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Review

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Hypernatremia: Epidemiology and Predictive Role in Emerging and Established Acute Kidney Injury

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Abstract

Hypernatremia (plasma sodium > 145 mmol/L) reflects impaired water balance, and affected patients can suffer from severe neurologic symptoms. Hyponatremia, on the other hand, is the most frequent electrolyte disorder in hospitals. It may be diagnosed in acute kidney injury (AKI), but hyponatremia prior to the diagnosis of AKI has also predictive or prognostic value in the short term. Aim of the article was to summarize data on both, epidemiology and outcomes of in-hospital acquired hypernatremia ("In-hospital acquired" refers to the diagnosis of either hypo- or hypernatremia in patients, who did not exhibit any of these electrolyte imbalances upon admission to the hospital). It also aimed to discuss its predictive role in patients with emerging or established AKI. Five databases were searched for references: PubMed, Medline, Google Scholar, Scopus, and Cochrane Library. Studies published between 2000 and 2023 were screened. The following keywords were used: "hypernatremia", "mortality", "pathophysiology", "acute kidney injury", "AKI", "risk prediction", "kidney replacement therapy", "KRT", "renal replacement therapy", "RRT", "hyponatremia", and "heart failure". A total of 16 studies were deemed eligible for inclusion. Among these, 13 studies had a retrospective design, two investigations were published as secondary analyses from prospective trial cohorts, and one study was prospective in nature. Out of the 16 studies, 11 focused on the epidemiology and outcomes of hypernatremia, while five investigations were related to AKI and/or AKI-associated endpoints. The prevalence of hypernatremia diagnosed during hospitalization varied from 1.9% to 6.8%, with one exception where it was 30.8%. All studies demonstrated associations between hypernatremia and mortality, even over extended periods after discharge. In AKI patients, hypernatremia shows potential for predicting in-hospital death. In conclusion, hypernatremic individuals are at higher risk of death during in-hospital therapy. Also, the electrolyte disorder potentially qualifies as a future biomarker for AKI onset and AKI-associated mortality.

Keywords: Hypernatremia; ICU; Prevalence; Mortality; AKI; Kidney replacement therapy

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Introduction

Hypernatremia is characterized by a plasma sodium concentration above 145 mmol/L. It is a condition that occurs when there is an imbalance in the body's water levels, resulting in a deficiency of total body water [1]. It can also be caused by an excess accumulation of water and sodium. Patients with hypernatremia are at risk of experiencing neurological symptoms, especially if the condition develops rapidly. In comparison to hyponatremia, which is the most common electrolyte disorder in hospitalized patients, hypernatremia has a lower prevalence during hospitalization. The literature on the prevalence, outcomes, and management of hyponatremia is extensive, with a search of medical databases using the terms "hyponatremia" and "heart failure", yielding over 1,200 references as of the end of March 2023.

The search for "hypernatremia" AND "heart failure" yielded 103 citations, with only six clinical trials included. In patients with heart failure, the diagnosis of hyponatremia is important for prognosis [2-5]. Hyponatremia frequently occurs as a complication in established acute kidney injury (AKI), especially if patients become oliguric and fluid therapy is not adjusted in a timely manner. Furthermore, the presence of hyponatremia before the diagnosis of AKI has prognostic value, particularly in terms of in-hospital mortality [6, 7]. Additionally, individuals with hyponatremia are at a higher risk of developing AKI during their hospital stay in general [8]. Therefore, this electrolyte imbalance may serve as a biomarker for AKI.

This article aimed to specifically examine hypernatremia, despite the abundance of observational and interventional studies conducted on hyponatremia. It will provide a summary of the epidemiological and outcome characteristics of hypernatremia diagnosed in hospitals. Additionally, the article will explore the predictive role of hypernatremia in patients with emerging or established AKI.

Methods

The following databases were searched for references: PubMed, Medline, Google Scholar, and Scopus. Studies from 2000 to 2023 were screened using the keywords "hypernatremia", "mortality", "pathophysiology", "acute kidney injury", "AKI", "risk prediction", "kidney replacement therapy", "KRT", "renal replacement therapy", "RRT", "hyponatremia", and "heart failure". The first topics of interest was the epidemiology and outcomes of in-hospital-acquired hypernatremia. "Outcomes" primarily referred to in-hospital mortality and the need for kidney replacement therapy (KRT). The second topic of interest was the prediction of *de novo* AKI during in-hospital therapy. Ethical approval was not mandatory.

