Review

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Diagnostic and Prognostic Values of Hypercalcemia in Patients With Breast Cancer Presenting to the Emergency Department: A Narrative Review

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Hypercalcemia is a potentially life-threatening metabolic condition that commonly occurs in advanced malignancies, particularly solid tumors such as breast cancer. This condition often presents nonspecific symptoms like nausea, confusion, or polyuria in the emergency department, frequently leading to misdiagnosis and delayed treatment. In breast cancer, hypercalcemia is typically driven by paraneoplastic mechanisms, including parathyroid hormone-related peptide (PTHrP) secretion and osteolytic bone metastases, both of which disrupt calcium homeostasis. Furthermore, immune dysregulation or ectopic vitamin D production may also contribute to disease progression. This manuscript summarizes current evidence on the emergency presentation, diagnosis, and acute management of hypercalcemia in patients with breast cancer. It highlights key risk factors, including tumor subtypes, endocrine therapies, and changes in bone microenvironment, and outlines practical diagnostic approaches to facilitate early identification. Moreover, it compares therapeutic options, including intravenous hydration, calcitonin, bisphosphonates, and denosumab. Additionally, the review examines the prognostic significance of hypercalcemia, which often indicates disease progression and is associated with increased rates of intensive care unit (ICU) admissions and mortality. Overall, these insights aim to guide clinical decision-making and support future research efforts to establish standardized protocols and predictive models for breast cancer–associated hypercalcemia.

Keywords: breast cancer; hypercalcemia; emergency care; PTHrP; bone metastasis; prognosis

Introduction

Breast cancer is the most commonly diagnosed malignancy among women globally and remains a leading cause of cancer-related death [1–3]. Although advancements in diagnostic approaches and systemic therapeutic regimens have considerably improved overall survival, clinical complications exist [4]. These challenges include bone metastases, resistance to endocrine treatment, and complex metabolic dysfunctions, thereby substantially limiting patient prognostic outcomes [5–7].

Hypercalcemia emerges as the most frequent and potentially life-threatening paraneoplastic complication in breast cancer, accounting for approximately 20–30% of malignancy-associated hypercalcemia (MAH) cases, particularly in those with skeletal metastases or elevated secretion of parathyroid hormone-related peptide (PTHrP) [8,9].

Despite its higher prevalence, hypercalcemia often presents atypically with nonspecific symptoms such as nausea, vomiting, polyuria, lethargy, or confusion [10,11]. These manifestations are easily falsified for various common conditions, such as gastroenteritis, infection, or dehydration, which can result in delayed diagnosis and inappropriate early management [12].

In severe cases, hypercalcemia can lead to serious complications, including renal impairment, cardiac arrhythmias, and even coma, in extreme cases [13]. In some patients, hypercalcemia may even serve as the initial manifestation of breast cancer progression, often resulting in a poor prognosis or transition to a more critical disease stage [14]. Thus, prompt identification and precise management in the emergency department (ED) are essential to improving prognostic outcomes.

Existing research on hypercalcemia in breast cancer has largely focused on oncology wards or inpatient cohorts, primarily emphasizing long-term disease management and associated tumor biology. In contrast, systematic management approaches and practical clinical guidance tailored to emergency physicians' needs remain limited. This gap is particularly crucial, as clinicians in ED often assess patients with vague, nonspecific clinical symptoms but usually lack oncology-focused protocols to guide rapid differential di-

agnosis and prompt intervention. The lack of standardized ED pathways likely contributes to under-recognition, therapeutic delay, and worse clinical outcomes in this patient cohort.

Therefore, this review aims to address these gaps by providing a comprehensive overview of the pathophysiology, risk factors, emergency manifestations, diagnostic approaches, and acute management of breast cancer–associated hypercalcemia. It also explores the prognostic implications of hypercalcemic episodes and underscores the need for standardized ED protocols and predictive models to guide timely intervention and improve patient outcomes.

Pathophysiology and Risk in Breast Cancer–Associated Hypercalcemia

The pathophysiology of hypercalcemia in breast cancer is generally categorized into two major mechanisms: humoral and osteolytic [15]. In the humoral type, tumor cells secrete PTHrP, which functionally mimics the actions of parathyroid hormone (PTH) by binding to the PTH/PTHrP receptor (PTH1R), activating osteoclasts and enhancing bone resorption [9,16]. PTHrP also reduces renal calcium excretion and upregulates renal 1-α hydroxylase activity, increasing the production of active vitamin D and thereby promoting intestinal calcium absorption [17]. These effects lead to a persistent increase in serum calcium levels [18]. In breast cancer, PTHrP overexpression is closely associated with tumor aggressiveness and a higher propensity for bone metastasis, and significant hypercalcemia may occur even when serum PTH levels are normal or suppressed [19].

