

REVIEW

Geographic variation in diagnosis, treatment, and outcomes of adrenocortical carcinoma in the Americas: a narrative review

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Abstract

Objective: Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy of the adrenal cortex. Given the heterogeneity of healthcare systems across the Americas, this review examines regional differences in access to diagnosis, treatment availability, and clinical outcomes, as well as their association with structural and socioeconomic factors.

Design: This is a narrative literature review of observational studies and relevant regional evidence.

Methods: PubMed, Scopus, and Web of Science were investigated for studies published between 2010 and 2025 reporting on diagnostic resources, treatment availability, clinical outcomes, or ACC-related population-specific genetic epidemiology across the Americas and the Caribbean. Due to substantial heterogeneity in study design, populations, and outcome measures, results were synthesized narratively and organized by geographic region and thematic domain.

Results: Available evidence, particularly from the United States, indicates greater representation of high-volume referral centers, specialized multidisciplinary care, and structured diagnostic and treatment pathways. Conversely, reports from selected settings in Central and South America and the Caribbean describe limitations related to healthcare funding, fragmented care networks, and access to specialized therapies. These differences may be associated with diagnostic delays and reduced access to specialized treatment; however, the strength, depth, and comparability of the available evidence vary substantially across regions.

Conclusion: Available evidence indicates regional variation in ACC diagnosis, treatment access, and reported outcomes across the Americas. Structural, socioeconomic, and geographic factors may contribute to these differences. Potential priorities include strengthening referral pathways, expanding specialized care, and supporting multidisciplinary management. More representative data are needed to enable robust regional comparisons and guide context-specific strategies.

Keywords: adrenal neoplasms; healthcare access; diagnostic delays; cancer treatment; comparative oncology; Latin America

Introduction

Adrenocortical carcinoma (ACC) is a rare and highly aggressive malignancy originating in the adrenal cortex, with an estimated global incidence ranging from 0.7 to 2.0 cases per million individuals annually (1). Despite its paucity, ACC presents a significant clinical challenge due to frequent late-stage diagnoses, rapid local progression, and high rates of recurrence. Advances in diagnostic imaging and surgical techniques have not substantially improved overall prognosis, which remains guarded, with five-year survival rates generally below 40% in contemporary patient cohorts (2, 3, 4).

Throughout the Americas, approaches to managing ACC vary considerably, reflecting differences in healthcare infrastructure, public health funding, epidemiologic surveillance capabilities, and access to specialized treatment centers. In the United States, population-based registries, such as SEER, have facilitated comprehensive analyses of ACC incidence, staging, and treatment patterns (3). Nonetheless, disparities in access to specialized care continue to exist, influenced by socioeconomic factors, race/ethnicity, and types of health insurance coverage (5, 6). In Latin America, including Central America and the Caribbean, data are comparatively limited. In these regions, delays in diagnosis, underreporting, and limited access to effective oncologic therapies contribute to delayed treatment and worse clinical trajectories (7, 8).

A significant focus within South America pertains to the TP53 p.R337H founder pathogenic variant, which is associated with a hereditary cancer predisposition syndrome prevalent in Southern Brazil. This genetic variant notably elevates the risk of pediatric adrenocortical tumors (pACTs) and has led to the implementation of regional public health initiatives. Studies analyzing the frequency and penetrance of the TP53 p.R337H variant in pACTs have demonstrated that neonatal screening and structured surveillance programs shorten diagnostic intervals and increase the proportion of children diagnosed with localized disease (9, 10). These initiatives exemplify how molecular epidemiology can inform and shape local cancer prevention and control strategies, ultimately enhancing early detection efforts and addressing health disparities.

Recent research highlights considerable interregional differences in access to definitive adrenalectomy, adjuvant mitotane therapy access to high-volume referral centers, and enrollment in clinical trials (6, 11). These disparities are influenced by a multifaceted combination of geographic, economic, institutional, and sociocultural factors, which have direct implications for the quality of care provided and patient outcomes (12).

This review offers a comprehensive analysis of regional disparities related to the diagnosis, treatment, and clinical outcomes of ACC across the Americas.

By integrating evidence from various healthcare contexts, the review aims to identify existing inequalities, uncover gaps in current knowledge, and propose strategies to promote equitable access to specialized care and advance evidence-based management of ACC throughout the region.

Methods

Literature search strategy

A structured narrative literature review was conducted to identify observational studies addressing regional disparities in the diagnosis, treatment, and clinical outcomes of adrenocortical carcinoma (ACC) across countries in North, Central, and South America, as well as the Caribbean. Searches were carried out in PubMed, Scopus, and Web of Science databases for articles published between January 1, 2010, and December 31, 2025.

Search terms included both Medical Subject Headings (MeSH) and free-text keywords related to ACC and healthcare inequalities: ‘adrenocortical carcinoma’, ‘Latin America’, ‘South America’, ‘North America’, ‘Caribbean’, ‘Central America’, ‘disparities’, ‘diagnosis’, ‘treatment’, ‘healthcare access’, ‘mitotane’, ‘TP53 R337H’, ‘pediatric ACC’, ‘epidemiology’, and ‘clinical outcomes’. Boolean operators (AND; OR) were used to refine queries, and search expressions were adapted for each database. The search was designed to provide broad coverage of the available regional literature rather than to support a quantitative systematic synthesis.

