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A Systematic Review of the Prevalence and Risk Factors Associated with Choriocarcinoma in Saudi Arabia

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ABSTRACT

Choriocarcinoma is a highly aggressive neoplasm of trophoblastic origin, which can be classified as either gestational or non-gestational. The majority of cases are gestational, arising from either normal or abnormal pregnancies. This review examines the prevalence and risk factors of choriocarcinoma by analyzing the available literature. The research team conducted a comprehensive search of databases such as ScienceDirect, PubMed, EBSCO, Web of Science, Cochrane Library, and Scopus. They screened articles based on titles and abstracts using Rayyan QCRI, followed by an in-depth review of the full text. 7 studies involving 353 patients diagnosed with gestational trophoblastic disease were considered, with patient ages ranging from 21 to 55 years. The observed decline in prevalence is attributed to improvements in the socio-medical landscape in Saudi Arabia. In terms of clinical manifestations, gastrointestinal symptoms, including melena and hemoptysis, were noted in two case reports. The review concluded that choriocarcinoma can present in a variety of ways, from asymptomatic lesions to metastatic conditions. In Saudi Arabia, this malignancy is rare, with the majority of reports being case studies. Identified risk factors include low socio-medical status, multiparity, abortion, and hypertension.

Keywords: Systematic review, Choriocarcinoma, Malignancy, Gestational trophoblastic disease

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Introduction

Choriocarcinoma is a malignant neoplasm derived from trophoblastic tissue and may arise from either gestational or non-gestational origins. The gestational variant is predominant and typically develops following a pregnancy, whether normal or pathological. Over half of these cases are linked to a complete hydatidiform mole (CHM), with others emerging from abnormal gestations such as ectopic pregnancies, miscarriages (spontaneous or induced), or even full-term and preterm births [1, 2].

One of the hallmark genetic markers of gestational choriocarcinoma is its paternal chromosomal dominance. CHM-associated choriocarcinomas are purely androgenetic, meaning their genome is entirely of paternal origin. Even in biparental cases, such as those linked to intra-placental choriocarcinomas, the paternal contribution remains a defining characteristic [3, 4].

The occurrence of choriocarcinoma exhibits notable geographic disparity. In regions like North America and Europe, approximately 1 in 40,000 pregnancies and 1 in 40 cases of hydatidiform mole give rise to this malignancy. In contrast, rates are higher in Southeast Asia and Japan, where about 3.3 out of 40 hydatidiform mole cases and 9.2 out of 40,000 pregnancies develop into choriocarcinoma [5, 6]. In China, the incidence is

around 1 in every 2,882 pregnancies [6]. Elevated susceptibility has been documented among women of Asian, American Indian, and African American backgrounds [5].

Research points to cytotrophoblasts as the progenitor cells in choriocarcinoma, functioning similarly to stem cells before undergoing neoplastic transformation. These cells eventually differentiate into intermediate and syncytiotrophoblastic forms [7]. Other gestational trophoblastic neoplasms reflect this pattern of cellular transition and are composed of elements that resemble a pre-villous blastocyst in developmental biology [8].

There is a marked difference in survival outcomes between gestational and non-gestational choriocarcinoma, with the non-gestational type having a notably poorer prognosis [9, 10]. Treatment outcomes for gestational choriocarcinoma are promising: nearly all low-risk cases are curable with chemotherapy, while 91–93% of patients with high-risk disease respond favorably to combination chemotherapy, possibly in conjunction with radiation or surgical intervention. Prognosis worsens in patients with a WHO risk score exceeding 12 or those diagnosed at stage IV [11].

Without medical intervention, choriocarcinoma is potentially fatal. However, chemotherapy has revolutionized management, allowing many affected individuals to achieve full remission. Despite its effectiveness, chemotherapy is not without adverse effects—patients may experience nausea, hair loss, secondary malignancies, gastrointestinal issues, fevers, infections, or may require blood transfusions [12]. Given the significant scarcity of focused research on choriocarcinoma within the Saudi population, this systematic review aims to consolidate and evaluate the existing literature regarding its prevalence and associated risk factors.

Materials and Methods

To ensure methodological rigor, this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Study design

The investigation was conducted as a systematic review.

Study duration

The data collection and analysis were performed during the period from November to December 2022.

Study condition

This review focuses exclusively on existing literature related to the prevalence and contributing risk factors of choriocarcinoma within the Saudi Arabian context.

Search strategy

An extensive search was performed across six major electronic databases—ScienceDirect, EBSCO, PubMed, Scopus, Web of Science, and the Cochrane Library—to gather relevant studies. Searches were limited to publications in English, and the strategies were adjusted individually to match each database's requirements. A combination of keywords and MeSH terms were employed, including "Choriocarcinoma," "Trophoblastic neoplasm," "Gestational trophoblastic disease," "prevalence," "risk factors," "hazardous factors," "Saudi Arabia," and "Saudi population." Boolean operators "AND" and "OR" were used to refine and structure the queries. The inclusion criteria favored English-language articles that were fully accessible, human-based, and available as complete texts.