The osteolytic mechanism is most frequently observed in patients with extensive bone metastases [6]. Breast cancer cells secrete proinflammatory cytokines and osteoclast-activating factors such as receptor activator of nuclear factor-κB ligand (RANKL), prostaglandin E2 (PGE2), and interleukin-6 (IL-6), which stimulate osteoclast proliferation and activity, leading to bone matrix degradation and subsequent calcium release into the bloodstream [20,21]. Compared with humoral hypercalcemia, osteolytic hypercalcemia is more often associated with localized bone pain, pathological fractures, and resistance to treatments [22].

Biological variation across breast cancer subtypes, particularly in PTHrP activity, contributes to differences in hypercalcemia risk [23]. Luminal B tumors, which are estrogen receptor (ER) positive and characteristically associated with bone-predominant metastatic patterns, often exhibit elevated PTHrP expression and are commonly linked to humoral hypercalcemia [24]. In contrast, triple-negative breast cancers, despite lower PTHrP expression, show aggressive progression with extensive skeletal involvement, predisposing to osteolytic hypercalcemia [6]. Although HR-positive/HER2-negative tumors exhibit strong bone tropism, hypercalcemia may also arise in this subtype when bone metastases disrupt skeletal remodeling through RANKL-mediated osteoclast activation [25]. Therapy-related factors can further destabilize calcium homeostasis. Aromatase inhibitors reduce peripheral estrogen production, accelerating bone loss and increasing bone turnover [26]. Gonadotropin-releasing hormone (GnRH) agonists induce an estrogen-deficient state in premenopausal women, thereby promoting osteoclast activity [27]. These effects are magnified in older patients and in those with dehydration, impaired renal function, or prolonged immobilization, all of which increase the risk of acute hypercalcemic episodes [22].

High-risk groups, as suggested by these mechanisms and clinical observations, include: (1) patients with known bone metastases; (2) those with PTHrP-overexpressing tumors, such as Luminal B and selected HER2-negative or triple-negative subtypes; (3) individuals receiving aromatase inhibitors, GnRH agonists, or other anti-estrogen therapy; (4) elderly patients or those with renal dysfunction, dehydration, or limited mobility; and (5) patients with a history of unexplained hypercalcemia. In these populations, regular assessments of serum calcium, PTH, PTHrP, creatinine, and phosphate are recommended in both outpatient follow-up and emergency care. Bone scans or PET-CT imaging may aid in assessing skeletal disease burden, facilitating early identification and personalized intervention.

Emergency Presentation and Diagnosis

Breast cancer-associated hypercalcemia often presents in the ED with nonspecific symptoms, which complicates early recognition [10]. Mild hypercalcemia may manifest as dry mouth, fatigue, constipation, or low-grade nausea. As calcium levels rise, patients may develop polyuria, irritability, muscle weakness, or confusion. In more severe cases, a hypercalcemic crisis may occur, characterized by altered mental well-being, seizures, cardiac arrhythmias, and potentially coma, requiring prompt management [13,14]. These clinical presentations are easily misattributed to common conditions such as gastroenteritis, dehydration, urinary tract infections, or heatstroke, particularly in individuals without a known cancer history or in those with previously stable disease [28].

A systematic diagnostic approach is therefore essential for identifying hypercalcemia in the emergency settings. Serum calcium should be adjusted for albumin to accurately determine the true calcium burden, particularly in patients with comorbid conditions. The corrected calcium is calculated as follows: Corrected calcium (mmol/L) = Total calcium + 0.02 $\times$ (40 – serum albumin in g/L) [29]. A corrected calcium level above 2.75 mmol/L indicates hypercalcemia, while values $>$3.5 mmol/L are generally indicative of a severe or potentially life-threatening condition [30]. Additional laboratory tests include serum

Table 1. Clinical grading of hypercalcemia and management considerations in ED.