Inclusion and exclusion criteria

Eligible articles were observational studies (retrospective or prospective), including cohort studies, case-control studies, registry-based studies, and institutional database analyses. Only studies conducted in countries across the Americas were included. Articles had to report at least one of the following: access to diagnostic services (e.g. imaging, hormonal assays, and histopathology), availability and use of therapeutic modalities (e.g. adrenalectomy, mitotane, chemotherapy, and radiotherapy), clinical outcomes such as recurrence or stage at diagnosis, or data on population-specific genetic epidemiology, including on the TP53 p.R337H variant. Articles in English, Spanish, or Portuguese were accepted.

Exclusion criteria included case reports, non-original narrative publications used solely for contextual discussion, opinion pieces, and conference abstracts. Studies were also excluded if they focused solely on molecular mechanisms or basic science without clinical relevance or geographic stratification, were conducted

entirely outside the Americas without comparison to American data, or lacked full-text availability.

Study selection and data extraction

Titles and abstracts identified through the database searches were screened for relevance according to the predefined eligibility criteria. Potentially relevant publications were subsequently reviewed in full text. Data were extracted using a structured form capturing study identifiers (authors, year, and country), geographic and socioeconomic setting, study design and population, diagnostic workflows and barriers, treatment modalities and access, clinical outcomes, and disparities associated with geography, healthcare coverage, race/ethnicity, or institutional capacity. Given the narrative scope of the review, study selection and data extraction were intended to support thematic and regional synthesis rather than quantitative pooling of effect estimates.

Synthesis and data analysis

Due to substantial heterogeneity in study designs, staging systems, patient populations, outcome reporting, and the availability of region-specific data, findings were synthesized narratively. Data were grouped by geographic region (North America, Central America and the Caribbean, and South America) and by thematic focus: diagnostic access, treatment availability, clinical trajectories, and structural determinants. Recurring patterns and gaps were identified to support future research and policy planning. Consistent with the narrative design of this review, no formal risk-of-bias or methodological quality assessment was conducted.

Ethical considerations

This review used only publicly available literature and did not require ethical committee approval.

Results

Epidemiology and geographic distribution

In pACTs, sex distribution differs more markedly from the modest female predominance observed in adult ACC. Several cohorts have demonstrated substantially higher female-to-male ratios in childhood, ranging from 3:1 to 5:1 in younger age groups (13). Recent data from a Canadian single-institution study reported a female-to-male ratio of 3.6:1 among children with ACC, along with a high prevalence of germline TP53 pathogenic variants, supporting the role of genetics in shaping both incidence and clinical behavior in this population (14). In addition, retrospective sex distribution analyses from the Texas Cancer Registry, encompassing 448 cases

diagnosed between 2000 and 2018, demonstrated a female predominance (60.3%) in a cohort comprising pediatric and adult populations (15).

Within the Americas, research indicates considerable variability in incidence rates, demographic characteristics, and the scope of epidemiological data collected. A retrospective study from Colorado, United States, reported an age-adjusted annual incidence between 0.68 and 1.36 cases per million, with regional differences potentially attributable to environmental exposures, socioeconomic factors, and access to specialized diagnostic services (16).

Similarly, analysis of data from the Texas Cancer Registry found a crude incidence rate of 0.104 per 100,000 person-years (15). Demographic analysis revealed a notable proportion of Hispanic patients (22.3%) and an unexpectedly high incidence among pediatric populations (7.4%) compared with international data. Although no significant spatial clustering was identified, cases appeared more concentrated in metropolitan areas, likely reflecting greater detection due to proximity to oncology and diagnostic centers.

In South America, particularly Southern and Southeast Brazil, epidemiological patterns are distinctive, mostly due to a higher incidence of pediatric ACC linked to the TP53 p.R337H germline variant, associated with Li-Fraumeni syndrome (17, 18). This genetic factor confers an increased risk of developing functional adrenocortical tumors in children, often presenting with signs of androgen excess (precocious puberty) and/or cortisol overproduction (Cushing's syndrome).

In the state of Paraná, public health initiatives have integrated neonatal screening for the TP53 p.R337H founder variant into routine practice, enabling early identification of carriers and enrollment into structured surveillance programs. Evidence from pilot implementations demonstrates that surveillance leads to significantly earlier tumor detection, smaller tumor size, stage I disease at presentation, and markedly improved survival when compared with unscreened children (19). Updated analyses also show that newborn screening and parental education reduce diagnostic delays and are highly cost-effective in high-incidence regions, while untreated populations continue to present with advanced disease and poor outcomes (20).

Regarding tumor functionality, hormone excess is frequently reported in ACC and is particularly common in pediatric patients, who often present with clinically evident androgen and/or cortisol excess (6).

Available studies suggest that differences in ACC presentation across the Americas are most clearly documented in pediatric populations. In Southern Brazil, the high prevalence of the TP53 p.R337H founder variant is associated with a distinctive burden of pediatric adrenocortical tumors, which frequently

present with clinically evident hormone excess. Surveillance of identified carriers has also been associated with earlier tumor detection and a higher proportion of localized disease (17, 19). In contrast, population-based studies from the United States predominantly describe adult ACC, with broad variation in age and stage at diagnosis (3). However, differences in study populations and data sources preclude robust direct comparisons of age, hormonal functionality, or stage at presentation across regions.