Selection criteria

Inclusion criteria

Eligibility was based on the relevance to the study objective, targeting male or female individuals diagnosed with choriocarcinoma. All types of study designs were considered, including case reports, provided they met the research focus.

Exclusion criteria

Articles that did not prioritize choriocarcinoma prevalence or risk factors, ongoing research, and secondary analyses like literature reviews were excluded from consideration.

Data extraction

To manage the large dataset, the Rayyan QCRI platform was utilized to eliminate duplicate entries [13]. After deduplication, the remaining articles underwent title and abstract screening following the predefined eligibility standards. Subsequently, full-text screening was conducted on those who passed the initial filter. Any disagreements during the evaluation were resolved through collaborative discussion among the authors. Studies deemed suitable were processed using a predesigned data extraction form. This form collected information on article titles, author names, publication year, methodology, sample size, participant gender, study population, reported risk factors, prevalence of choriocarcinoma, and key findings.

Risk of bias assessment

The risk of bias for each non-randomized study included in the review was assessed using the ROBINS-I tool [14]. The reviewers worked collaboratively to address and correct discrepancies during the assessment process.

Strategy for data synthesis

The extracted data were organized into summary tables that qualitatively presented the features and outcomes of each selected study. After reviewing the content of the eligible papers, only those providing specific insights into the prevalence and risk factors of choriocarcinoma in the Saudi population were retained. Papers lacking such data were excluded from the final synthesis.

Results and Discussion

Search results

The initial comprehensive database search yielded a total of 400 publications. After removing 80 duplicate entries, 320 unique records remained for title and abstract screening. From these, 271 were excluded due to irrelevance or failure to meet inclusion criteria. Of the 49 records retrieved for full-text review, 10 could not be accessed. Among the 39 studies evaluated in full, 10 were eliminated due to incongruent study outcomes, 15 lacked data concerning diabetes as a cancer risk factor, and 7 did not focus on the correct target population. Ultimately, 7 studies met all inclusion criteria and were incorporated into the review. The complete selection process is visually illustrated in **Figure 1**.

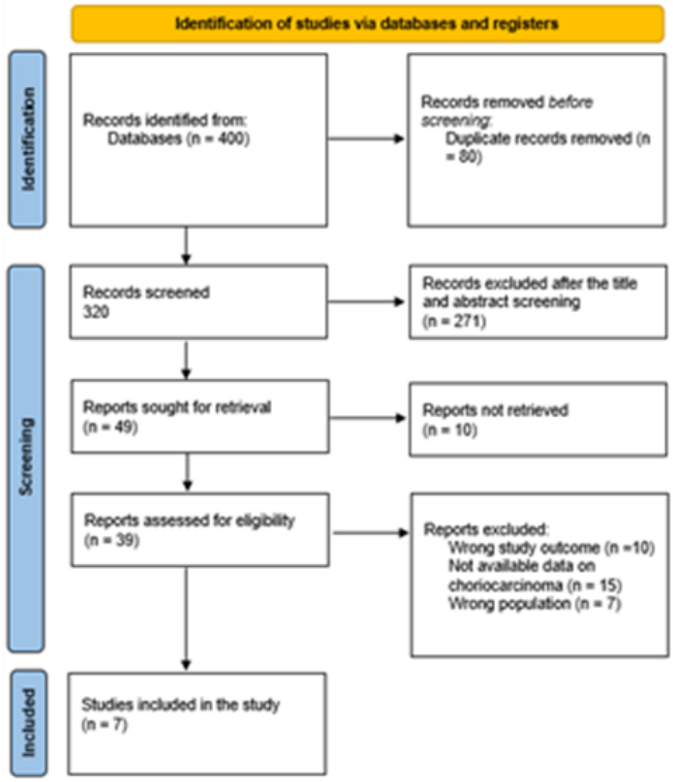

Figure 1. The study selection process is summarized by the PRISMA flowchart.

Specifications of the included studies

A total of seven research articles were selected for inclusion in this systematic review, encompassing data from 353 individuals diagnosed with gestational trophoblastic disease. Among these, 352 were female patients, with only a single male case documented [15]. The age range of the affected individuals extended from 21 years [16] to 55 years [17].

Out of the 7 studies, 2 were retrospective in design—1 of which analyzed 289 cases [18], while the other examined 59 cases [19]. The remaining five were documented as case reports [15-17, 20, 21]. In terms of geographical distribution, four investigations were based in Riyadh [15, 19-21], while the others were conducted in El-Madinah [18], Jeddah [16], and Dammam [17].

Regarding prevalence data, one retrospective study published in 2022 recorded a choriocarcinoma rate of 0.7% [18], whereas an earlier study from 2003 reported a significantly higher prevalence of 5.1% [19]. The marked reduction over time was linked to enhanced sociomedical conditions across Saudi Arabia.

Symptomatically, gastrointestinal bleeding—manifested as melena and hemoptysis—was noted in two of the case reports [15, 20]. Neurological manifestations such as headache and periorbital swelling, attributed to orbital metastasis, were documented in another case [16]. Menorrhagia appeared in two cases [20, 21], and unusual dermatological symptoms were identified in two separate instances [17, 21].

