ORIGINAL ARTICLE

Epidemiologic, histopathological, and prognostic analysis of cancer of unknown primary in an Iranian population

Mohammad Rayati[1,2], Hamzeh Ahmadi[3], Mitra Heidarpour[4], Nadia Najafizade[5], Mehrdad Zeinalian[1,2,6]

[1]Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Iranian Cancer Control Center (MACSA), Isfahan, Iran, [3]Department of Epidemiology and Biostatics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Radiooncology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [6]Pediatric Inherited Disease Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran

Background: Cancer of unknown primary (CUP) is characterized by metastatic cancer cells with no identifiable primary tumor despite extensive diagnostics. This study investigates the epidemiologic, histopathological, and prognostic factors in 352 CUP cases in Iran. **Materials and Methods:** This retrospective study reviewed the clinical documents of CUP patients registered in MACSA, a charity-based referral center in central Iran, Isfahan, within 2016–2021. The patients' data were analyzed, and survival associations were assessed using Cox proportional hazards regression models. **Results:** Altogether 352 CUP patients were included in the study. The mean age at diagnosis was 65.9 ± 14.3 years, with 52.6% being male. Abdominal pain (32.1%) was the most common presentation. Metastatic adenocarcinoma (31.5%) was the most frequent histopathological type, with the liver (48.6%) as the most prevalent metastatic site. Single-site metastasis was seen in 55.4% of patients. Immunohistochemistry, conducted in 40.3% of patients, was inconclusive in identifying the primary site. The median overall survival was 5 months (95% confidence interval [CI]: 4.0–7.0). Multivariable Cox regression analysis showed older age increased risk of death (hazard ratio [HR]: 1.028, 95% CI: 1.019–1.037). Neuroendocrine tumors were linked to a lower risk (HR: 0.553, 95% CI: 0.313–0.978), while metastasis to the liver (HR: 1.382, 95% CI: 1.076–1.774) and pancreas (HR: 2.138, 95% CI: 1.094–4.176) increased mortality risk. **Conclusion:** This study provides large-scale evaluation of CUP in an Iranian population, revealing its poor prognosis and the limited diagnostic utility of IHC. The findings align with global data and highlight the urgent need for improved diagnosis and treatment to enhance patient outcomes.

Key words: Epidemiology, Iranian population, prognosis, unknown primary neoplasm, unknown primary tumor

How to cite this article: Rayati M, Ahmadi H, Heidarpour M, Najafizade N, Zeinalian M. Epidemiologic, histopathological, and prognostic analysis of cancer of unknown primary in an Iranian population. J Res Med Sci 2025;30:46.

INTRODUCTION

Cancer of unknown primary (CUP), primary metastatic cancer, or malignancy of unknown origin is a metastatic syndrome characterized by the presence of metastatic cancer cells without an identifiable primary tumor, even after extensive diagnostic workup.[1] This enigmatic condition poses significant challenges in both diagnosis and treatment. The incidence rate of CUP is difficult to determine precisely, as some cases initially classified as CUP are later found to have identifiable primary sites.[2] Nevertheless, CUP is estimated to account for approximately 2%–5% of all cancer diagnoses globally.[3]

CUP cases are often marked by early dissemination and an aggressive clinical course.[4] Patients are typically diagnosed at advanced stages with severe metastasis-related symptoms. Epidemiologic data on CUP are limited, making it difficult to establish a specific risk factor profile for this condition.[5] Despite advances in clinical diagnostics, including imaging,

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_520_24

Address for correspondence: Dr. Mehrdad Zeinalian, Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: zeinalianmehrdad@gmail.com
Submitted: 10-Sep-2024; **Revised:** 24-May-2025; **Accepted:** 07-Jul-2025; **Published:** 30-Sep-2025

endoscopy, and histopathological evaluations using classical immunohistochemical (IHC) biomarkers, the primary site remains elusive in many cases.[6,7] IHC is employed to predict the probable origin of the cancer; however, it successfully identifies the primary site in less than 30% of cases using various immunostaining panels.[4] Consequently, CUP remains a significant challenge for clinicians.

Generally, CUP malignancies are difficult to treat for some reasons. At diagnosis, CUP has typically already metastasized beyond the primary site, making curative treatments such as surgery or radiation therapy less effective. Moreover, the unidentified cancer type hinders the selection of the most appropriate treatment. Meanwhile, most of the CUPs are aggressive and rapidly progressing.[8]

Within the heterogeneous classification of CUP, distinct subsets with more favorable prognoses have been identified, where median survival extends to 15–20 months with chemotherapy.[6] These subsets, comprising approximately 10%–20% of cases, are characterized by clinical and pathological features that strongly suggest the site of origin, even if it is not directly detected.[3] Unfortunately, the majority of newly diagnosed CUP cases fall into the unfavorable subset category. The median overall survival (mOS) for these patients ranges from 4 to 10 months. These survival rates have remained largely unchanged over the years, despite the introduction of new chemotherapeutic agents.[9]

The variability in disease registration and diagnostic approaches across the countries worldwide makes it challenging to compare CUP incidence globally, identify trends, and assess etiology.[5] Uncovering the feature of CUP is crucial due to its unique clinical presentation and the need for tailored therapeutic approaches leading to improved diagnostic techniques, better management strategies, and enhanced patient outcomes. Moreover, exploring the epidemiologic, histopathological, and prognostic factors associated with CUP can provide new insights into cancer biology and metastasis, potentially helping the management of other metastatic cancers.