Severity	Corrected calcium	Common symptoms	Clinical risk	Suggested ED action
Mild	2.75–3.0 mmol/L	Fatigue, dry mouth, constipation, nausea	Often overlooked	Monitor, fluid support, identify cause
Moderate	3.0–3.5 mmol/L	Polyuria, irritability, muscle weakness, confusion	May be misdiagnosed	IV fluids + consider calcitonin, initiate workup
Severe	>3.5 mmol/L	Delirium, arrhythmia, dehydration, seizure	Hypercalcemic crisis	Urgent treatment, prevent complications

Abbreviations: ED, emergency department; IV, intravenous.

Note: Table 1 was compiled based on current authoritative evidence and clinical guidelines regarding hypercalcemia management [33–36].

phosphate (often decreased), PTH (typically suppressed in malignancy-related hypercalcemia), PTHrP (frequently elevated in humoral types), creatinine (to assess renal function), and vitamin D metabolites [31]. Electrocardiographic findings such as QT interval shortening or characteristic T-wave changes can further support the diagnosis [32].

A symptom-based severity classification can support clinical decision-making in emergency settings. As summarized in Table 1 (Ref. [33–36]), mild hypercalcemia is often overlooked, moderate cases carry a significant risk of misdiagnosis, and severe hypercalcemia constitutes a medical emergency that requires immediate intervention. In addition to these static indicators, dynamic, process-based recognition models are helpful in enhancing diagnostic efficiency. A simplified recognition pathway is shown in Fig. 1, which integrates clinical symptoms, corrected calcium thresholds, and key laboratory indicators to facilitate timely diagnosis and intervention in the ED.

Clinicians should be particularly cautious in patients without a known malignancy or in those considered to be in remission. In older women presenting during summer months with dehydration-like symptoms, hypercalcemia should be included in the differential diagnosis [13]. "Silent" or borderline hypercalcemia, in which total calcium appears normal due to hypoalbuminemia, can only be detected. Elevated PTHrP levels support a humoral mechanism, while suppressed PTH helps exclude primary hyperparathyroidism [31].

Hence, the early recognition of hypercalcemia in patients with breast cancer relies on careful clinical assessment, a symptom-guided severity framework, and the integrated interpretation of biochemical and electrocardiographic findings. Standardized ED protocols not only enable rapid triage and appropriate treatment but also provide a basis for evaluating the prognostic impact of hypercalcemic episodes during subsequent care.

Acute Management and Treatment Options

Once hypercalcemia is confirmed in a patient with breast cancer, immediate intervention is essential to prevent clinical deterioration and the development of hypercalcemic crises. Most cases encountered in the ED fall within the moderate to severe intensity, and therapeutic delay can lead to severe complications, including arrhythmias, renal failure, and impaired consciousness. Therefore, the acute management strategy should focus on three primary goals: rapid reduction of serum calcium, stabilization of electrolyte balance, and preservation of vital organ function. These measures should be tailored to the severity of hypercalcemia and the patient's underlying comorbidities.

Initial treatment typically begins with intravenous isotonic saline to correct volume depletion, improve renal perfusion, and increase urinary calcium excretion. Normal saline (0.9% NaCl) is generally infused at a rate of 200–300 mL/hour, with the rate adjusted based on age, body weight, urine output, and underlying cardiac or renal function [37]. Once adequate hydration is established, loop diuretics such as furosemide may be considered in selected cases to promote calciuresis; however, evidence does not support their routine use, and they should be employed with great caution due to the risks of volume depletion and electrolyte disturbances, particularly in older adults or patients with heart failure [38,39].

Calcitonin is often administered alongside initial rehydration to achieve rapid symptom relief. It begins to act within 4–6 hours and generally reduces serum calcium by approximately 0.5–1.5 mmol/L by inhibiting bone resorption and enhancing renal calcium clearance. As it is well-tolerated and widely accessible, it is particularly instrumental in patients with acute cardiac or neurological manifestations [40,41]. However, due to receptor desensitization, its efficacy diminishes after 48 hours, so it is best used as a short-term bridging treatment until longer-acting therapies take effect [42].