Identified risk factors included low sociomedical background [18, 19], high parity among women [17-21], a history of abortion [20, 21], and the presence of hypertension [20].

A summary of the specifications of the included research articles is presented in **Table 1**.

Table 1. A summary of specifications of the included research articles

Study	Study design	Country	Population type	Gender	Age (years)	Key findings	ROBINS-I
Mohammadi [18]	Retrospective study	Madinah	Patients affected by gestational trophoblastic disease.	Females (289)	33.47 ± 9.3	The current research also reports a lower occurrence of choriocarcinoma: two instances of gestational carcinoma (2.15%) and a single case of choriocarcinoma with lung metastasis (0.9%).	Moderate
Khashoggi [19]	Retrospective study	Riyadh	Individuals with gestational trophoblastic disease.	Females (59)	40	Two instances of choriocarcinoma were documented. Due to the rapid sociomedical progress in the KSA, the frequency of GTD has diminished.	High
Alshammery *et al.* [20]	Case report	Riyadh	A patient showed symptoms of gastrointestinal bleeding (melena) along with irregular menstrual cycles.	Female	37	The patient had a history of hypertension, multiple pregnancies, and two prior abortions. Upon the onset of complications, histopathological examination revealed metastatic choriocarcinoma.	Moderate
Ahamed *et al.* [16]	Case report	Jeddah	A patient arrived with complaints of a headache, gradual left periorbital swelling, and blurred vision, which had been ongoing for four weeks.	Female	21	Visual disturbances and orbital swelling due to orbital metastasis in patients with gestational choriocarcinoma are rare occurrences that require a heightened level of suspicion.	High
Althwanay *et al.* [17]	Case report	Dammam	The patient initially presented with metastases in the liver, kidneys, and lungs, along with skin lesions and worsening back pain.	Female	55	She first appeared with metastases in the liver, kidneys, and lungs, accompanied by skin lesions and increasing back pain.	High
Hashim Amer *et al.* [21]	Case report	Riyadh	A patient with a six-year history of menorrhagia following a pregnancy that ended in a miscarriage at five months of gestation.	Female	40	A miscarriage at five months of gestation was documented. This patient presented with bullous pemphigoid, a rare skin manifestation linked to choriocarcinoma.	High

El-Sharkawy and Al-Jibali *et al.* [15]	Case report	Riyadh	A patient presented with hemoptysis, unexplained weight loss, and abdominal pain lasting for two weeks.	Male	22	This patient had a poor prognosis, with hemorrhagic metastases in both the lungs and brain.	High

Choriocarcinoma is considered a rare malignancy, with its prevalence differing significantly across various global regions [5]. This review highlighted the broad spectrum of choriocarcinoma presentations, from asymptomatic lesions to severe metastatic conditions. In Saudi Arabia, it remains an uncommon malignancy, with most published cases being reported individually. Females make up the majority of affected individuals. Several factors, including ethnicity, blood type, age, parity, diet, contraceptive use, socioeconomic status, immunological factors, and genetic predispositions, have been suggested as contributors to the regional variations in incidence. Additionally, the high rates of consanguinity and the sociocultural belief that hysterectomy is defeminizing make the epidemiology of GTD in the country particularly interesting to study [5, 6, 19].

The majority of patients in this study were middle-aged, with only a small number being younger [15, 16]. The decrease in disease prevalence is believed to be linked to the sociomedical advancements in Saudi Arabia. These observations align with previous research, which noted that improvements in nutrition and healthcare in developed nations have contributed to a decline in the disease's prevalence [22, 23]. Known risk factors include a history of hydatidiform mole (which increases risk by a factor of 100), advancing age, prolonged use of oral contraceptives, and blood type A [3].

Metastasis of choriocarcinoma typically affects the liver, lungs, lymph nodes, and peritoneum. Most patients die due to liver failure induced by widespread tumor spread, bleeding, and disseminated intravascular coagulation [24]. The small intestine, especially the jejunum, followed by the duodenum and ileum, is the most common site for metastasis. Though rare, severe lower gastrointestinal bleeding occurs in approximately 5% of cases [25], with symptoms such as abdominal pain, vomiting, bowel intussusception, and perforation being possible [26].

Several conditions can contribute to lower gastrointestinal bleeding, with the most frequent being neoplastic tumors, vascular malformations, Meckel's diverticulum, inflammatory bowel diseases like Crohn's, lymphangiectasia, radiation-induced injuries, and arteriovenous malformations. Additionally, metastases to the small intestine from melanoma, breast cancer, or Kaposi's sarcoma can present with lower GI bleeding [25].

This study's limitations include the scarcity of comprehensive research on choriocarcinoma, both globally and locally within Saudi Arabia. This suggests that the disease's rare occurrence and unclear risk factors make it difficult to draw definitive conclusions. The majority of available studies are limited to case reports, which hinders the establishment of effective treatment protocols, clinicopathological profiles, and prognostic factors.

Conclusion

This review reveals that choriocarcinoma can manifest in a range of presentations, from silent lesions to severe metastatic forms. In Saudi Arabia, malignancy is rare, with most data coming from individual case reports. Factors like lower sociomedical status, previous abortions, multiparity, and hypertension appear to increase risk.

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