Despite regional insights, the overall epidemiological picture of ACC in the Americas remains limited by a lack of comprehensive, standardized cancer registry data, particularly in Latin American and Caribbean countries. While the Surveillance, Epidemiology, and End Results (SEER) program provides robust data in the United States for analyzing trends in incidence, mortality, and survival, many nations in the region lack comparable population-based surveillance systems. This data gap hampers effective epidemiological monitoring and impedes the development of targeted public health strategies for rare tumors such as ACC (21, 22).

Disparities in diagnosis

Timely diagnosis of ACC is frequently impeded by structural, socioeconomic, and institutional obstacles that restrict access to essential services, such as imaging, hormonal testing, and histopathological assessment. These barriers compromise diagnostic accuracy and promptness, often leading to presentation at more advanced disease stages and poorer prognosis.

Systematic studies demonstrate that socioeconomic disadvantages, structural disparities, and weaknesses in primary care are among the main factors contributing to delays in cancer diagnosis, even in health systems equipped with adequate technologies (20). These issues are especially evident in Latin America and the Caribbean, where the lack of organized screening programs and limited diagnostic coverage deepen regional disparities in disease stage at presentation (23).

Research by Aljehani *et al.* highlighted that limited access to histopathological evaluation can undermine diagnostic precision and adversely affect clinical outcomes. Expanding access to high-quality pathology services is widely regarded as essential to promote equity in cancer care (24). Additionally, variations in referral pathways from primary to specialist care influence diagnostic timelines and patient outcomes across different countries (25).

The organization of health systems plays a significant role in determining the interval from initial clinical suspicion to definitive diagnosis. Comparative analyses of international healthcare models demonstrate that structural arrangements can markedly impact

diagnostic delays (26). Furthermore, disparities related to ethnicity and sociodemographic factors have been documented, with underrepresented groups experiencing longer delays at both primary and secondary care levels, particularly in cancers such as colorectal and prostate cancer (27). These findings emphasize the importance of targeted strategies to promote racial and ethnic equity within diagnostic processes.

Socioeconomic status (SES) is a critical determinant affecting access to primary care and the timing of confirmatory investigations. The Oncology Nursing Society (ONS) underscores that SES profoundly influences diagnostic trajectories, reflecting broader structural inequities related to race, geographic location, and healthcare coverage (28).

Systems-based models indicate that diagnostic delays are multifactorial, resulting from the interplay of service organization, resource availability, workforce training, and care network infrastructure (25). These insights advocate for coordinated, systemic interventions aimed at reducing cumulative delays along the patient care continuum.

Recent evidence suggests that approaches such as telepathology, community health education, and reorganization of care pathways hold promise in addressing diagnostic disparities, particularly in resource-limited settings (23, 29). Longitudinal data reveal a decline in emergency presentations for cancer diagnosis; however, disparities persist based on age and socioeconomic status (26). These ongoing gaps highlight the necessity for continuous surveillance and public health policies designed to ensure equitable access to timely diagnosis for all patient populations.

Disparities in treatment modalities

Management of ACC exhibits considerable variation across the Americas, largely due to disparities in healthcare infrastructure, the capacity of referral centers, and the availability of specialized oncologic treatments. Regional differences in access to definitive adrenalectomy, mitotane therapy, combination chemotherapy, and clinical trial participation may contribute to variation in treatment delivery and clinical outcomes, particularly in resource-constrained settings (1, 30).

Studies from the United States, particularly those based on large referral networks and national databases, report greater access to high-volume centers, multidisciplinary management, specialized surgical care, mitotane therapy and monitoring, and clinical trial participation. However, these resources are not uniformly available across North America or even within the United States. In South America, access also varies substantially between countries and healthcare settings, with reports describing greater concentration of specialized surgical

expertise and systemic treatment resources in tertiary referral centers and major urban areas, as well as challenges related to referral pathways and continuity of care (11, 31, 32).

Although the implementation of care varies across healthcare systems and institutions, recommended diagnostic and therapeutic principles for ACC are broadly similar across regions and generally follow established international protocols (see Fig. 1). The diagnostic process begins with hormonal evaluation, including measurements of cortisol, adrenocorticotrophic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), androstenedione, testosterone, and estradiol, as well as cortisol measurement after a dexamethasone suppression test and urinary free cortisol. For adult patients, tumor staging is primarily based on the European Network for the Study of Adrenal Tumors (ENSAT) classification, supplemented by pathological assessments including Weiss score, margin status, and Ki-67 proliferation index (1). For pediatric patients, tumor staging is primarily based on the IPACTR and supplemented by assessments including Wieneke score and Ki-67 (33).

Management strategies subsequently vary according to disease stage, resectability status, recurrence patterns, and clinical behavior, encompassing localized/resectable, recurrent, and advanced/metastatic disease scenarios (Fig. 1). Patients with localized or resectable disease are generally managed with surgical resection followed by risk-adapted adjuvant therapy and surveillance, whereas recurrent and advanced/metastatic ACC require individualized multidisciplinary approaches based on disease-free interval, tumor burden, and expected response to systemic therapy (1).