For sustained hypercalcemia control, antiresorptive agents should be initiated without delay. Bisphosphonates remain the first-line agents for malignancy-associated hypercalcemia [43]. Intravenous pamidronate and zoledronic acid are commonly used and act by inhibiting osteoclast-mediated bone resorption. There onset of action is usually observed within 24–48 hours, with therapeutic effects lasting 2–4 weeks [44]. Zoledronic acid is more potent and is usually preferred in patients with extensive bone metas-

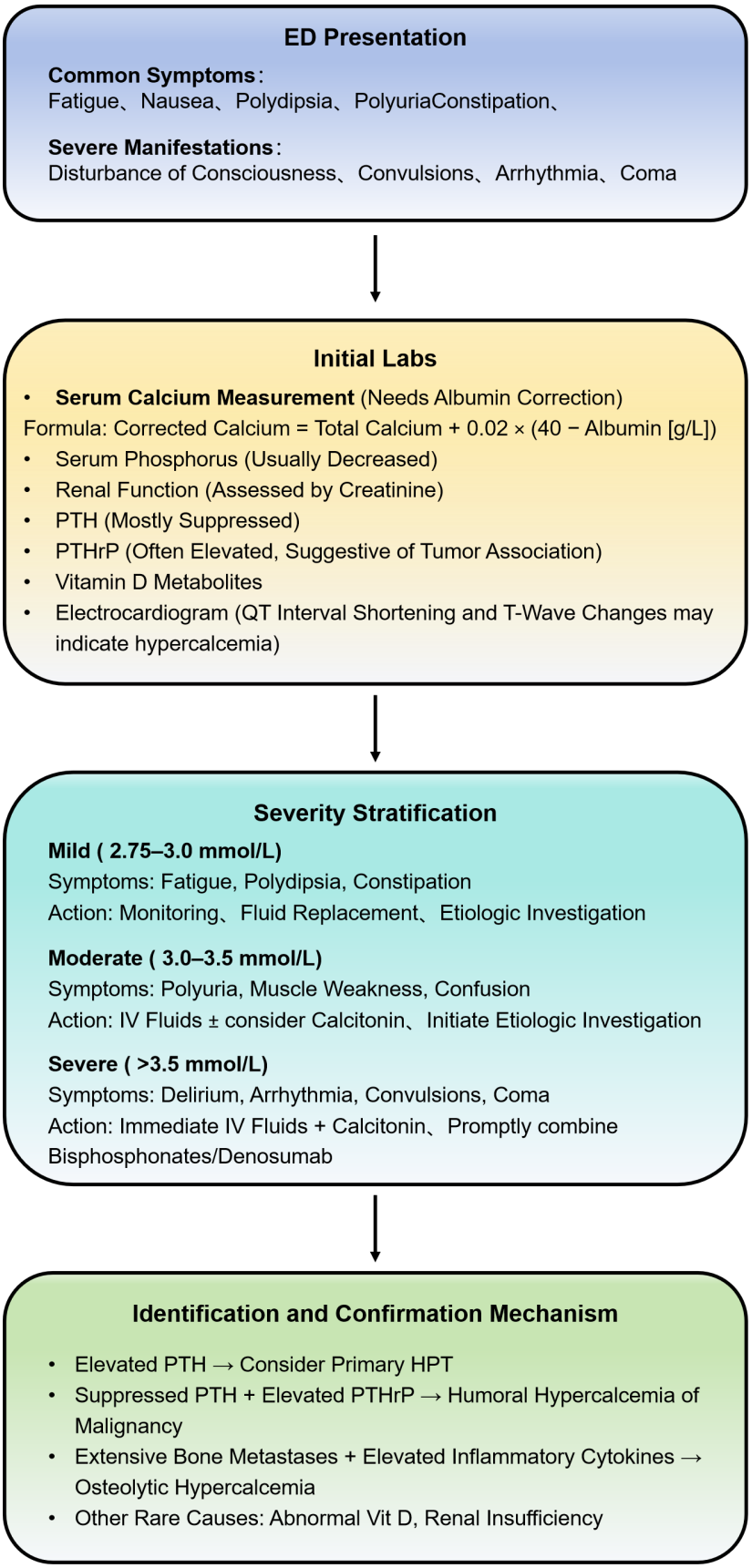

Fig. 1. Simplified ED diagnostic algorithm for breast cancer–associated hypercalcemia. ED, emergency department; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; IV, intravenous; HPT, hyperparathyroidism. This figure was drawn using Microsoft PowerPoint.

Table 2. Comparison of common agents used in breast cancer-related hypercalcemia.