To the best of our knowledge, there is no comprehensive study on CUP in the Iranian population. Accordingly, this study aims to investigate the epidemiologic, histopathological, and prognostic factors in Iranian CUP cases, providing valuable insights into this challenging condition within the Iranian population.

PATIENTS AND METHODS

Affiliated center

This study was conducted at the MACSA center in Isfahan, Iran. MACSA is a charity-based referral institute providing comprehensive supportive and palliative care services including psycho-oncology, nursing, rehabilitation, and more. These services are offered in various settings comprising outpatient clinics, inpatient wards, home care networks, and hotline counseling centers for all cancer patients at any stage and their families, regardless of their socioeconomic status.[10] Upon admission, the trained interviewers collect demographic data, past and family medical history, and details of the current disease (including diagnostic tests and their results and previous treatments) through face-to-face interviews. Patients are followed up regularly, and all their conditions and complaints are documented until death or voluntary service rejection. Informed consent is voluntarily obtained from those patients who have willingness to cooperate in research projects.

Study design and patients

All clinical documents of cancer patients registered at MACSA, Isfahan, within 2016–2021 were reviewed retrospectively. Patients diagnosed with CUP,[11] confirmed by a board-certified oncologist or internist, were included. Patients with substantial data deficits in their files were contacted. Those who were inaccessible were excluded. The Ethical Review Committee of Isfahan University of Medical Sciences granted approval for this study (IR.MUI.MED.REC.1400.004).

Statistical analysis

The numerical variables were presented as mean and standard deviation, while the categorical ones were expressed as frequency and percentage. Charts were created using Tableau 2019.4 (Salesforce, United States). The associations of clinical features with survival were assessed using univariate and multivariable Cox proportional hazards regression models. All significant variables in univariate analysis were included in the multivariable analysis. The results were reported as hazard ratio (HR) with 95% confidence interval (CI). Overall survival (OS) was defined as the time from diagnosis to the date of death or last follow-up. Kaplan-Meier curves were used for illustrative purposes to visualize survival differences based on variables that remained significant in the multivariable Cox regression model. mOS was also calculated and reported for the studied population overall and for each significant variable in the multivariable Cox model. Data were analyzed using STATA 17 (STATA Corp., United States), and $P < 0.05$ was considered statistically significant.

RESULTS

Among the 6,245 cancer patients registered at MACSA-Isfahan within 2016–2021, finally 352 (5.6%) subjects were enrolled in the study.

Demographic information

Out of the 352 patients, 185 (52.5%) were male. The mean age at diagnosis was 65.9 ± 14.3 years, with an age range of 7–95 years. The most common primary presentation was abdominal pain (32.1%). Notably, 20 (5.7%) patients were asymptomatic, with their disease diagnosed incidentally. Dyspnea and weight loss were the next most common presentations, occurring in 12.8% and 12.2% of the patients, respectively. Most of the patients (n = 197, 56%) were under palliative care due to their poor prognosis or clinical situation [Table 1].

Table 1: Comprehensive demographic information of the cancer of unknown primary patients

	Frequency (n=352), n (%)
Gender	
Male	185 (52.5)
Female	167 (47.5
Life status	
Dead	327 (92.9)
Alive	25 (7.1)
First presentations (most frequent)	
Abdominal pain	113 (32.1)
Dyspnea	45 (12.8)
Weight loss	43 (12.2)
Bone pain	25 (7.1)
Treatment	
Chemotherapy	104 (29.5)
Radiotherapy	13 (3.7)
Both	38 (10.8)
Palliative	197 (56)

Histopathological features

In total, 112 (31.8%) patients had not undergone a biopsy. Among the patients tolerated biopsy, metastatic adenocarcinoma (31.5%) and metastatic undifferentiated carcinoma (26.4%) were the most common histopathological features. The liver, lung, and bone were the most prevalent targets for metastatic cells, affecting 48.6%, 27.6%, and 22.4% of the patients, respectively. Patients were categorized according to the number of organs with metastasis, with single-site metastasis being the most common (195 cases, 55.4%) [Table 2].

