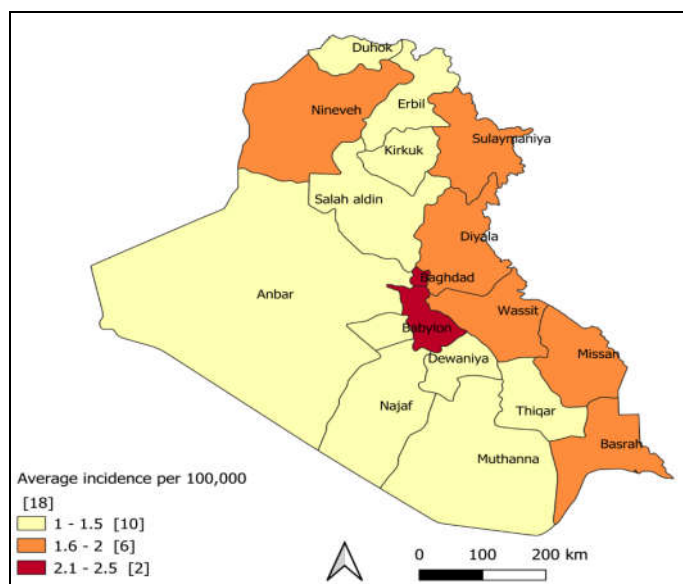


Figure 3: The average incidence rate of CUP in Iraqi governorates, 2005-2015.

The total number of CUP patients registered in Al-Amal Hospital for Cancer Management between 2010 to 2019 was 1,698 but the actual number of patients' files obtained from the archive section was only 540, as many files were distorted, lost, or lack the needed data.

It is noticeable that the number of CUP patients and the proportion among the total admitted patients were decreasing through these ten years. There is a significant progressive decline in the proportion of CUP over time ($p=0.019$) (Table 3).

Table 3: Annual numbers of CUP patients and the proportion to the total admitted cancer patients, Al-Amal Hospital, 2010-2019.

Year	No. of Total Admitted Patients	No. of CUP Patients	%
2010	5,086	222	4.36%
2011	4,738	220	4.64%
2012	4,872	204	4.19%
2013	3,942	203	5.15%
2014	4,819	189	3.92%
2015	4,775	145	3.04%
2016	3,876	136	3.51%
2017	4,531	160	3.53%
2018	4,424	139	3.14%
2019	3,734	80	2.14%

Most CUP patients were in the age group 56-65 (170, 31.5%) at presentation and the median age

was 57±14 years. The number of male patients was 291 (53.9%) of the cases.

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Table 4: Distribution of CUP patients managed in AL-Amal hospital by age and gender, 2011-2015 .

Age groups	Gender		Total
	Male	Female	No. (100%)
≤25	6 (50.0%)	(50.0%)	12 (2.2%)
26-35	13 (38.2%)	21 (61.8%)	34 (6.3%)
36-45	29 (44.6%)	36 (55.4%)	65 (12%)
46-55	54 (46.6%)	62 (53.4%)	116 (21.5%)
56-65	101 (59.4%)	69 (40.1%)	170 (31.5%)
66-75	71 (53.4%)	41 (46.6%)	112 (20.7%)
76+	17 (54.8%)	14 (45.2%)	31 (5.7%)
Total	291 (53.9%)	249 (46.1%)	540 (100%)

Single site metastasis was reported in 349 (64%) patients, and the affected organs were lymph nodes (98,18.1%) liver (85,15.7%), bones (47, 8.7%), lung (17, 3.1%), peritoneum (8,1.5%) and others (94,17.4%). The commonest histological subtype of the metastatic site of CUP was adenocarcinoma (302; 55.9%), followed by squamous cell carcinoma (75; 13.9%), undifferentiated carcinoma (37; 6.9%), and others (125; 23.3%).

DISCUSSION:

Compared to international data [3-9], the average incidence rate of CUP in Iraq is generally low (1.88/100,000), with some fluctuation across the years. The highest incidence was reported in 2006 (2.6/100,000) and 2007 (2.4/100,000) and it declined later. Likewise, CUP is also uncommon in some countries in the region as Saudi Arabia, where it accounted for only 1.8% of all cancer cases over the age of 35 years from 1975 to 2010^[10]. Significantly higher CUP incidence rates were reported in Australia (13.4 and 9.2 per 100,000 in men and women, respectively in 2011)^[17]. In Korea, a declining incidence has been observed to 32/100,000 for both sexes in 2015^[18] whereas, in Sweden, the incidence is about 12/100,000 in 2007^[19].