Pathophysiological Considerations

Sodium plays a crucial role in determining the volume of fluid outside the cells, known as extracellular fluid volume [9]. When there is a deterioration in the total amount of sodium in the body, it can result in either volume depletion (negative sodium balance) or volume expansion (positive sodium balance). If the balance of water in the body is affected, it can lead to an increase in serum sodium concentration (negative water balance) or a decrease in serum sodium concentration (positive water balance). Hypo- and hypernatremia, which refer to low and high levels of sodium in the blood respectively, can cause a net movement of water either into the cells (hyponatremia) or into the extracellular space (hypernatremia).

Hypernatremia can occur due to the loss of sodium-depleted or sodium-free water, such as in cases of diarrhea, osmotic diuresis, diabetes insipidus, or the use of loop diuretics [10]. It can also develop when sodium-enriched solutions accumulate in the body, for example through the ingestion of seawater or overdosing on sodium bicarbonate solution [11]. In general, older age has been identified as a risk factor for hypernatremia. Gender, on the other hand, is not considered a direct risk factor [12]. Both hypo- and hypernatremia can potentially lead to severe neurological symptoms. Hypernatremia, in particular, has been associated with symptoms such as rapid breathing (tachypnea), muscle weakness, restlessness, insomnia, lethargy, coma, and seizures [13]. In severe cases, hypernatremia-induced high osmolality can cause brain cells to shrink, leading to vascular damage and hemorrhage [14].

Isolated hypo- or hypernatremia is rarely diagnosed. As mentioned, hypernatremia often occurs as a result of the loss of sodium-depleted water (polyuria in diabetes mellitus or AKI). This polyuria can also lead to potassium loss, resulting in hypokalemia. Cancer patients are particularly prone to both hypernatremia and hypokalemia [15]. Additionally, hypernatremia is accompanied by an increase in extracellular chloride levels. Both ions are available in equimolar quantities extracellularly. Hyperchloremia can potentially increase the risk of AKI, as several studies have shown an increased risk of AKI in adults who received normal saline compared to balanced electrolyte preparations [16].

Hypernatremia: Epidemiology and Outcomes

Meanwhile, a significant number of studies have focused on the prevalence and outcomes of hypernatremia in hospitalized patients. Most of these studies have analyzed data from subjects who received intensive care treatment. The references have been arranged in chronological order, from older to more recent publications.

A retrospective study published in 2014 [17] collected data from January 2010 to January 2011. The study aimed to screen for hypernatremia in all patients admitted to a single emergency department in France. A total of 54,753 admissions were documented, and 85 individuals were diagnosed with severe hypernatremia (serum sodium ≥ 150 mmol/L). More than 50% of these individuals were institutionalized, and 28% suffered from dementia. Unfortunately, almost 25% of the patients did not survive in-hospital therapy. Interestingly, the study found that the rate of correction of hypernatremia, rather than the severity of the condition itself, was identified as an independent predictor of death.

In 2015, a retrospective analysis [18] compared the outcomes of hypernatremic patients with those of all other subjects. The data were collected from a single 36-bed department of internal medicine over a period of 28 months, totaling 1,945 hospitalizations. Among these hospitalizations, 49 patients (2.6%) had a plasma sodium concentration above 149 mmol/L, indicating hypernatremia. In-hospital mortality was significantly higher in these hypernatremic patients compared to all other individuals (43% vs. 2%). Additionally, approximately one-third of the patients with hypernatremia were diagnosed as hypervolemic.

In 2016, Alansari et al [19] published a retrospective investigation conducted at the King Khalid University Hospital (KKUH) in Riyadh. The study collected data over a 2-year period, during which 864 patients were treated in a surgical intensive care unit (SICU). The study included patients who experienced an increase in serum sodium levels above 145 mmol/L starting from day 2 after SICU admission. Patients who required hypernatremia treatment (e.g., brain injury) were not included. Among the total subjects, 50 patients (5.8%) developed hypernatremia during the follow-up period, and the mortality rate in the intensive care unit (ICU) was 40%. The authors also identified several risk factors for developing hypernatremia, including post-gastrointestinal surgery, weekend, and night admissions.