Treatment strategies are tailored to disease stage and clinical presentation. For adult patients with localized disease (ENSAT stages I–III), management typically involves complete surgical resection with negative margins (R0), with adjuvant mitotane therapy considered in cases identified as high risk. In advanced disease (stage IV), treatment often includes mitotane combined with chemotherapy regimens, such as etoposide, doxorubicin, and cisplatin (the EDP regimen), with radiotherapy employed in selected cases (see Fig. 1). For pediatric patients with localized disease (IPACTR stages I–II), only complete surgical resection is indicated. In locally advanced or

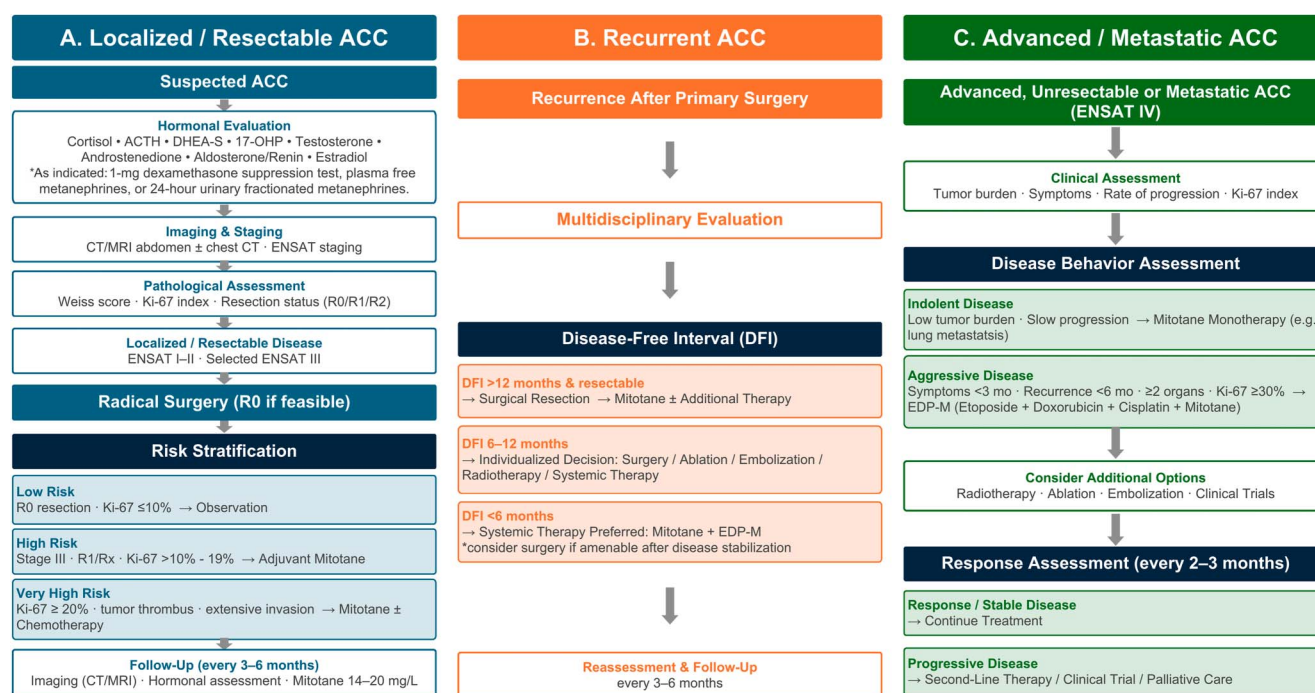


Figure 1

Clinical management algorithms for adrenocortical carcinoma (ACC), developed by the authors and informed by the clinical framework described by Fassnacht *et al.* (1), with updates based on contemporary evidence discussed in this review. (A) Diagnostic evaluation, staging, surgical management, risk stratification, and follow-up of localized/resectable ACC. (B) Management of recurrent ACC according to disease-free interval (DFI) and resectability. (C) Therapeutic approach for advanced/metastatic ACC based on disease behavior, treatment response, and additional therapeutic options. CT, computed tomography; MRI, magnetic resonance imaging; ENSAT, European Network for the Study of Adrenal Tumors; DFI, disease-free interval; EDP-M, etoposide, doxorubicin, cisplatin, and mitotane; 17-OHP, 17-hydroxyprogesterone.

metastatic disease (IPACTR stages III–IV), mitotane combined with the EDP regimen is recommended (34).

Follow-up protocols involve periodic imaging and hormonal assessment every three to six months, ensuring mitotane plasma levels are maintained within the therapeutic range of 14–20 mg/L (1, 30, 35).

The principal diagnostic and therapeutic pathways for adrenocortical carcinoma are summarized in Fig. 1. The revised algorithm illustrates the management of localized/resectable ACC, recurrent disease, and advanced/metastatic ACC, highlighting key decision points related to risk stratification, disease-free interval, resectability, and response to systemic therapy (1, 28, 35).

Adrenalectomy remains the preferred primary treatment for patients with localized ACC. Conducting surgical procedures at high-volume centers is associated with reduced postoperative complications, enhanced adherence to established clinical guidelines, and improved overall survival outcomes (36). However, patients treated at low-volume facilities or residing in regions distant from specialized referral centers are more likely to encounter delays in treatment, less optimal surgical margins, and limited access to necessary adjuvant therapies (37).