Table 2: Histopathological features of tumors in the cancer of unknown primary patients

	Frequency (n=352), n (%)
Pathology	
No biopsy	112 (31.8)
Undifferentiated carcinoma	93 (26.4)
Adenocarcinoma	111 (31.5)
Melanoma	9 (2.6)
Neuroendocrine	16 (4.5)
Sarcoma	8 (2.3)
Others	3 (0.9)
Site of metastasis (most frequent)	
Liver	171 (48.6)
Lung	97 (27.6)
Bone	79 (22.4)
Peritoneum	51 (14.5)
lymph node	38 (10.8)
Number of involved organs	
One site	195 (55.4)
Two sites	96 (27.3)
More than two sites	61 (17.3)

IHC analysis had been performed in 142 (40.3%) patients by referring laboratories for tissue-of-origin markers based on the recommended guidelines.[11,12] These analyses yielded inconclusive results in all evaluated cases. The most frequently observed positive markers were CK7 in adenocarcinoma (77.8%) and undifferentiated carcinoma (68%), chromogranin and synaptophysin in neuroendocrine tumors (57.1%), vimentin in sarcoma (57.1%), and MelanA and HMB45 in melanoma (75%) [Figure 1a]. As for negative markers, CK20 was predominantly absent in adenocarcinoma (60.3%), undifferentiated carcinoma (56%), and neuroendocrine tumors (57.1%). Moreover, sarcoma cases frequently lacked HER2 and CK7 (71.4%), while CD34 was the most common negative marker in melanoma patients (50%) [Figure 1b].

Prognostic factors

Overall, the mOS was 5 months (95% CI: 4–7 months). In the univariate Cox regression analysis, age was found to be a significant factor, with the HR increasing with age (HR = 1.028, P < 0.001). Several symptoms were associated with an increased risk of death, including abdominal pain (HR: 1.313, P = 0.02), anorexia (HR: 2.534, P < 0.001), weight loss (HR: 1.741, P = 0.001), jaundice (HR: 2.166, P = 0.002), and malaise (HR: 1.716, P = 0.02). Interestingly, low back pain (HR: 0.605, P = 0.04) and neck mass (HR: 0.423, P = 0.02) were associated with a decreased HR. In terms of pathology, neuroendocrine tumors (HR: 0.54, P = 0.03) and sarcomas (HR: 0.359, P = 0.02) were associated with a lower risk of mortality. Metastasis to the liver (HR: 1.72, P < 0.0001) and pancreas (HR: 2.212, P = 0.01) were associated with an increased risk, while lymph node metastasis was associated with a decreased risk of mortality (HR: 0.63, P = 0.02) [Table 3].

In the multivariable Cox regression analysis, age remained a significant factor, with each additional year of age associated with a 2.8% increase in risk of death (HR: 1.028, 95% CI: 1.019–1.037, P < 0.001). Neuroendocrine tumors had a lower HR (0.553, 95% CI: 0.313–0.978, P = 0.04), indicating a lower mortality risk in the multivariable model. Metastasis to the liver (HR: 1.382, 95% CI: 1.076–1.774, P = 0.01) and pancreas (HR: 2.138, 95% CI: 1.094–4.176, P = 0.04) were associated with an increased risk of death [Table 3 and Figure 2].