Another retrospective, monocentric evaluation from 2016 [20] reported on the predictive value of hypernatremia in ICU patients. This study exclusively recruited patients (n = 450) from a neurologic ICU, who initially had normal sodium levels upon admission. Interestingly, patients with impaired kidney excretory function were not considered in this study. The patients were divided into three groups based on their serum sodium dynamics during the follow-up period: normonatremia (n = 222), mild hypernatremia (n = 142), and severe hypernatremia (n = 86). The study found that hypernatremia was an independent prognostic factor, and the peak serum sodium level predicted death with a sensitivity of 79.4% and specificity of 74.5%. The optimal cut-off for peak serum sodium was determined to be 147.55 mmol/L.

A prospective investigation conducted in 2016 [21] involved over 90,000 patients who were hospitalized between October 2014 and September 2015. The study found that 16.8% of the patients were diagnosed with hyponatremia, while only 1.9% developed hypernatremia. Mixed dysnatremia, which refers to the occurrence of both electrolyte disorders in the same patient during one hospital stay, was also observed. The study revealed that in-hospital-acquired hypernatremia, as well as persistent hypernatremia in general, strongly predicted in-hospital death, with odds ratios ranging from 13.3 to 22.9. Additionally, overcorrection of hyponatremia increased the risk of death, with an odds ratio of 2.2.

Imaizumi et al (2017) [22] conducted a retrospective study involving adult patients who required ICU therapy for at least 3 days and did not have dysnatremia upon admission to the ICU. The primary endpoint of the study was in-hospital mortality on day 28. Out of the 1,756 individuals included in the analysis, 121 (approximately 6.8%) were diagnosed with ICU-acquired hypernatremia. This electrolyte disorder was found to be associated with a higher risk of mortality at day 28, with a hazard ratio of 3.07. Interestingly, the interaction between hypernatremia and cerebrovascular disease further increased the hazard ratio to a similar extent (3.03).

In 2020, Thongprayoon et al [23] published long-term outcome data from a total of 55,901 discharged patients recruited between 2011 and 2013. The endpoint of interest was survival after 1 year. To determine the relationship between mortality and serum sodium levels, the researchers categorized the patients into five groups based on their last measured serum sodium: ≤ 132, 133 - 137, 138 - 142, 143 - 147, and ≥ 148 mmol/L. Initially, the analysis revealed a U-shaped relationship, with the highest risk of death observed in the 138 - 142 mmol/L category. However, after adjusting for confounding factors, the risk of mortality was found to be higher in both the ≤ 137 mmol/L and ≥ 143 mmol/L categories compared to the 138 - 142 mmol/L category, respectively. Ultimately, the highest mortality risk was identified in subjects assigned to the highest serum sodium category (≥ 148 mmol/L).

A subgroup analysis of the “need-speed trial” [24] was published by Castello et al in 2021 [25]. The trial aimed to identify biomarkers that could distinguish between infectious and noninfectious systemic inflammatory response syndrome. Castello and colleagues categorized septic patients into three groups based on their serum sodium levels at the time of admission to the emergency department (hypo-, eu-, or hypernatremia). Hyponatremia was diagnosed in 40.3% of the patients, while hypernatremia was found in 5.7% of the individuals. The presence of hypernatremia was associated with higher mortality rates compared to hypo- and eunatremia. Both moderate-to-severe hyponatremia and hypernatremia independently predicted death at 7 and 30 days.

The prevalence and outcomes of hospitalized cancer patients with hypernatremia were reported in a monocentric evaluation published in 2022 [26]. The study included a total of 2,945 individuals who all had solid malignancy. The prevalence of hypernatremia in this cohort was found to be 3.16%. To better understand the impact of hypernatremia, the researchers compared this group with a matched control cohort consisting of patients diagnosed with hyponatremia. The groups were adjusted for age, diagnosis, and gender. The results showed a significant difference in median survival between the two groups. The hypernatremia group had a median survival period of 1.5 months, while the hyponatremia group had a median survival period of 11.7 months. In addition, the hypernatremic individuals had a higher overall mortality rate of 30.1% compared to 8.6% in the hyponatremia group. They also required a longer duration of in-hospital therapy. These findings emphasize the importance of recognizing and managing hypernatremia in cancer patients, as it is associated with worse outcomes and increased healthcare needs.