Agent	Onset of action	Duration of effect	Mechanism	Ideal candidates	Notable side effects
Calcitonin	4–6 hours	<48 hours	Inhibits bone resorption; promotes renal excretion	First-line for hypercalcemic crisis, symptomatic patients	Flushing, nausea, tachyphylaxis
Pamidronate	24–48 hours	2–3 weeks	Osteoclast inhibition	Moderate hypercalcemia, preserved renal function	Fever, mild nephrotoxicity
Zoledronate	24–48 hours	3–4 weeks	Potent osteoclast inhibition	Severe hypercalcemia, high skeletal burden	Renal toxicity, electrolyte shifts
Denosumab	48–72 hours	4–6 weeks	RANKL inhibition	Renal impairment, bisphosphonate resistance	Hypocalcemia, rare osteonecrosis of the jaw

Abbreviations: RANKL, receptor activator of nuclear factor-κB ligand.

Note: Data in Table 2 were derived from recent reviews and clinical resources on hypercalcemia treatment [35,36,51–55].

Table 3. Association between hypercalcemia severity and clinical outcomes in breast cancer.

Corrected calcium level	ICU admission (%)	Median hospital stay (days)	In-Hospital mortality (%)
<3.0 mmol/L (Mild)	8–10%	5–6	4–5%
3.0–3.5 mmol/L (Moderate)	15–20%	7–8	9–11%
>3.5 mmol/L (Severe)	30–35%	10–12	20–23%

Abbreviations: ICU, intensive care unit.

Note: The values shown in Table 3 represent estimated ranges derived from the overall trends described in recent studies on malignancy-related hypercalcemia. Previous studies consistently correlate severe hypercalcemia with higher mortality, greater need for intensive care, and more extended hospitalization [34,45,57–59].

tases or when rapid calcium correction is needed; however, it carries a higher risk of nephrotoxicity, warranting close monitoring of renal function [45,46].

In patients with renal impairment, poor response to bisphosphonates, or recurrent episodes of hypercalcemia, denosumab provides a compelling alternative [47]. By inhibiting RANKL, denosumab suppresses osteoclast differentiation and activity, resulting in a sustained reduction in serum calcium. Its onset of action is generally 48–72 hours, with therapeutic effects lasting 4–6 weeks [48,49]. Unlike bisphosphonates, denosumab is not renally excreted and is particularly suitable for patients with chronic kidney disease [50]. Table 2 (Ref. [35,36,51–55]) summarizes the comparison of commonly used agents, including their mechanisms of action, onset and duration of therapeutic effect, optimal clinical indications, and significant adverse effects.

Additionally, any special clinical cohorts require tailored intervention. Older patients, who are more vulnerable to volume shifts, should be carefully monitored during intravenous hydration to avoid cardiac overload. In those with renal impairment, zoledronic acid should be avoided or dose-adjusted, and denosumab is often preferred as a safer option. For patients with a history of recurrent hypercalcemic episodes, early incorporation of long-term antiresorptive therapy alongside oncologic treatments may help reduce the risk of recurrence.

In clinical settings, acute management of breast cancer–associated hypercalcemia can be adopted as a "fast–stable–sustained" approach: initiate prompt hydration and calcitonin for rapid symptom management, then transition to bisphosphonates or denosumab for prolonged calcium normalization. Treatment should be individualized based on serum calcium levels, renal function, comorbidities, and previous treatment response, enabling a stepwise, time-sensitive strategy that improves both immediate stabilization and long-term outcomes.

Prognosis and Clinical Implications of Hypercalcemia

Hypercalcemia in breast cancer is not only an acute metabolic emergency but also an indicator of tumor aggressiveness and systemic decompensation. Increasing evidence indicates a strong association between the severity of hypercalcemia and adverse clinical outcomes, particularly when it is first identified in the ED. Furthermore, corrected calcium levels are positively associated with increased clinical deterioration. When serum calcium exceeds 3.5 mmol/L, severe hypercalcemia is associated with acute organ dysfunction requiring closer monitoring, including an increased likelihood of intensive care unit (ICU) evaluation, as well as a higher risk of adverse in-hospital outcomes [56]. As summarized in Table 3 (Ref. [34,45,57–59]), outcomes worsen with increasing calcium levels, as reflected in higher rates of ICU admission, longer hospital stays, and mortality. These findings highlight the prognostic significance of early identification and severity-based triage in both emergency and inpatient settings [58,60].

Persistent or recurrent hypercalcemia in breast cancer is increasingly recognized as more than a transient metabolic complication; it often indicates increasing disease burden, emerging endocrine resistance, or progression of skeletal metastases [22]. Clinical evidence suggests that patients with sustained hypercalcemia are at higher risk for ICU admission, early hospital readmission, and reduced long-term survival, especially in the presence of extensive bone involvement or renal dysfunction [54]. These findings support the use of calcium derangements as dynamic indicators of disease destabilization in advanced breast cancer.