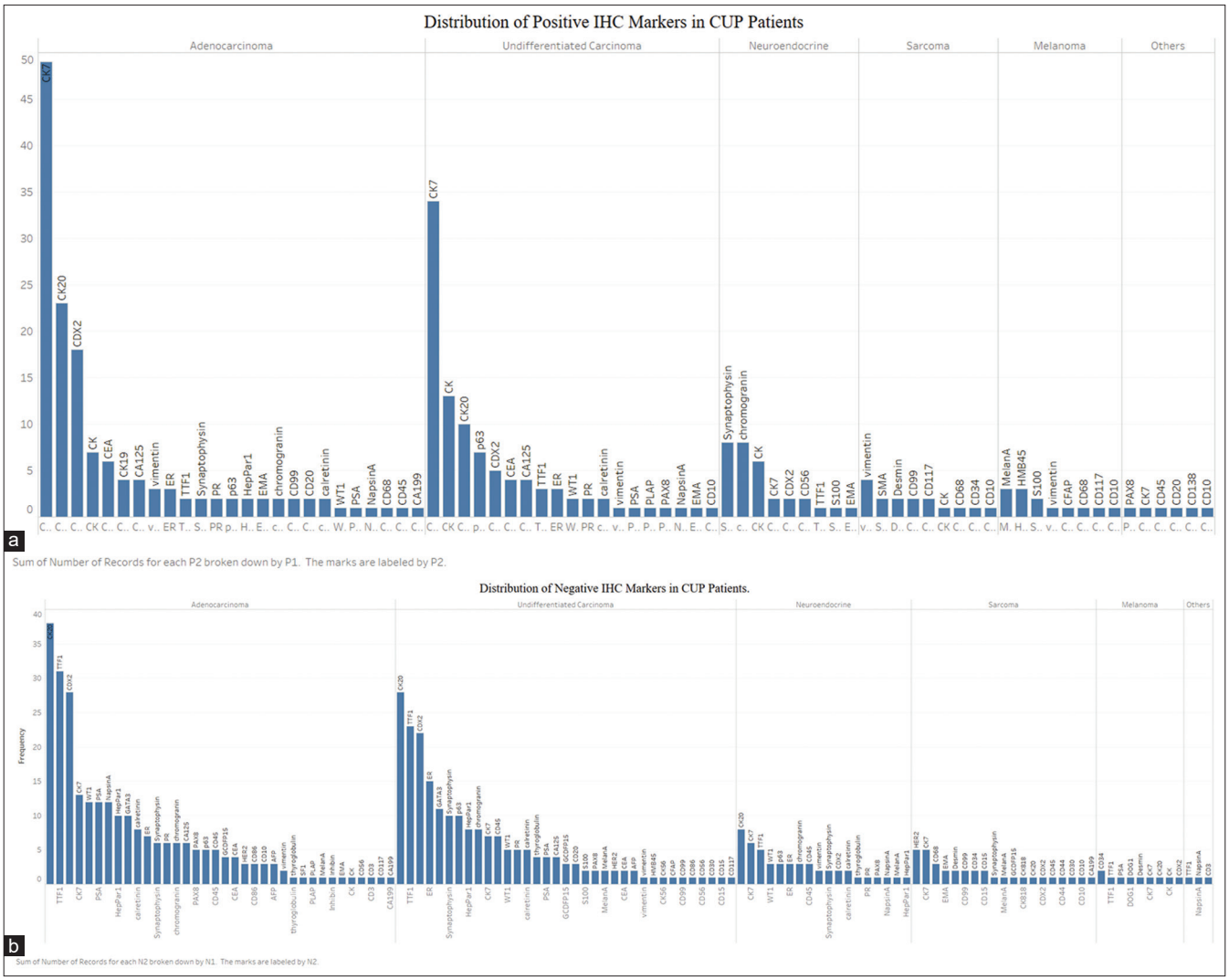

Figure 1: Distribution of immunohistochemical (IHC) markers across different cancer types in cancer of unknown primary (CUP) patients. This figure illustrates the frequency of (a) positive and (b) negative IHC markers detected in various types of cancers among CUP patients. The cancer types include adenocarcinoma, undifferentiated carcinoma, neuroendocrine tumors, sarcoma, melanoma, and others. Each bar represents the percentage of patients within each cancer type exhibiting positive or negative staining for specific markers. ICH = Immunohistochemical; CUP = Cancer of unknown primary

DISCUSSION

In the current study, the epidemiologic, histopathological, and prognostic feature of CUP has been evaluated within an Iranian population. Accordingly, to provide a comprehensive insight into clinical characteristics and outcomes of the disease, 352 CUP patients were studied.

Demographic features

As mentioned, 52.6% of the patients were male, with a mean age at diagnosis of 65.9 ± 14.3 years. This age distribution aligns with other studies, though variations exist. For instance, in a German study, the median age was 46 years,[13] while in an American population, it was 72 years,[14] indicating a wide age range in different populations. Our gender distribution also aligns with other reports, with some studies showing a slight male predominance[1,15,16] and others reporting a higher percentage of female patients.[17-19] It worth noting that although there is no exact explanation for these differences, it can be attributed to the genetic variety of studied populations.

Abdominal pain was the most common presentation in our study (32.1%), followed by dyspnea (12.8%) and weight loss (12.2%). Notably, 5.6% of our patients were asymptomatic, with their condition discovered incidentally. Cachexia and weight loss are prevalent symptoms in patients with CUP. However, due to the heterogeneous nature of CUP, patients may exhibit a wide range of signs and symptoms depending on the site of malignant involvement.[3,9] Additionally, paraneoplastic syndromes can occur and often present prior to a definitive diagnosis. The prompt recognition of these syndromes can facilitate earlier cancer diagnosis, potentially significantly

improving the prognosis for CUP patients.[3,9] A Chinese study highlighted anemia, fever, and enlarged lymph nodes as prevalent symptoms.[1] Another study observed constitutional symptoms, including weight loss (20.3%) and other general symptoms such as anorexia, fatigue, and fever, in 81.6% of patients.[20] These findings reflect variations in clinical presentations across different studies.

Notably, our study adds to the understanding of CUP demographics by providing specific insights into an under-researched Middle Eastern population, offering a regional perspective that complements global data. Moreover, by emphasizing the varied clinical presentations in our cohort, our findings can inform tailored diagnostic approaches in similar healthcare settings.

Histopathologic features

Our study found that metastatic adenocarcinoma (31.5%) was the most frequent histopathological type. Several studies also reported adenocarcinoma as the predominant histologic type,[1,13-15,17,18] though the prevalence of other cancer types varies across different studies. The liver, lung, and bone were the most common metastatic sites in our study, affecting 48.6%, 27.6%, and 22.4% of patients, respectively. Consistent with our findings, Yoon *et al*.[18] reported liver involvement in 39% of cases as the most frequently involved organ. Other studies have shown variability in metastatic sites: one found frequent liver and lymph node involvement (56% and 51%),[13] another identified lymph nodes as the most prevalent site (38%),[16] and another reported primary metastatic sites as lymph nodes (60%), liver (31%), bone (25%), and lung (20%).[19] These results highlight the liver as a consistently common site of metastasis, while the involvement of other organs varies across different populations.