The prognostic role of admission hypernatremia in another group of cancer patients was evaluated by Seo et al in 2022 [27]. As discussed in the introduction section, prognostic assessment plays a crucial role in the care of patients with malignant disorders. However, electrolyte abnormalities have been understudied in this context. The study screened 487 patients with terminal cancer who were receiving hospice-palliative care. Upon admission, hypernatremia was diagnosed in 15 individuals (3%). The median survival time for all subjects was 26 days. Hypernatremia was identified as a predictor of mortality, along with other variables such as hypoalbuminemia and leukocytosis.

A more recent study conducted in 2023 [28] favored the use of a propensity score matching approach. The study took place in a single center trial at a neurosurgical ICU, with an observation period lasting from January 2013 until December 2019. A total of 1,146 individuals were screened; and among them, 353 patients (30.8%) were diagnosed with hypernatremia. After employing propensity score matching, 290 pairs were included in the analysis. The study found that both moderate and severe hypernatremia were associated with increased in-hospital and 28-day mortality rates compared to patients without hypernatremia. Interestingly, subjects with mild hypernatremia exhibited the highest survival rates.

In summary, the prevalence of hypernatremia diagnosed during hospitalization varies from 1.9% [21] to 6.8% (9.2%) [22, 23]. One study even reported a prevalence of 30.8% [28], but it should be noted that this particular study focused on a neurosurgical ICU where hypernatremia may be intentionally induced to reduce intracranial pressure. It is important to mention that most of the studies conducted so far have been retrospective in design. Additionally, a common finding among these studies is the association between hypernatremia and an increased risk of mortality, both in the short-term and long-term. Similar observations have been reported by other researchers as well [29-31]. A comprehensive overview of the studies discussed in this text is shown in Table 1 [17-28], which provides information on the prevalence of hypernatremia and its associated outcome variables.

Hypernatremia in Emerging and Established AKI

In recent years, a significant number of new or alternative biomarkers for AKI have been identified. These biomarkers can

Table 1. Epidemiology and Outcomes of In-Hospital Diagnosed Hypernatremia

Reference	Design	Hypernatremia prevalence	Outcomes
Bataille et al, 2014 [17]	Observational, retrospective, 54,753 emergency department admissions	Severe hypernatremia (> 150 mmol/L) in 85 individuals	Mortality rate 25%, slow correction of serum sodium independently death predictive
Felizardo Lopes et al, 2015 [18]	Observational, retrospective, single-center, 1,945 hospitalizations considered	2.6%	In-hospital mortality of hypernatremic patients significantly higher as compared to all other individuals (43 vs. 2%)
Alansari et al, 2016 [19]	Observational, retrospective, single-center (one surgical ICU), exclusion of patients with therapeutic need of hypernatremia, n = 865	5.8%	Intensive care mortality 40%
Hu et al, 2016 [20]	Observational, retrospective, single-center (neurologic ICU), normonatremia on admission, exclusion of patients with impaired kidney function, n = 450	Mild hypernatremia in 142 individuals, severe hypernatremia in 86 patients	Peak serum sodium independently death predictive
Hu et al, 2017 [21]	Prospective investigation in more than 90,000 individuals	1.9%	Hypernatremia in general, in-hospital-acquired, and persistent hypernatremia predicted in-hospital death
Imaizumi et al, 2017 [22]	Retrospective study, intensive care-treated patients without dysnatremia on admission	6.8%	Hypernatremia predictive of 28-days mortality (hazard ratio 3.07)
Thongprayoon et al, 2020 [23]	Retrospective data from 2011 to 2023, long-term outcome data from 55,901 discharged patients, last measured serum sodium before discharge defined category	About 9.2%	Highest 1-year mortality risk in patients with serum sodium ≥ 148 mmol/L
Castello et al, 2021 [25]	Subanalysis of the need-speed trial [24], septic individuals, serum sodium analysis at the time of emergency department admission	5.7%	Hypernatremia associated with higher mortality than eu- and hyponatremia; hypernatremia predicted death at days 7 and 30
Del Rio et al, 2022 [26]	Retrospective, monocentric evaluation, 2,945 hospitalized cancer patients, comparisons to matched controls with hyponatremia	3.16%	Higher mortality (30.1 vs. 8.6%) and lower median survival times (1.5 vs. 11.7 months) in hyper- as compared to hyponatremic patients
Seo et al, 2020 [27]	Retrospective study in patients with terminal cancer, n = 487, serum sodium analysis on admission to hospice-palliative care	3%	Hypernatremia mortality predictive
Lee et al, 2023 [28]	Retrospective, monocentric evaluation, neurosurgical ICU, screening of 1,146 patients from a 6-years period, propensity score matching	30.8%	Moderate and severe hypernatremia associated with in-hospital and 28-days mortality; mild hypernatremia associated with the highest survival rates at all