In South America, disparities in access to adrenalectomy and specialized centers are prominent. In Brazil, nationwide public health data suggest that many adrenalectomies are performed outside high-volume referral centers, potentially reflecting structural disparities in access to specialized surgical and oncologic care (38). Similarly, studies from countries such as Peru and Colombia highlight difficulties in timely referrals to specialized centers due to fragmented healthcare systems and a shortage of surgeons trained specifically in adrenal tumor management (27).

In the United States, data from the National Cancer Database reveal that only 68% of patients with ACC undergo surgical resection. Factors such as age of 56 years or older, male gender, black race, government-funded health plans, and treatment at community hospitals are independently associated with lower surgical rates and decreased survival outcomes (31). In Central America, infrastructural limitations, the absence of robust national cancer registries, and a scarcity of specialized centers further complicate the delivery of optimal ACC care (31).

For patients with advanced or unresectable ACC, the EDP-M regimen, composed of etoposide, doxorubicin, cisplatin, and mitotane, is an established systemic treatment regimen (39). Its administration, however, requires robust oncology infrastructure capable of managing significant treatment-related toxicities, ensuring therapeutic drug monitoring for mitotane and providing continuous supportive care.

Such resources are predominantly available in high-complexity referral centers. In Argentina, referral institutions report that within the public healthcare system, completion of EDP-M is often challenged by treatment delays, periodic medication shortages, and limited supportive care capacity, whereas access and continuity of therapy tend to be more stable in the private sector. The exact proportion of patients who complete the full regimen remains undetermined (39).

Participation in clinical trials offers valuable opportunities for patients with metastatic or refractory ACC. Nonetheless, involvement remains limited among ethnic minorities and low-income populations due to geographic barriers, scarcity of recruiting centers, and limited accessible information regarding eligibility criteria (40, 41). In Latin America, clinical trial enrollment is particularly constrained, typically confined to academic institutions engaged in international collaborations. In the United States, racial disparities extend to biomarker-based eligibility for targeted therapies, with Black and Asian patients being less likely to meet genomic criteria necessary for participation in precision oncology trials (42).

Healthcare financing models substantially impact patient access to treatment services. Privately insured individuals typically experience reduced wait times for diagnostic procedures and medication approval processes. Conversely, public and hybrid healthcare systems may encounter financial constraints, administrative delays, and medication supply challenges that can affect the timely commencement of therapy (43). In countries such as Mexico and Bolivia, supply interruptions in public health systems have led to treatment delays or discontinuations for affected patients (43).

These observations highlight the critical need for public policy initiatives aimed at ensuring equitable access to ACC treatment. Strategies should include expanding surgical oncology capacities at regional centers, securing a consistent supply of essential medications such as mitotane, enhancing chemotherapy infrastructure, and promoting the inclusion of underserved populations in clinical research (44). Developing comprehensive referral networks, training multidisciplinary care teams, and adopting evidence-based treatment protocols are essential steps toward reducing disparities and improving outcomes for all patients with ACC (38, 43).

Clinical outcomes and survival

ACC is associated with a consistently poor prognosis, particularly in cases diagnosed at advanced stages. Clinical outcomes, including overall survival, disease-free survival, and recurrence rates, exhibit significant variability across regions in the Americas, often reflecting disparities in access to specialized care,

adherence to evidence-based treatment protocols, and healthcare infrastructure capacity (39).

In the United States, population-based data indicate poor overall survival in ACC, with outcomes varying according to disease characteristics and stage at diagnosis (3). Factors associated with poorer prognosis include advanced ENSAT stage and cortisol secretion (45).

Multidisciplinary team (MDT) management has been correlated with improved clinical outcomes in patients with ACC. A retrospective analysis reported a median overall survival of approximately 31 months among patients with ACC evaluated through a multidisciplinary team, with shorter survival observed among those managed without such evaluation (46).

In South America, implementation of neonatal screening programs for the TP53 p.R337H founder variant in Brazil has enabled earlier clinical evaluation and tumor detection among pediatric carriers, resulting in smaller tumor sizes and fewer cases diagnosed at advanced stages, as well as substantially shorter diagnostic delays compared with unscreened children (19). ACC-specific evidence on access to specialized oncology services and systemic therapies among adult populations in South America remains limited, restricting direct assessment of their relationship with survival outcomes.

Key prognostic factors influencing ACC outcomes include ENSAT staging, vascular invasion, autonomous cortisol secretion, and use of adjuvant mitotane therapy. Tumors secreting cortisol are associated with higher recurrence rates and increased mortality (45). Adjuvant mitotane treatment has demonstrated survival benefits, particularly in patients with stage III and IV disease (47).

Sociodemographically, evidence indicates that patients with lower income levels and limited insurance coverage are less likely to participate in clinical trials, which restricts access to innovative therapies. This underrepresentation may adversely affect long-term survival outcomes and perpetuate existing disparities in ACC management across low- and middle-income settings (48).

Structural and social determinants of disparities

Regional disparities in the management of ACC are primarily influenced by structural and social determinants that hinder timely diagnosis, adherence to evidence-based treatment protocols, and continuity of specialized care (31, 48). Factors such as socioeconomic status, geographic accessibility, ethnic and racial disparities, healthcare infrastructure limitations, and coverage gaps substantially impact clinical outcomes across different regions within the Americas (31, 45, 48).