In general, the variations in the incidence rate between different countries reflect changes in the risk factors for cancer in a given population, the incidence trends of the primary cancers that potentially contribute to CUP, and changes in the diagnostic technologies and practice [20]. The low incidence in Iraq could be related to the lower overall incidence rate of cancer in Iraq (91.66 / 100,000 Iraqi population in 2019) [21]. Other factors could include the relatively shorter life expectancy compared to the developed countries. The average life expectancy in Iraq in 2020 is; 71.1 years for both sexes (73.2 years for

females, and 69.0 years for males [22], and the suboptimum registration due to insecurity experienced in some governorates. The latter had negatively affected morbidity and mortality registration of different diseases including cancers. Also, despite increasing oncology centers in the country, many patients prefer to have treatment outside the country.^[23]

Observational studies had demonstrated the importance of age as the strongest risk factor. CUP is a disease of elderly people. It is usually uncommon under the age of 40 years and the incidence increases above the age of 70 years.^[10,24] In the current study, 80% of CUP cases were reported above the age of 50 years with a median age at diagnosis of 57 years.

CUP was slightly more frequent in males than females; males to female ratio was 1.17:1. This finding is consistent with the findings reported in Saudi Arabia^[10].

While there were no known etiological factors that contribute to developing the CUP, different studies demonstrated the importance of certain risk factors in the etiology like heavy smoking (which is associated with about four folds increased risk), high alcohol consumption, obesity particularly central obesity and sun exposure.^[13,16,19,25,26]

A declining incidence has been observed in developed countries, and this has been attributed mainly to increasing utilization of advanced diagnostics and detailed pathology investigations, using genomics and transcriptomics to identify the origin of a tumor^[27], resulting in a significant improvement in the detection of primary cancer and expansion of therapy units^[17].

CUP cases were almost uniformly distributed among Iraqi governorates. The highest average incidence was in Baghdad and Babylon based on the Iraqi cancer registry data. The highest percentage of CUP cases managed in AL-Amal

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hospital were also from Baghdad (58%). This is clearly due to the availability and accessibility to specialized centers for cancer diagnosis and treatment. In general, cases of CUP were more common in the mid and southern Iraqi governorates compared to the northern governorates and on the eastern side more than western. It seems that the unstable security situation in the country, the most important of which is the incursion of ISIS that led to difficult access to certain oncology centers besides the possible variation in accuracy and completeness of the registration among the governorates are the most probable causes behind this variation rather than an actual variation in CUP risk. A link between exposure of certain areas in the south of country especially AL-Basra to depleted Uranium munition used during the Gulf war 1 and 2 with the increasing incidence of different cancers had been postulated^[28] although others denied the possibility of this association.^[29]

Pathological confirmation is recommended where feasible as it could assist in proper diagnosis and help guide appropriate therapeutic interventions. The use of histopathology assisted by immunohistochemistry provides additional information necessary to create a tailored treatment algorithm for CUP patients.^[14,16,24] The most common histological type was adenocarcinoma which is the dominant histological subtype among CUP patients followed by not otherwise specified (NOS) morphology manifested as poorly differentiated carcinoma. The commonest metastatic sites were the lymph nodes and the liver. These findings are consistent with other studies.^[10]

CONCLUSION:

Iraq is considered a country with low CUP incidence, affecting mostly elderly people with slightly more frequently reported among males. The trend was not static along the study period peaking in 2006 and 2007 and declining later. While this is the first study that highlighted the CUP in Iraq, the Iraqi cancer registry lacks important variables on diagnosed cancer patients that make the cancer patients' profile incomplete. Also, the quality of documentation at the cancer treatment centers is unfavorable and not computerized particularly the files of the previous years. The Iraqi Cancer Council is urged to address these gaps to strengthen the population-based cancer registry as an essential approach to national cancer control and policy planning.

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