The studies have been listed according to the publication date (older to more recent). ICU: intensive care unit.

be categorized into three groups: markers of impaired kidney function, markers of structural damage, and stress markers [32]. In 2020, Ostermann et al [33] published a conference report titled "Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement". This report summarized the data on the most important alternative AKI biomarkers that have been identified so far. The clinical usability of each individual biomarker was assessed in relation to various outcome categories, including AKI risk prediction and AKI severity, among others. However, it is important to note that, as of now, no individual biomarker or combination of biomarkers can reliably replace serum creatinine. In terms of AKI risk prediction, serum electrolytes have the potential to provide valuable information.

In 2015, Kumar et al [34] published retrospective data from patients with subarachnoid hemorrhage. These patients are often treated with hypertonic sodium solution to reduce intracranial hypertension or correct hyponatremia. The study included 736 individuals, and the diagnosis of AKI was made according to the Acute Kidney Injury Network (AKIN) criteria [35]. The incidence of AKI was found to be 9%. The administration of sodium was significantly associated with the onset of AKI, independent of variables such as age, gender, pre-existing kidney disease, diabetes mellitus, exposure to radiocontrast media, duration of mechanical ventilation, and Glasgow Coma Scale score upon admission. For every increase in serum sodium level of 1 mmol/L, there was a 5.4% increase in the hazard ratio for AKI. Therefore, hypernatremia was identified as a risk factor for AKI during the follow-up period of 72

Table 2. Hypernatremia in AKI Risk Prediction

Reference	Design	Endpoints	Findings
Kumar et al, 2015 [34]	Retrospective study in patients with subarachnoid hemorrhage, n = 736	AKI incidence from 72 h until 14 days after admission, AKI diagnosis according to KDIGO [40]	Therapeutic sodium administration associated with AKI onset *per se*, every increase in serum sodium by 1 mmol/L associated with an AKI hazard ratio increase of 5.4%
Peres et al, 2015 [36]	Retrospective, single-center analysis, ICU, n = 152	AKI onset and ICU mortality	Hypernatremia predicted ICU death but not AKI
Mendes et al, 2015 [37]	Secondary analysis of 772 individuals from a 2011 published prospective trial [38]	In-hospital mortality	Highest mortality in subjects with hypernatremia and AKI, hypernatremia independently mortality-predictive
Woitok et al, 2020 [6]	Retrospective cross-sectional study in emergency department patients	Death in AKI patients	Hypo- and hypernatremia death predictive
Marahrens et al, 2023 [39]	Retrospective, observational, inclusion of patients with *de novo* AKI, serum sodium analysis at five pre-defined timepoints	Need of KRT, in-hospital death	Increase of the relative risk of in-hospital death by 8% with every unit of serum sodium increase

ICU: intensive care unit; AKI: acute kidney injury; KRT: kidney replacement therapy; KDIGO: Kidney Disease: Improving Global Outcomes.

h to 14 days after admission.