In the United States, Hispanic patients with ACC are typically diagnosed at a younger age and more often present with locally advanced disease compared with non-Hispanic White patients. However, studies have shown that cancer-specific survival remains comparable between both groups after adjusting for relevant prognostic factors (6). Among African American patients with ACC, tumor stage at diagnosis and cancer-specific mortality are comparable to those observed in non-Hispanic White patients when access to surgery is achieved; however, African Americans are significantly less likely to undergo surgical resection at high-volume or academic cancer centers, particularly those covered by government insurance or treated in community facilities (31).

In Central America, the absence of comprehensive population-based cancer registries and a limited number of specialized oncology centers hinder effective epidemiological monitoring and the standardization of treatment protocols (31). Even in countries with universal healthcare systems, such as Costa Rica, regional disparities persist (particularly in rural and border regions), with access to high-complexity care due to fragmented healthcare networks and socioeconomic barriers that affect continuum of care (49).

In South America, Brazil faces a disproportionately high incidence of pediatric ACT driven by the TP53 p.R337H founder variant, particularly in the southern and southeastern regions (19). Although neonatal screening and structured surveillance programs implemented in these areas have facilitated earlier detection and contributed to improved outcomes in selected cases, late presentation and treatment delays remain frequent, reflecting persistent disparities in access to specialized care (20). These inequalities are especially evident in the north and northeast, where infrastructure gaps, shortages of trained personnel, and limited public investment contribute to worse prognosis and hinder the expansion of successful regional models into a nationwide strategy (20, 50).

Healthcare coverage remains a vital determinant of care access. In countries with predominantly public health systems, such as many Latin American nations, financial and logistical limitations often restrict access to essential medications such as mitotane, diagnostic testing, and ongoing treatment monitoring (32). Conversely, private healthcare systems generally offer faster access to therapies and procedures but predominantly serve wealthier populations (43, 50).

Participation in clinical research represents another aspect of structural inequality. Patients from lower socioeconomic backgrounds and those residing in remote areas are less likely to be enrolled in clinical trials, due to limited research infrastructure, logistical challenges, and lack of information regarding eligibility criteria. Evidence indicates that income level correlates

with research participation even in high-income countries such as the United States (48). Furthermore, patients receiving care at community centers or covered by public insurance are less frequently referred to experimental protocols, highlighting institutional barriers that limit access to innovative therapies (38).

Discussion

This comprehensive review highlights significant regional variations in the diagnosis, management, and clinical outcomes associated with ACC across the Americas. Data derived from clinical research in diverse healthcare settings indicate that structural and social determinants (such as primary care accessibility, health insurance coverage, availability of specialized treatments, and participation in clinical trials) play a crucial role in influencing access to oncology services and patient prognosis (22, 31, 38, 48). A comparative overview of North, Central, and South America reveals distinct regional patterns and identifies key areas for advancing equity in cancer care.

In North America, access to diagnostic services generally allows for early detection. Patients often benefit from curative surgeries performed at specialized centers, continuous availability of mitotane, and active participation in clinical trials within academic institutions (Table 1). Available North American data

suggest comparatively favorable outcomes in selected cohorts, although survival varies substantially according to disease stage, treatment setting, and patient characteristics (6, 31).

Conversely, available evidence from Central America describes diagnostic pathways characterized by restricted access to specialized centers, with delayed diagnosis reported in some settings. Curative procedures are typically restricted to a few centers, with intermittent or absent availability of mitotane, and opportunities for clinical trial participation are scarce (Table 1). However, ACC-specific survival data from Central America remain limited, precluding reliable regional survival estimates (49, 51).

In South America, access to diagnostic services varies across settings and is more concentrated in major urban and referral centers (Table 1). Surgical intervention is primarily available in major urban centers, mitotane procurement is dependent on referrals, and enrollment in clinical trials remains low and concentrated in capital cities (19, 20, 45). Available survival data are heterogeneous and largely derived from selected institutional or pediatric cohorts, limiting the reliability of regional survival estimates.

ACC-specific evidence from the Caribbean remains sparse; available reports describe restricted access to specialized diagnostic and surgical services, inconsistent availability of mitotane, and limited

Table 1 Summary of regional disparities in the management of adrenocortical carcinoma (ACC) across the Americas. This table provides a descriptive comparison of access to diagnostic services, availability of curative surgery, mitotane supply, participation in clinical trials, and reported survival patterns across regions in North America, Central America, South America, and the Caribbean. The data suggest substantial interregional inequities, with earlier diagnosis, wider availability of specialized therapies, and greater integration into clinical research networks. However, comparisons of survival outcomes across regions remain limited by substantial differences in data availability, study design, and patient populations.