In our study, 195 (55.4%) patients exhibited involvement of only a single organ. Two-organ involvement was observed

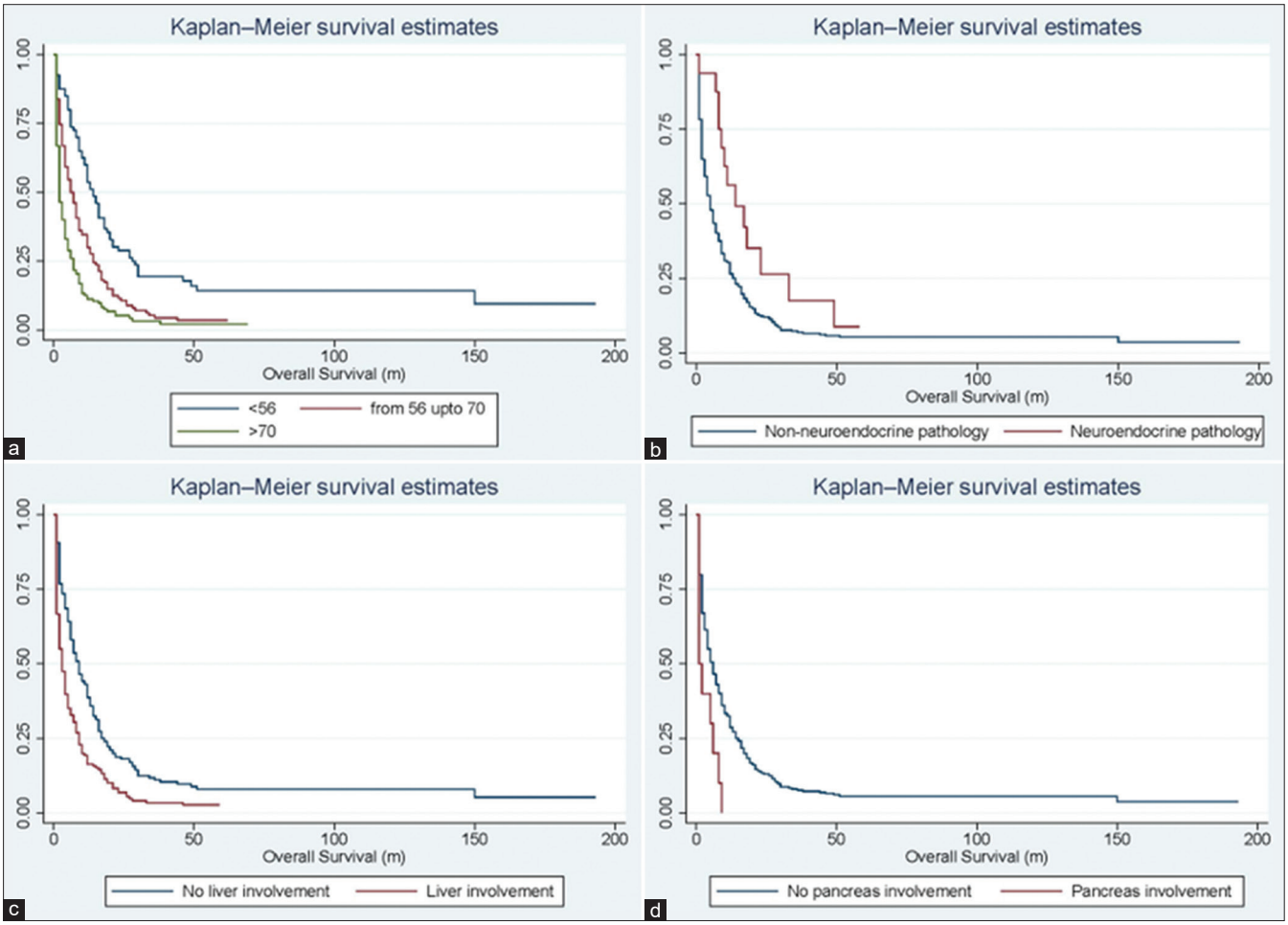

Figure 2: Kaplan-Meier survival curves for significant factors in the multivariable cox regression analysis of factors influencing survival in cancer of unknown primary patients.(a) Age: Patients are categorized into three age groups with median overall survival (mOS) of 14 months for those less than 56 years old, 6 months for those aged 56 to 70 years, and 2 months for those over 70 years old, (b) Neuroendocrine pathology: Patients with neuroendocrine tumors have a mOS of 14 months, whereas those with nonneuroendocrine pathology have an mOS of 5 months, (c) Metastasis to the liver: Patients without liver involvement have a mOS of 9 months, compared to an mOS of 3 months for those with liver metastasis, (d) Metastasis to the pancreas: Patients without pancreatic involvement have a mOS of 6 months, while those with pancreas metastasis have an mOS of 1 month