Patients presenting with new-onset hypercalcemia are frequently under-triaged, especially when symptoms are nonspecific, such as confusion, dehydration, or fatigue. Furthermore, older adults and those with renal impairment are particularly vulnerable to delayed recognition, which significantly increases the likelihood of ICU admission and worsens prognosis [58,61]. From a systems perspective, calcium-based triage tools and standardized early recognition mechanisms are urgently needed to improve emergency management in this high-risk cohort.

Investigations on biomarkers increasingly support the role of hypercalcemia, particularly in PTHrP-positive breast cancer, as a real-time indicator of tumor progression or therapeutic failure [62,63]. In some models, increasing PTHrP levels have been shown to precede radiographic evidence of metastases and to correlate with poor treatment response [64,65]. Integrating trends in serum calcium kinetics, PTHrP, and clinical context may enhance early decision-making in acute oncologic presentations.

Therefore, hypercalcemia in breast cancer patients has both immediate and long-term prognostic implications, which, beyond its acute metabolic consequences, guide the need for intensified monitoring or escalated treatment. Future real-world, longitudinal studies that combine ED data, treatment history, and biochemical markers are warranted to validate hypercalcemia as a predictive biomarker of oncologic deterioration.

Discussion

Hypercalcemia in breast cancer is a clinically crucial but usually under-recognized emergency. Its heterogeneous clinical presentation, reliance on PTHrP-driven mechanisms, and strong link to advanced disease result in diagnostic delays and inappropriate management in emergency settings. The nonspecific manifestations of this condition, ranging from mild gastrointestinal distress to significant neurological dysfunction, enable early implications to be misattributed to chronic infection, dehydration, treatment-related adverse effects, or progression of the underlying malignancy [66–68]. These challenges highlight the need for greater clinical speculation among emergency physicians who routinely examine patients without a significant oncology background.

Although current diagnostic approaches, including corrected serum calcium, ECG evaluation, and targeted laboratory testing, are well established, their timely application in the ED is inconsistent, and standardized protocols are rarely integrated into routine practice [69,70]. Existing evidence also indicates considerable heterogeneity in acute management strategies, including differences in fluid resuscitation protocols, selection of antiresorptive therapy, and approaches for patients with renal impairment, reflecting both institutional preferences and incomplete implementation of existing guidelines [45,70]. These gaps highlight the need for standardized, ED-specific management protocols.

From a prognostic perspective, hypercalcemia clearly reflects disease burden and clinical severity. Elevated calcium levels correlate with higher ICU admission rates, prolonged hospitalization, and increased short-term mortality [56,58,71]. Despite these associations, hypercalcemia is rarely incorporated into clinical prognostics or risk stratification frameworks for breast cancer [58,67]. Future studies should evaluate whether calcium levels, PTHrP kinetics, or dynamic changes in calcium can serve as reliable prognostic biomarkers and guide emergency triage decisions.

Key priorities and core areas for future investigation include: (1) development and validation of ED-based diagnostic and treatment mechanisms; (2) prospective evaluation of calcium- and PTHrP-based risk prediction models; (3) comparison of outcomes from early versus delayed initiation of antiresorptive therapy in emergency presentations; and (4) identification of predictive markers capable of distinguishing reversible metabolic instability from irreversible late-stage disease [72]. Addressing these questions will improve early recognition and more consistent, evidence-based management for this high-risk population.

Conclusion

Hypercalcemia in breast cancer is a critical metabolic emergency that often indicates advanced or rapidly progressing disease. Its predominantly PTHrP-driven pathogenesis leads to nonspecific clinical manifestations, making early recognition challenging in the emergency setting. Effective management requires rapid hemodynamic stabilization with intravenous hydration, followed by appropriately selected antiresorptive therapy. Increasing severity of hypercalcemia is consistently associated with poorer clinical outcomes, including higher ICU admission rates, more extended hospitalization, and increased mortality. Given these prognostic implications, hypercalcemia monitoring should be incorporated into routine clinical risk assessment.

Future investigations should focus on developing standardized ED-specific care pathways and the validation of calcium-based prognostic models to improve earlier identification and optimize prognostic outcomes.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding authors upon request.

Author Contributions

ZZ, WJ, JZ, HW, XL and JX contributed to conception and design. ZZ has been involved in drafting the manuscript. All authors have been involved in revising it critically for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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