Peres et al [36] conducted a retrospective analysis to identify risk factors associated with poor clinical outcomes in patients with AKI receiving intensive care. The study was conducted at a single center and included 152 patients with a mean age of 57.1 ± 20 years. Among them, 100 patients developed AKI during their stay in the ICU, with 81 (53.2%) not requiring KRT and 19 (12.4%) receiving dialysis at least once. The overall mortality rate for all 152 patients was 35.9%. Among the AKI patients, those who did not require KRT had a mortality rate of 43.2%, while those who required KRT had a significantly higher mortality rate of 84.2%. The study identified several independent risk factors for AKI, including invasive mechanical ventilation, elevated levels of creatinine and urea upon admission. Hypernatremia was found to be a predictor of mortality in the ICU population as a whole, but not specifically in AKI patients.

A 2015 investigation [37] was conducted to analyze the prognostic role of predialysis hypernatremia in AKI patients requiring KRT. This study was a secondary analysis of data from a 2011 prospective cohort study [38]. The included patients were categorized into three groups (normo-, hypo-, and hypernatremia) based on their serum sodium levels before initiating the first KRT session. Among the 772 individuals included, almost half (47.3%) exhibited dysnatremia. Interestingly, hypernatremia was found to be more common than hyponatremia (33.7% vs. 13.6%, P = 0.001), which differed from previous studies. The overall in-hospital mortality rate was 64.6%, while AKI patients with severe hypernatremia had a mortality rate of 89.1%. Further analysis showed that the respective electrolyte disorder was independently predictive of mortality.

In 2020, Woitok et al [6] published the findings of a cross-sectional investigation that spanned 2 years (January 2017 to December 2018). The study focused on patients exclusively from the emergency department. Among the participants, 8% were diagnosed with AKI, while the prevalence of hyponatremia (low sodium levels) and hypernatremia (high sodium levels) were found to be 23.16% and 1.4% respectively. Both electrolyte imbalances were identified as independent predictors of mortality during the follow-up period.

In a recent study conducted by our group [39], *de novo* AKI was detected using an in-hospital AKI alert system. This system automatically notifies the responsible nephrologist if either criterion 1 or 2 of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for AKI [40] is met. A total of 160 individuals with AKI were included in the study, of which 57 were females. The average duration of in-hospital treatment was 16 ± 13.3 days, and 23.1% of the patients died before discharge. The study examined two electrolytes, serum sodium and potassium, at five predetermined timepoints: hospital admission, AKI onset, minimum estimated glomerular filtration rate (eGFR), and the minimum and maximum levels of the respective electrolyte during the treatment period. The results showed that patients who died in the hospital had significantly higher serum sodium levels at AKI onset compared to the survivors (145.7 ± 2.13 mmol/L vs. 138.8 ± 0.636 mmol/L, P = 0.003). Furthermore, logistic regression analysis revealed that the relative risk of in-hospital death increased by 8% with each unit increase in serum sodium. Patients with serum sodium levels above the upper normal range at AKI onset were also more likely to experience in-hospital death (P = 0.001). Although the study was designed retrospectively, it demonstrated the significant prognostic value of serum sodium in predicting outcomes in emerging AKI. Table 2 [6, 34, 36-40] provides a summary of studies investigating the risk prediction of hypernatremia in AKI.

Finally, the mechanisms by which hypernatremia potentially increases the risk of AKI may be discussed. It is highly likely that chloride, which is available extracellularly in equimolar quantities to sodium, contributes to a higher risk of AKI during follow-up. A recent meta-analysis conducted by Wang et al in 2023 [16] examined 13 studies in the ICU setting, including 10 randomized controlled trials and three cohort studies, with a total of over 38,000 patients. The findings clearly demonstrated that crystalloids enriched with chloride, such as normal saline, increase the risk of AKI in adults (but not in children).

Conclusions and Perspective

In contrast to hyponatremia, hypernatremia occurs less frequently in hospitalized patients. Individuals with hypernatremia have a higher risk of death during in-hospital therapy. Most studies on hypernatremia and its outcomes are retrospective in nature. Hypernatremia has the potential to be a future biomarker for the onset of AKI and AKI-associated mortality. The analysis of sodium levels has the significant advantage of being widely available, and the costs are negligible.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Clara Jansch, Igor Matyukhin, Rebecca Lehmann, Benedikt Marahrens, and Baschar Khader performed the literature search. Oliver Ritter assisted in writing. Susann Patschan assisted in the table preparation. Daniel Patschan wrote the article.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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