Table 3: Univariate and multivariable cox regression analysis of factors influencing survival in cancer of unknown primary patients

	Univariable			Multivariable		
	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.028	1.02–1.036	<0.001	1.028	1.019–1.037	<0.001
First presentation						
Abdominal pain	1.313	1.042–1.655	0.02	1.174	0.92–1.5	0.20
Anorexia	2.534	1.617–3.973	<0.001	1.529	0.942–2.481	0.09
Weight loss	1.741	1.255–2.415	0.001	1.286	0.91–1.819	0.15
Jaundice	2.166	1.323–3.546	0.002	1.49	0.888–2.498	0.13
Low back pain	0.605	0.371–0.986	0.04	0.6	0.364–0.988	0.05
Neck mass	0.423	0.209–0.855	0.02	0.638	0.294–1.387	0.26
Malaise	1.716	1.089–2.704	0.02	1.186	0.73–1.926	0.49
Pathology						
Neuroendocrine	0.54	0.31–0.94	0.03	0.553	0.313–0.978	0.04
Sarcoma	0.359	0.148–0.873	0.02	0.529	0.214–1.312	0.17
Metastasis site						
Liver	1.72	1.379–2.142	<0.0001	1.382	1.076–1.774	0.01
Lymph node	0.63	0.434–0.913	0.02	0.746	0.493–1.13	0.17
Pancreas	2.212	1.172–4.174	0.01	2.138	1.094–4.176	0.04

All variables were tested in the univariate Cox regression. Variables significant in the univariate analysis were included in the multivariable model. The table displays all variables that were significant in the univariate and subsequently were included in the multivariable analysis. CI=Confidence interval; HR: Hazard ratio

in 27.3% of patients, while 17.3% had metastasis in three or more organs. Similar findings have been reported in other studies, where single-site metastasis is the predominant form.[13,19] In another study, 62.5% of patients had metastasis involving fewer than three organs.[1] In our study, this percentage was 82.7%.

Among our CUP population, IHC analysis was performed in 142 (40.3%) patients for tissue-of-origin markers, which did not result in specific findings. There is currently no global agreement on the optimal pathological methodology; however, existing European and US guidelines endorse a step-wise approach.[12] Tumors can typically be broadly categorized as carcinoma, rather than melanoma, lymphoma, or sarcoma, based on initial hematoxylin and eosin (H and E) staining. Carcinoma can be further classified into squamous, urothelial, neuroendocrine, solid organ, or adenocarcinoma subtypes. For adenocarcinomas, the probable site of origin can be suggested using markers in a lineage-specific panel.[9] Nevertheless, interpreting the results is more complex and certain diagnostic challenges persist. It is essential to recognize that tumors are heterogeneous, and a single biopsy may not represent the entire tumor. Additionally, unusual staining patterns can complicate diagnosis. Cytokeratin expression can also be misleading. Furthermore, aberrant expression of epithelial markers has been observed in melanomas with epithelioid morphology, and the loss of conventional melanocytic marker expression has been reported in metastatic lesions, necessitating careful exclusion of other tumor types.[9] Moreover, results of H and E and IHC can conform to the patterns of several organs. Additionally, despite specific patterns, there might be no detectable tumor in the recommended organ.[21] Our study underscores the limitations of IHC in CUP diagnosis, especially in resource-constrained settings, and highlights the need for integrating molecular diagnostics in future studies.

Prognostic factors

The mOS in our study was 5 months. Patients with neuroendocrine pathology in our study demonstrated improved survival outcomes, consistent with the favorable categorization.[3] Although single-site metastasis is considered a factor indicative of a favorable subgroup,[3] our study did not find a significant relationship between the number of metastases and survival. None of our patients had an IHC panel profile of CK20+, CDX2+, and CK7–, precluding evaluation of this particular favorable subgroup.[3] Further exploration of other factors related to the favorable subset was not feasible due to the lack of detailed information of our cases. In our study, older age and metastasis to the liver or pancreas were significantly associated with decreased survival in multivariable Cox regression analysis. No other factors demonstrated a significant relationship with survival.

A significant proportion of our patients (56%) were under palliative care due to poor prognosis and/or clinical situation. In other patients, chemotherapy and/or radiotherapy were unsuccessful in improving survival. Most of the recommended treatment regimens are primarily supported by data from single-arm, phase II trials at best.[22-24] Moreover, randomized study data are scarce and typically derive from small trials, offering suggestions rather than definitive guidance on preferred regimens.[25-27] There has been no significant advancement in biologically targeted

therapies. In conclusion, while empiric chemotherapy has long been the cornerstone of treatment for CUP patients with adequate performance status, clinical outcomes remain largely unsatisfactory.[6]

Finally, this study provides critical insights into the epidemiological, histopathological, and prognostic characteristics of CUP, which have significant implications for health policy and prioritization. The findings can guide the identification of high-risk populations and the development of targeted diagnostic strategies. By highlighting the aggressive nature and diagnostic challenges of CUP, the study emphasizes the need for advanced screening tools and protocols. Furthermore, it underscores the importance of integrating research findings into actionable health policies, such as risk stratification guidelines and specialized diagnostic centers, paving the way for improved patient outcomes and more efficient healthcare systems.