Region	Diagnostic access	Curative surgery	Mitotane availability	Clinical trial participation	Representative references
North America (USA & Canada)	Early access supported by structured referral pathways, endocrine oncology networks, and national cancer registries (e.g. SEER).	Readily available at high-volume cancer centers with multidisciplinary expertise.	Consistently available, including therapeutic monitoring.	Frequent enrollment through academic and cooperative group trials (NCI programs).	Hammad <i>et al.</i> (31), Ayala-Ramirez <i>et al.</i> (2), Pearlstein <i>et al.</i> (5)
Central America	Fragmented access with delayed diagnosis due to limited endocrine testing and weak referral systems.	Restricted to few tertiary hospitals; prolonged waiting times.	Intermittent supply in public systems.	Minimal participation due to limited research infrastructure.	Buteau <i>et al.</i> (51), Guerron-Gomez <i>et al.</i> (23)
South America	Stronger access within urban centers in Argentina and Southern Brazil; delays persist in under-resourced areas.	Concentrated in national cancer institutes; limited availability outside capitals.	Inconsistent supply and therapeutic monitoring often unavailable.	Mostly through international collaborations; few national trials.	Piñeros <i>et al.</i> (21), Custódio <i>et al.</i> (9), Tosin <i>et al.</i> (20), Olijnyk <i>et al.</i> (38)
Caribbean	Major diagnostic barriers and lack of structured endocrine oncology networks.	Many patients require referral abroad for surgery.	Low or absent availability; dependency on importation.	Very limited participation; few or no ACC-specific trials.	Barrios <i>et al.</i> (32), Buteau <i>et al.</i> (51)

opportunities for participation in clinical trials (Table 1) (6, 7). ACC-specific survival data from the Caribbean remain particularly sparse, limiting reliable estimates and direct comparisons with other regions of the Americas.

Regarding diagnostic capabilities, the United States benefits from broader access to hormonal assays, advanced imaging modalities, and experienced pathology services, facilitating earlier detection of ACC (6, 52). In contrast, Latin American and Caribbean countries often face fragmented care networks, shortages of specialized personnel, and limited organized screening programs. These issues lead to delayed diagnoses and poorer prognostic outcomes (48, 49).

Treatment disparities in ACC mirror those observed in diagnostic access. Studies from the United States, particularly those from high-volume referral centers, report access to comprehensive multimodal management, including surgery by experienced adrenal surgeons, mitotane monitoring, EDP-M, and clinical trials. In contrast, reports from some Central and South American settings describe limitations in referral pathways, access to specialized surgical care, systemic therapies, and continuity of treatment (31, 32, 47, 48). These determinants operate at different points along the ACC care pathway and should not be interpreted as equivalent contributors to outcomes.

Over the study period, the literature has reported gradual advances in ACC management across the Americas, particularly through increasing centralization of care in specialized referral centers, broader implementation of multidisciplinary management, and greater dissemination of evidence-based clinical guidelines. However, these advances have not been uniformly implemented across regions or healthcare settings. Moreover, the depth and quality of the available evidence vary substantially, with more robust registry-based data from the United States and considerably more limited ACC-specific evidence from Central America and the Caribbean. Therefore, regional comparisons should be interpreted cautiously, and the relative contribution of individual determinants to differences in outcomes cannot be reliably quantified from the available evidence.

These systemic inequities may also be reflected in clinical outcomes; however, direct survival comparisons between regions remain limited by substantial differences in study design, patient populations, stage distribution, treatment settings, and the availability of ACC-specific data. More robust registry-based and institutional evidence is available from the United States (3, 6, 31), whereas evidence from Brazil and other South American settings is more frequently derived from selected institutional or pediatric cohorts (7, 19), limiting direct interregional comparisons. Contributing factors include the lack of standardized

treatment protocols, concentration of specialized services in specific locations, and unequal access to medications and healthcare professionals (43, 49).

Structural issues such as underfunded public health systems and the absence of targeted policies for rare cancers such as ACC hamper the development of integrated care pathways, especially in rural or peripheral regions (43, 49). Even within universal healthcare systems, such as Costa Rica's, the PAHO has documented persistent regional and socioeconomic disparities in access to services and health outcomes. These inequities highlight the need for intersectoral strategies that strengthen equity-focused policies and ensure more balanced distribution of resources across the country (45).

Several priority gaps have been identified through regional analysis. Region-specific biomarkers, such as the TP53 R337H founder mutation prevalent in Southern Brazil, can be leveraged as tools to improve early detection and outcomes (20, 47). Greater inclusion of underrepresented populations and efforts to reduce structural barriers to clinical trial participation have been proposed to improve equity in access to investigational therapies (48). Broader investment in cancer research and research infrastructure has also been identified as a policy priority for reducing disparities (43).

Addressing these disparities requires consideration of broader structural barriers. Evidence from the oncology literature indicates that socioeconomic disadvantage, fragmented care pathways, and limited access to primary and specialist services may contribute to delays in cancer diagnosis (25, 29). A lack of clearly defined clinical pathways and limited availability of mitotane in resource-poor settings reduce treatment efficacy (34). Additionally, patients' socioeconomic status and insurance type significantly influence participation in clinical trials and access to novel therapies, particularly affecting high-risk groups (46).

In the United States, insurance status is a key determinant of access to cancer treatment. Evidence shows that privately insured patients are significantly more likely to receive surgical intervention and recommended therapeutic strategies compared with individuals covered by public insurance or those without insurance. Additionally, racial and ethnic minority groups exhibit lower surgical treatment rates even after adjusting for clinical factors, indicating persistent disparities at the intersection of insurance coverage and race (32). Although early mortality disparities are less pronounced, prompt treatment remains a key determinant of prognosis.

In Central America and the Caribbean, populations facing structural disadvantages and residents of remote areas continue to experience significant shortages of

healthcare personnel and essential oncology medications, despite ongoing institutional advancements (52). This underscores the importance of implementing coordinated regional strategies and maintaining sustained investments in healthcare infrastructure and workforce development.