Limitations and future directions

This study has several limitations that should be considered when interpreting its findings, alongside opportunities for future research to address these gaps. The retrospective nature of the study may introduce biases in data collection and patient selection. However, all CUP patients registered at the MACSA center during the study period were included, and standardized data collection protocols minimized inconsistencies. While IHC was performed in 40.3% of patients, the inconclusive results reflect the diagnostic challenges inherent in CUP rather than a shortcoming of the study. Moreover, the reliance on a single-center dataset, despite its broad referral base and diverse patient demographics, may limit the generalizability of the findings to the wider Iranian population or other regions.

Certain demographic and epidemiological factors, such as environmental exposures, lifestyle influences, and genetic predispositions, were not assessed in this study due to the constraints of the available data. Additionally, the follow-up duration was limited by the poor prognosis of CUP patients, restricting the ability to evaluate long-term outcomes or late recurrences. Although the Cox proportional hazards model was appropriate for identifying prognostic factors, it does not fully explore complex interactions among variables.

Future research should prioritize multi-center studies to enhance the generalizability of findings and provide a broader perspective on CUP epidemiology and outcomes. Prospective studies are essential to systematically collect detailed demographic, lifestyle, environmental, and genetic data, enabling a more comprehensive understanding of CUP's risk factors and prognosis. Integrating advanced molecular profiling techniques alongside IHC could improve diagnostic accuracy and refine classification systems. Longer follow-up durations are needed to capture long-term survival and recurrence patterns, especially for patients with more favorable prognoses. Additionally, employing advanced statistical methods, such as nonlinear models or machine learning approaches, may uncover complex relationships between variables, offering deeper insights into survival predictors and guiding future patient management strategies.

CONCLUSION

Our study provides a comprehensive analysis of the epidemiologic, histopathological, and prognostic features of CUP in an Iranian population, highlighting its poor prognosis and the need for tailored diagnostic and therapeutic approaches. This study represents large-scale investigation of CUP in an Iranian population, addressing a critical gap in regional data and offering insights into the unique epidemiological and clinical characteristics of CUP in Middle Eastern settings. The results match global trends, highlighting the need to improve CUP management for better patient survival and quality of life. Specifically, this study underscores the diagnostic challenges inherent in CUP, particularly the limited utility of IHC in identifying the primary site, which is a consistent issue in resource-constrained settings. Further research is essential to refine the current strategies for better outcomes in this challenging condition. Future directions should include integrating advanced molecular profiling with traditional diagnostic approaches to enhance the identification of the primary site and improve prognostic evaluations. Additionally, multi-center and prospective studies with longer follow-up periods are needed to validate these findings and explore long-term outcomes, particularly for favorable CUP subsets.

Authors' contribution

MR and MZ designed the study. MR was responsible for data preparation and curation and drafting the manuscript. MR also conducted the data visualization. MR and HA performed the data analysis. MH supervised and provided consultation for the histopathological aspects. NN provided consultation for the treatment and survival aspects. MZ supervised the overall study. All authors contributed to the revision of the manuscript.

Acknowledgments

This article was approved by the Ethical Review Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.004). The authors extend their gratitude to the dedicated healthcare professionals at the MACSA Center in Isfahan, Iran, and to the cancer patients and their families who participated in this study.

Financial support and sponsorship

The current study was funded by Isfahan University of Medical Sciences as a general practitioner thesis with ID: 399972.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yang H, He F, Xu W, Cao Z. Clinical features of cancer with unknown primary site (clinical features, treatment, prognosis of cancer with unknown primary site). BMC Cancer 2022;22:1372.
2. Key Statistics for Cancers of Unknown Primary. Available from: https://www.cancer.org/cancer/types/cancer-unknown-primary/about/key-statistics.html. [Last accessed on 2024 Jun 21].
3. Lee MS, Sanoff HK. Cancer of unknown primary. BMJ 2020;371:m4050.
4. Tian F, Liu D, Wei N, Fu Q, Sun L, Liu W, *et al.* Prediction of tumor origin in cancers of unknown primary origin with cytology-based deep learning. Nat Med 2024;30:1309-19.
5. Hermans KE, Kazemzadeh F, Loef C, Jansen RL, Nagtegaal ID, van den Brandt PA, *et al.* Risk factors for cancer of unknown primary: A literature review. BMC Cancer 2023;23:314.
6. Kolling S, Ventre F, Geuna E, Milan M, Pisacane A, Boccaccio C, *et al.* Metastatic cancer of unknown primary or "primary metastatic cancer"? Front Oncol 2019;9:1546.
7. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). Crit Rev Oncol Hematol 2009;69:271-8.
8. Posner A, Sivakumaran T, Pattison A, Etemadmoghadam D, Thio N, Wood C, *et al.* Immune and genomic biomarkers of immunotherapy response in cancer of unknown primary. J Immunother Cancer 2023;11:e005809.
9. Beauchamp K, Moran B, O'Brien T, Brennan D, Crown J, Sheahan K, *et al.* Carcinoma of unknown primary (CUP): An update for histopathologists. Cancer Metastasis Rev 2023;42:1189-200.
10. Iranian Cancer Control Center. Iranian Cancer Control Center (MACSA). Available from: https://macsa.ir/fa/. [Last accessed on 2024 Jul 03].
11. Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G, *et al.* Cancers of unknown primary site: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v133-8.
12. Qaseem A, Usman N, Jayaraj JS, Janapala RN, Kashif T. Cancer of unknown primary: A review on clinical guidelines in the development and targeted management of patients with the unknown primary site. Cureus 2019;11:e5552.
13. Möhrmann L, Werner M, Oleś M, Mock A, Uhrig S, Jahn A, *et al.* Comprehensive genomic and epigenomic analysis in cancer of unknown primary guides molecularly-informed therapies despite heterogeneity. Nat Commun 2022;13:4485.
14. Samadder NJ, Smith KR, Hanson H, Pimentel R, Wong J, Boucher K, *et al.* Familial risk in patients with carcinoma of unknown primary. JAMA Oncol 2016;2:340-6.
15. Varghese AM, Arora A, Capanu M, Camacho N, Won HH, Zehir A, *et al.* Clinical and molecular characterization of patients with cancer of unknown primary in the modern era. Ann Oncol 2017;28:3015-21.
16. Clynick B, Dessauvagie B, Sterrett G, Harvey NT, Allcock RJ, Saunders C, *et al.* Genetic characterisation of molecular targets in carcinoma of unknown primary. J Transl Med 2018;16:185.
17. Gatalica Z, Xiu J, Swensen J, Vranic S. Comprehensive analysis of cancers of unknown primary for the biomarkers of response to immune checkpoint blockade therapy. Eur J Cancer 2018;94:179-86.
18. Yoon HH, Foster NR, Meyers JP, Steen PD, Visscher DW, Pillai R, *et al.* Gene expression profiling identifies responsive patients with cancer of unknown primary treated with carboplatin, paclitaxel, and everolimus: NCCTG N0871 (alliance). Ann Oncol 2016;27:339-44.
19. Löffler H, Pfarr N, Kriegsmann M, Endris V, Hielscher T, Lohneis P, *et al.* Molecular driver alterations and their clinical relevance in cancer of unknown primary site. Oncotarget 2016;7:44322-9.
20. Petrakis D, Pentheroudakis G, Voulgaris E, Pavlidis N. Prognostication in cancer of unknown primary (CUP): Development of a prognostic algorithm in 311 cases and review of the literature. Cancer Treat Rev 2013;39:701-8.
21. Dunn C, Brettle D, Cockroft M, Keating E, Revie C, Treanor D. Quantitative assessment of H and E staining for pathology: Development and clinical evaluation of a novel system. Diagn Pathol 2024;19:42.
22. Warner E, Goel R, Chang J, Chow W, Verma S, Dancey J, *et al.* A multicentre phase II study of carboplatin and prolonged oral etoposide in the treatment of cancer of unknown primary site (CUPS). Br J Cancer 1998;77:2376-80.
23. Briasoulis E, Fountzilas G, Bamias A, Dimopoulos MA, Xiros N, Aravantinos G, *et al.* Multicenter phase-II trial of irinotecan plus oxaliplatin [IROX regimen] in patients with poor-prognosis cancer of unknown primary: A hellenic cooperative oncology group study. Cancer Chemother Pharmacol 2008;62:277-84.
24. Pentheroudakis G, Briasoulis E, Kalofonos HP, Fountzilas G, Economopoulos T, Samelis G, *et al.* Docetaxel and carboplatin combination chemotherapy as outpatient palliative therapy in carcinoma of unknown primary: A multicentre Hellenic Cooperative Oncology Group phase II study. Acta Oncol 2008;47:1148-55.
25. Hainsworth JD, Daugaard G, Lesimple T, Hübner G, Greco FA, Stahl MJ, *et al.* Paclitaxel/carboplatin with or without belinostat as empiric first-line treatment for patients with carcinoma of unknown primary site: A randomized, phase 2 trial. Cancer 2015;121:1654-61.
26. Gross-Goupil M, Fourcade A, Blot E, Penel N, Négrier S, Culine S, *et al.* Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: Results of the randomised GEFCAPI 02 trial. Eur J Cancer 2012;48:721-7.
27. Huebner G, Link H, Kohne CH, Stahl M, Kretzschmar A, Steinbach S, *et al.* Paclitaxel and carboplatin versus gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: A randomised prospective phase II trial. Br J Cancer 2009;100:44-9.