Furthermore, reports from Central America and the Caribbean suggest that specialized referral centers are more likely to provide comprehensive cancer care, whereas resource limitations in other settings may restrict access to multidisciplinary and advanced treatment modalities (51).

To promote equitable access to ACC care across the Americas, efforts must extend beyond technological advancements. Strengthening primary care systems to facilitate early clinical suspicion, establishing integrated referral centers equipped to provide specialized surgery, EDP-M chemotherapy, and mitotane monitoring, as well as increasing public funding for clinical research, represent potential priorities for reducing disparities in ACC care. Additionally, countries should explore the implementation of biomarker-based screening programs (such as TP53 R337H testing in Brazil) as adaptable models for other Latin American and Caribbean contexts. The experience with neonatal testing and surveillance for the TP53 p.R337H founder variant in Southern Brazil illustrates how region-specific genetic epidemiology can inform targeted early detection strategies for pediatric adrenocortical tumors (19).

Policy initiatives targeting rare tumors, the integration of local evidence into clinical practice, and fostering international collaboration are essential components in ensuring timely, equitable, and evidence-based ACC care for patients, irrespective of geographic location or socioeconomic background.

This review has several limitations that should be acknowledged. First, the available literature on ACC in Latin America and the Caribbean remains limited, with most studies being retrospective, single-center analyses conducted at tertiary care institutions. This constrains the generalizability of the findings and may introduce selection bias and publication bias. Because tertiary referral centers typically concentrate specialized expertise and resources, the care patterns reported in these studies may not fully reflect access to care and treatment conditions at the population level.

Second, substantial heterogeneity in study designs, patient populations, staging systems, outcome definitions, and reporting standards prevented the possibility of quantitative synthesis or meta-analysis, thereby limiting the capacity for direct interregional comparisons. Third, variations in healthcare system organization, cancer registry coverage, and diagnostic criteria across different countries are likely to contribute to disparities in reported incidence and survival rates. The quantity, granularity, and sources of

available evidence also differ across regions, further limiting the comparability of regional estimates. Furthermore, data from underrepresented regions, particularly Central America and the Caribbean, remain scarce, which may result in underestimation of the true magnitude of disparities, especially among patients living in rural or resource-limited settings. These limitations underscore the need for multicenter, prospective research and standardized cancer registry practices to improve the accuracy and comparability of ACC data across the Americas.

Conclusions and future perspectives

This review underscores the noteworthy variations in diagnostic strategies, access to treatment, and clinical outcomes related to ACC across different regions within the Americas. Available evidence suggests that these variations occur across and within regions and are associated with differences in healthcare resource allocation, availability of specialized therapies, and broader structural and social determinants of oncology care.

Studies from the United States, particularly registry-based analyses and reports from specialized centers, provide more extensive evidence on access to specialized care, evidence-based treatment, and clinical research participation. Available reports from Latin American and Caribbean settings describe challenges, including limitations in healthcare funding, availability of multidisciplinary specialist teams, access to essential medications, and policies addressing rare cancers; however, ACC-specific evidence remains uneven across countries. These variations highlight the necessity for tailored context-specific cancer care strategies that address the unique epidemiological, economic, and geographic considerations of each subregion.

Addressing these disparities from both clinical and organizational perspectives requires more than technological innovations alone. Potential priorities include strengthening primary care services through targeted training for early suspicion and diagnosis; developing regional referral networks capable of delivering complex procedures, such as adrenalectomy, EDP-M chemotherapy, and mitotane monitoring; and increasing regional research capacity with greater inclusion of underserved populations. The experience with neonatal screening for the TP53 p.R337H founder variant in Southern Brazil illustrates how region-specific genetic epidemiology can inform targeted screening and surveillance strategies in populations with documented genetic susceptibility to pediatric adrenocortical tumors.

The existing scientific literature pertaining to ACC in Central America and the Caribbean remains limited in scope and depth, primarily comprising retrospective

analyses based on tertiary hospital records, which restricts broader applicability. Future prospective, multicenter studies should incorporate sociodemographic, ethnic, and geographic variables into analyses of ACC presentation, treatment, and outcomes. The lack of comprehensive, standardized population-based cancer registries hampers the development of evidence-based public policies and impairs efforts to accurately identify and address health inequities. Strengthening regional cancer registries and fostering inter-institutional research collaborations could improve the quality and comparability of ACC-specific evidence across the Americas.

Looking forward, strengthening scientific and technical cooperation across the Americas is essential for the development of region-specific ACC management protocols, continuous professional development in endocrine oncology, broader access to molecularly targeted therapies, and the removal of logistical and institutional barriers to clinical trial participation. Overall, strengthening regional collaboration, referral networks, research infrastructure, and access to specialized care may help reduce disparities in ACC management. However, the substantial regional imbalance in available evidence underscores the need for more representative ACC-specific data before the magnitude and determinants of these disparities can be reliably compared across the Americas.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this work.

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Author contribution statement

HT conceived and structured the manuscript and contributed to content development. JDR contributed to the conceptualization of the review and critically revised the manuscript. GIK, MLI, MD, MCBVF, LECP, and SRA provided critical review and contributed to content refinement.

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